LYMPHOCYTIC BRONCHOALVEOLITIS IN IDIOPATHIC CHRONIC COUGH
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We have recently reported an excess of cases of organ specific autoimmune diseases amongst patients with idiopathic chronic cough and have suggested that the cough may be due to homing of activated lymphocytes from the primary site of autoimmune inflammation to the lung. We tested this hypothesis in comparative immunopathology study of 19 patients with idiopathic chronic cough recruited over a two year period (mean age 54y, 79% female, mean duration of cough 2y), 11 healthy subjects, and 14 patients with explained chronic cough of similar severity. Organ specific autoimmune disease was present in six of idiopathic cough patients (32%) but no normals/explained cough subjects. All subjects had a bronchoscopy, bronchoalveolar lavage (BAL) and bronchial biopsy using standard techniques.

We obtained cytopsins from the BAL for a differential cell count and studied BAL T-cell status (CD4/8), activation (CD103, CD25, CD49a, HLA-DR) and chemokine receptors (CCR3,5,6,11, CXCR3) using 3-colour flow cytometry. Bronchial biopsies were embedded in glycolmethacrylate and immunohistochemistry for CD3,4,8 (lymphocytes), CD14 (monocytes), CD45 (leukocytes), CD56 (NK cells), EG2 (eosinophils), Neutrophil Elastase (neutrophils), AA1 (mast cells), Interferon-γ, IL5, 3H4(I4) was performed. The mean (SEM) BAL differential lymphocyte count was 6.8 [1.3]% in normals, 15.1 [2.6]% in idiopathic cough [mean difference from normals 8.3%; 95% Confidence Interval 1.6 to 15.0; p=0.02] and 7.0 [1.7]% in explained cough. The proportion of BAL T-cells expressing CD4 was similar in all three groups and there were no differences in activation status of T-cells or chemokine receptor expression. CD56 and IFNγ expression in biopsies (cells/mm² submucosa) were reduced in subjects with idiopathic cough compared to normals and subjects with explained cough (p<0.03 and 0.047; Kruskal-Wallis). EG2 and 3H4 expression were raised in explained cough (p=0.02 & 0.03) but there were no differences in expression of CD3 and other markers between groups. In conclusion, we have made a novel observation of lymphocytic bronchoalveolar inflammation in patients with idiopathic chronic cough. The association with organ specific autoimmune disease suggests that this might be due to homing of activated lymphocytes from primary sites of autoimmune inflammation or a hitherto unrecognised autoimmune bronchitis. Further studies are required to investigate the interaction between T-cells and the cough reflex.

TGF-β ACTIVATION IS DIMINISHED FOLLOWING BLEOMYCIN-INDUCED LUNG INJURY IN MICE LACKING NEUTROPHIL ELASTASE
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Transforming growth factor-beta (TGF-β) is widely implicated in the pathogenesis of pulmonary fibrosis. We have previously reported that mice lacking neutrophil elastase (NE1) are resistant to pulmonary fibrosis induced by bleomycin instillation. We hypothesised that decreased TGF-β activation may contribute to the resistance of these null animals against fibrosis. Active TGF-β was quantitated in bronchoalveolar lavage fluid (BALF) and lung tissue from wild type (WT) and NE1 mice seven days following instillation of 0.05 unit bleomycin or saline. Levels of active TGF-β in bleomycin-treated WT BALF averaged 0.36 ± 0.02 mg/ml, two-fold greater than in saline controls (p<0.001). In contrast, active TGF-β levels in bleomycin-treated NE1 BALF (0.23 ± 0.01 mg/ml, p<0.001 v WT values) were not different from saline controls. Conversely, a greater amount of TGF-β was detected in lung tissue from bleomycin-treated NE1 mice (p=0.05 v WT). No differences in inflammatory cellularity, alveolar-capillary leak, TGF-β, or TGF-β mRNA expression were apparent between the two genotypes at this time point. Furthermore, in bleomycin-treated WT lungs, immunocytochemical staining for active TGF-β (LC1–30 antibody, Dr. K. Flanders, NIH) was widespread, with prominent localization to areas of interstitial or alveolar inflammation. In contrast, staining for active TGF-β in bleomycin-treated NE1 lungs was minimal, and limited to peribronchial and perivascular locations. In conclusion, TGF-β activation was diminished in alveolar fluid from bleomycin-treated NE1 mice and correlated with decreased staining for active TGF-β in lung tissue. These data provide the first in vivo evidence that neutrophil elastase may play a critical role in modulating TGF-β activation. In particular, this study suggests that neutrophil elastase inhibitors may have a therapeutic potential in abrogating TGF-β-mediated fibrotic lung disease.

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THE COST EFFECTIVENESS OF AN ASTHMA MANAGEMENT STRATEGY DIRECTED AT NORMALISING THE INDUCED SPUTUM EOSINOPHIL COUNT
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We have recently shown that a management strategy directed at normalising the induced sputum eosinophil count reduces asthma exacerbations and hospital admissions compared to a traditional approach. We now report the results of a concurrent health economic evaluation designed to determine the cost effectiveness of this sputum management strategy. Seventy four subjects with moderate to severe asthma recruited from hospital clinics were randomised into two groups: one managed by standard British Thoracic Society asthma guidelines (BTS management group) and one managed using an algorithm aimed at normalising the induced sputum eosinophil count as well as minimising symptoms (sputum management group). Patients were seen nine times over 12 months and on each occasion sputum was induced and processed, but the results were not disclosed in the BTS guidelines group. Throughout the study patients completed daily diary cards recording medication use, days off work, emergency GP or hospital visits and hospital admissions. The overall cost of each management strategy was calculated using our estimates of the cost of sputum induction and processing, the 2001 Unit Costs of Health and Social Care, the Department of Health 2001 reference costs and the British National Formulary. Total costs for each patient were calculated as the sum of the costs of hospital out-patient appointments, primary care visits, hospital admissions and medication use throughout the 12 months, with the addition of the costs of sputum induction and processing for patients in the sputum management group only. Patients in the sputum management group experienced significantly fewer severe asthma exacerbations than patients in the BTS management group (35 v 109, p=0.01) and significantly fewer patients were admitted to hospital with asthma (1 v 6, p=0.047). Amongst the 49 (24 v 25) patients in regular employment, the mean (SEM) days off work was 2.2 (0.8) in the sputum management group and 8.3 (2.1) in the BTS management group (p=0.01). The estimated annual total mean (SEM) cost per patient was £17755 (119) in the sputum management group and £1954 (164) in the BTS management group (p=0.30). A treatment strategy directed at normalising the induced sputum eosinophil count reduces asthma exacerbations and hospital admissions without incurring additional costs to the health service. In addition, by reducing work days lost due to asthma, this approach may result in significant cost savings to society.

THE vδ15 INTERNIN INDUCES ANOIKIS IN SQUAMOUS CELL CARCINOMA (SCC) CELLS BY ACTIVATING THE INTRINSIC AND EXTRINSIC DEATH PATHWAYS AND INHIBITING AN AKT/PKB SURVIVAL SIGNAL

Introduction: Focal or extensive loss of vδ15 is a feature of the most poorly differentiated SCCs, while an increase in vδ15 is associated...
with invasiveness and metastatic spread (Watt. Dev Suppl 1993:185–92). Epithelial cells normally undergo apoptosis on detachment from their extracellular matrix (anokiasis), but transformed cells do not. Hence failure to express a particular integrin may render tumour cells “deaf” to specific signals determining apoptosis. We hypothesised that expression of αv on H357 cells (which completely lack αv) and SCC4 cells (which have low expression) would restore their ability to undergo anokiasis.

Methods: αv or α4 integrin subunits were transfected into H357 and SCC4 cells using the pBabeNeo retroviral vector giving high expressing polyclonal populations. Anokiasis was assessed by FACs analysis for sub-G1 cells and by TUNEL staining. Signalling pathways were investigated using MEK, p38MAPK, and PI3K inhibitors, and a constitutively active Akt construct. The apoptotic pathway was investigated using specific caspase inhibitors, Western blotting for activated pro and anti apoptotic molecules and a dominant negative FADD construct. Anokiasis was examined using a chimeric molecule with the cytoplasmic domain of J5 attached to the extracellular domain of β6.

Results: The αv subunit formed a functional heterodimer with J5 as measured by FACs and adhesion to vitronectin. Anokiasis was dramatically increased in the αv infected cells (both H357s and SCC4s) compared to the parental populations, empty vector controls and α4 infected cells at 48 and 72 hours (p<0.01). Anokiasis was not increased in αvβ6 expressing cells. The pathways involved in αvJ5 induced anokiasis include a suppression of activation of the survival factor Akt/PKB, possibly via the cytoplasmic domain of J5 and both the intrinsic (mitochondrial) and extrinsic (death receptor mediated) cell death pathways.

Conclusion: Re-introduction of the αv integrin subunit increased SCCs ability to undergo anokiasis via the αvJ5 heterodimer. Both the intrinsic and extrinsic apoptotic pathways are required, and a cell survival mechanism of activating Akt/PKB is suppressed.


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Phosphodiesterase4 (PDE4), a family of cAMP hydrolysing enzymes is widely expressed in immune cells. Four genes encode PDE4A, PDE4B, PDE4C, and PDE4D. Differential mRNA splicing produces variability within these families. Structural differences between isoforms suggest specific roles in cell regulation. I have shown PDE4 isoform expression regulation with macrophage differentiation. Such monocytes lose specific expression, but gain PDE4A and PDE4B isoforms. I hypothesised important roles for PDE4B isoforms in macrophage behaviour.

Methods: RAW 264.7 cells were treated with 1ng/ml/lps +/- rolipram. PDE4 inhibitor rolipram, PDE3 inhibitor cilostamide or signal transduction inhibitors. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, PDE4 isoform activity or ERK 1/2 activity was measured. ERK activity was assessed by the phospho-ERK/Total ERK ratio on western blot. Total PDE4, PDE3, and PDE4 isoform activity from immunoprecipitates were assessed, TNFα and prostaglandin E2 (PGE2) production were measured in growth medium by ELISA. RAP-1A G-protein activity mutants were used to investigate rolipram’s action.

Results: Rolipram, not cilostamide caused indomethacin sensitive increase in iNOS expression, but indomethacin resistant increase in COX-2 expression in lps stimulated macrophages. PGE2 production was dose dependently increased by rolipram while TNFα production was inhibited in an indomethacin resistant fashion. Rolipram caused an increased and early activation of ERK 2. Lps led to a MEK dependent increase in PDE4 activity by 40% and PDE4B by 42%. Transfected RAP-1A activity mutants did not influence inflammatory mediator production.

Discussion: Rolipram increases the expression of COX-2, PGE2, and iNOS while inhibiting TNFα. TNFα inhibition is not due to increased PGE2 production. Complex crosstalk between the cAMP and MAPKinase signal cascades suggests increased PDE4B activity acts to regulate pro-inflammatory signal propagation. Rolipram alters the response of ERK 2 to lps, promoting a “proliferative” response. The G-protein RAP-1A did not mediate the interaction between cAMP and MAPKinase.

T5 NASAL MUCOCILIARY CLEARANCE IS NORMAL IN CHILDREN WITH CF: EVIDENCE AGAINST A PRIMARY CFTR-RELATED MECHANISM IN THE UPPER AIRWAY

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Studies in adult CF patients have reported impaired mucociliary clearance (MCC) in both the nose and lungs, which has been implicated in the pathogenesis of airway plugging and bacterial lung infection. We studied young children to explore a primary versus secondary cause of impaired nMCC. Saccharin clearance times were measured in 18 children with CF (median age 111 (9.5-16y)) and 21 non-CF children (median age 121 (9.5-16y)). Eleven children with Primary Ciliary Dyskinesia (PCD) served as controls. Anokiasis was assessed using a chimeric molecule with the cytoplasmic domain of J5 attached to the extracellular domain of β6.

Results: The αv subunit formed a functional heterodimer with J5 as measured by FACs and adhesion to vitronectin. Anokiasis was dramatically increased in the αv infected cells (both H357s and SCC4s) compared to the parental populations, empty vector controls and α4 infected cells at 48 and 72 hours (p<0.01). Anokiasis was not increased in αvβ6 expressing cells. The pathways involved in αvJ5 induced anokiasis include a suppression of activation of the survival factor Akt/PKB, possibly via the cytoplasmic domain of J5 and both the intrinsic (mitochondrial) and extrinsic (death receptor mediated) cell death pathways.

Conclusion: Re-introduction of the αv integrin subunit increased SCCs ability to undergo anokiasis via the αvJ5 heterodimer. Both the intrinsic and extrinsic apoptotic pathways are required, and a cell survival mechanism of activating Akt/PKB is suppressed.
Lung cancer outcomes

S1 CARBOPLATIN AND VINORELBINE AS FIRST LINE OUTPATIENT TREATMENT IN NSCLC

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Outpatient chemotherapy offers advantages for the Health Service in terms of resource utilisation and expense compared to the patient treatment, and is preferred by the vast majority of patients and their families. We have treated 130 patients (84 male, mean age 65.8 years, 46 female, mean age 62.2 years) with stage III or Stage IV NSCLC and performance status 0–2 with outpatient chemotherapy using Carboplatin and Vinorelbine using the following regimen: Carboplatin AUC 5 day 1, Vinorelbine 25 mg/m2 day 1, day 8

The intended duration of treatment was 3 or 4 courses of chemotherapy using a 21 day treatment cycle. The mean number of courses given was 3.2 (range 1–6).

With 102 patients so far having completed treatment, response rates are as follows: Complete Responses 2%, Partial Responses 34.8%, Stable Disease 32%, and Progressive Disease 17.1%. Over all median survival is 9.1 months.

Treatment was generally tolerated. Toxicity included neutropenic sepsis in 22% and anaemia requiring blood transfusion in 29%. There were 8 (7.8%) treatment related deaths. Patients with performance status 2 at commencement of treatment were at significantly greater risk of serious morbidity and treatment related death compared to patients with performance status 0–1. Patients aged >70 were more likely to require blood transfusions but were not at increased risk of neutropenic sepsis or treatment related death. We conclude that Carboplatin and Vinorelbine is a relatively safe and effective regimen for the outpatient treatment of patients with NSCLC.

S2 A COMPARISON OF ACE AND CE CHEMOTHERAPY IN SCLC


Background: Chemotherapy plays an important role in the treatment of Small Cell Lung Cancer (SCLC). Several standard regimens are in existence but there have been few direct comparisons with regard to toxicity. In this retrospective audit we compare the toxicity of ACE (Adriamycin, Cyclophosphamide and Etoposide) with CE (Carboplatin and Etoposide).

Methods: Over a 12 month period from April 2000 28 patients with SCLC received chemotherapy with either ACE or CE chemotherapy. Toxicity was evaluated by a retrospective audit of case notes looking in particular at neutropenia, neutropenic sepsis, clinically significant anaemia, in hospital duration of stay and toxic death.

Results: Eleven patients (39.2%) received ACE, 12 patients (42.8%) received CE and five patients (17.8%) received both. In total 63 ACE and 80 CE chemotherapy cycles were given.

Severe neutropenia (neutrophils <0.5%) complicated 21 (33.3%) ACE compared with 11 (13.7%) CE chemotherapy sessions (p=0.005). Neutropenic sepsis occurred in 14 (22.2%) ACE sessions compared with 2 (2.5%) CE sessions (p=0.0002). Thirty (46.8%) ACE sessions were complicated with clinically significant anaemia compared to 18 (22.5%) in the CE group (p=0.002). The average in-hospital stay per patient was 19.3 days for patients receiving ACE and 3.6 days for patients receiving CE. Toxic death happened in 1 patient in the ACE group and 1 patient in the CE group (p=0.9).

Conclusion: This retrospective audit indicates that in our experience ACE chemotherapy for SCLC is associated with greater toxicity than the CE regimen. This led to a greater use of resources in terms of antibiotic therapy, blood transfusion, and hospital bed usage and has led us to adopt the CE regimen as first choice chemotherapy for this group of patients.

S3 PROLONGED SURVIVAL IN INOPERABLE NSCLC WITH CONCURRENT CHEMO-RADIOThERAPY

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Synchronous chemotherapy and radiotherapy is a highly effective treatment modality for a number of solid tumours including inoperable Non-Small Cell Lung Cancer, and has been adopted as a standard therapy for lung cancer in the United States. However, experience with this form of treatment for lung cancer in the UK is limited.

We have treated 54 patients with locally advanced, inoperable NSCLC (8 Stage IIIB, 46 Stage IIIB) with concurrent chemoradiotherapy using a tumour dose of 52.5 Gy given in 20 daily fractions over four weeks, together with cisplatinum 20 mg/m2 concurrent with fractions 1–5 and 16–20. Thirty four patients received 2–4 courses of chemotherapy after concurrent chemoradiotherapy. Toxicity was acceptable, with three cases of severe but self-limiting oesophagitis, a 70% incidence of mild to moderate oesophagitis and no treatment related deaths.

One, two, and three year survival rates for patients with Stage IIIB disease are 74%, 35%, and 32% respectively. Patients with Stage IIIB disease treated with concurrent chemo-radiotherapy followed by systemic chemotherapy have a median survival of 25 months, 3 year survival of 49%, and a local control rate of 89.5%.

Concurrent chemo-radiotherapy is a highly effective treatment modality for patients with locally advanced inoperable NSCLC, but this form of treatment is only suitable for patients who have good performance status (PS 0–1), minimal co-morbidity and disease which can be encompassed within a radical radiotherapy treatment volume.

S4 OUTCOME OF PATIENTS OVER SEVENTY YEARS OLD WITH SMALL CELL LUNG CANCER TREATED WITH CHEMOTHERAPY

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Introduction: Small cell lung cancer (SCLC) accounts for 25% of all newly diagnosed cases of lung cancer over seventy years. No standard treatment is defined for elderly patients with SCLC, and prognosis remains poor.

Methods: We performed a retrospective review of all SCLC cases over 70 years treated with carboplatin and etoposide between 01/01/2000 and 31/12/2001. Prophylactic cranial irradiation (PCI), chest and palliative radiotherapy were used when indicated.

Results: 29 patients were treated, median age 73.7 years, four patients over 80 years. 52% had limited disease. 7% had performance status (PS)=0, 41% PS=1, 35% PS=2, 17% PS=3. The average number of cycles given was 3.27, 55% receiving a dose reduction. PCI and chest radiotherapy was used in 4 patients, 5 patients received palliative radiotherapy. The overall response rate was 65%. Actuarial median survival was 30 weeks (95% CI 22.1–37.9), 1 year survival = 23%, 18 month survival = 18%, 2 year survival =10%. Four patients are still alive (range 33 B 121.4 weeks) Febrile neutropenia occurred in 17% and neutropenic death in 10%. 21% of patients received blood transfusions. There were 5 (17%) early deaths (<21 days), 3 of which were neutropenic.

Conclusions: This review confirms that the treatment of unselected SCLC elderly patients with chemotherapy causes significant risks with lower response rates and survival than previously reported. Despite this palliation is achieved in a significant number with prolongation of survival. Co-morbidity and quality of life issues should be carefully considered when treating such patients.
WHAT PERCENTAGE OF PATIENTS WITH LUNG CANCER PRESENT WITH POTENTIALLY CURABLE DISEASE?
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Background: Since 1995 there has been concern that the 5 year survival of patients undergoing lung cancer surgery in the UK (6–7%) was significantly less than that quoted for America and other western countries (14–15%). This might represent differences in recording, differences in disease or differences in treatment. The aim of this audit was to define the number of patients with curable disease at presentation.

Method: We prospectively filled in audit sheets based on the diagnostic module of the RCP (London) lung cancer data sheets from 1/1/2001–1/5/2002. At the end of the audit period we checked the hospital databases in the catchment area for any additional patients recorded as having lung cancer and retrospectively collected data for these patients.

Results: 175 patients were identified. Patients had a mean age of 70.4 (SD 9.8) yrs, 93 (54%) were female and 49 (28%) were smokers. There were no significant differences in smoking status, age or sex between patients with surgically resectable and NSCLC.

Conclusion: Our data suggest that the 5 year survival rates around 20% seem unrealistic, although with current targets for surgical resection rates around 10% in the UK there may be some subjects who are suitable for surgery to whom it is not offered. Offering surgery or radical radiotherapy to these patients might result in some improvement in survival.

COPD: Cellular activation and inflammation

RELATIONSHIP BETWEEN BRONCHIAL BIOPSY INFLAMMATORY CELL POPULATIONS AND PHYSIOLOGICAL PARAMETERS IN COPD
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This study was designed to evaluate the relationships between patterns of bronchial biopsy inflammation and physiological parameters in COPD. Bronchoscopic biopsies were taken from 36 patients with COPD (mean [SD] age 69.5 (8.7) yrs, FEV1 1.36 (0.59) l, FVC 2.6 (0.88) l, FEV1/FVC predicted 45.6 (16.2)%, Pao2 8.8 (1.2) kPa, Paco2 5.4 (0.65) kPa, PaCO2 46.2 (3.18) Pack years of smoking, MRC dyspnoea score 3.06 (1.24), daily inhaled steroid dosage 747 (810) µg, 16 current smokers). Samples were wax embedded and stained for CD3, CD4, CD8, CD68, and EG2 positive inflammatory cells by immunohistochemistry. Intraepithelial CD3 positive cells (per 100 epithelial cells) were related to daily inhaled steroid dosage (rho=0.675, p=0.046) and inversely related to the PaO2 (rho= −0.714, p=0.047). Patients with symptoms of daily dyspnoea had significantly higher numbers of intraepithelial CD3 cells than those without (median [IQR] CD3 cells/100=17 (8.5) versus 9.3 (6.75), p=0.016). Numbers of intraepithelial EG2 positive cells/100 were related to daily inhaled steroid dosage (rho=0.753, p=0.016) and the MRC dyspnoea score (rho=0.815, p=0.007). Patients with symptoms of daily dyspnoea also had significantly higher numbers of intraepithelial CD68 cells than those without (median [IQR] CD68 cells/100 = 9 (7) versus 4 (3), p=0.027). Intraepithelial CD4 positive cells/100 were related to inhaled steroid dosage (rho=0.850, p=0.032). An inverse relationship was seen between numbers of intraepithelial EG2 positive cells/100 and the FEV1% predicted (rho= −0.753, p=0.031). Numbers of EG2 cells per high powered field also increased with increasing daily inhaled steroid dosage (rho=0.442, p=0.074). No effect on cell numbers was seen with current smoking.

Bronchial wall inflammation in COPD increases with increasing indices of disease severity, as measured by Pao2, FEV1% predicted, inhaled steroid dosage and the symptom of daily dyspnoea. Supported by the Joint Research Board, St. Bartholomew’s Hospital.

NEUTROPHILS FROM PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE DEMONSTRATE ENHANCED ENDOTHELIAL CELL INTERACTIONS
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Chronic obstructive pulmonary disease (COPD) is usually caused by smoking, yet only 10–15% of smokers develop clinically significant disease. Given that neutrophils (PMN) recruitment, and subsequent activation, is central to the development of COPD, it is possible that PMN from smokers who develop the disease are primed to migrate from the bloodstream into the lung. The aim of this study was to compare endothelial cell interactions, under flow conditions, and adhesion molecule expression of PMN from non-smokers (NS), smokers without COPD (HS) and patients with COPD (COPD).

PMN were isolated from 8 NS, 8 HS and 10 COPD patients. The three groups were age and sex matched, and the mean [SD] FEV1 % predicted were 101.8 (10.9), 97.4 (12.9), and 45.9 (20.9), respectively. Pack year smoking history was similar in the HS and COPD groups (52.1 [10.0] v 47.0 [19.3], p=ns). To assess endothelial adhesion and migration, PMN were perfused at a physiological flow rate over inter leukin-1β stimulated human umbilical vein endothelial cells cultured in microslides. Adherent and migrated PMN were counted by phase contrast microscopy. CD11b/CD18 (Mac-1) and CD62l (L-selectin) expression were assessed by flow cytometry. Mean (SE) PMN-endothelial cell interaction results are tabulated in the table.

There were no significant differences in PMN expression of Mac-1 and L-selectin between the three groups. The data suggest that PMN from smokers who develop COPD are primed to adhere to, and migrate across, vascular endothelium. This appears to be independent of Mac-1 or L-selectin expression. Further work is needed to clarify the mechanism, but the PMN priming seen here in COPD provides a potential target for new therapy.

DIFFERENCES IN AIRWAY NEUTROPHIL NUMBERS, ACTIVATION AND TLR-2 EXPRESSION IN SUBJECTS WITH COPD AND AGE-MATCHED CONTROLS
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Rationale: Subjects with COPD have higher numbers of airway neutrophils and these numbers correlate with airflow limitation (Lacoste, et al 1993). The activation status of these neutrophils, and the effect of smoking on this, is unknown. The toll-like receptor family is responsible for innate immune responses against a wide variety of bacterial molecules. Their presence on airway neutrophils has not previously been investigated.

Methods: 15 subjects with COPD and 18 healthy age-matched controls underwent flexible bronchoscopy for collection of bronchoalveolar lavage fluid (BALF). Both groups contained a mix of smokers and ex/non-smokers. A BALF differential cell count was performed. The neutrophils were labelled with fluorochrome-conjugated antibodies against surface markers of activation (CD63, CD14) and the toll-like receptor 2 (TLR-2), and analysed using flow cytometry. The percentage of cells expressing the antibodies was calculated. Statistical analysis was performed using an unpaired t test.

Results: All data are expressed as means [SD]. There was an increase in the percentage of neutrophils within the BALF of subjects with COPD when compared with controls (1.644 [1.717] v 0.343 [0.084]; p=0.0037) irrespective of smoking status. However, the percentage of CD63+ve neutrophils was significantly lower in current smokers when compared to ex/non-smokers (14.78 [17.06] v 45.64 [22.86]; p<0.001) regardless of airflow limitation. The same was true for CD14+ve neutrophils (11.18 [15.65] v 40.98 [25.78];
p=0.0002). Similarly, the percentage of T12 expression was reduced in current smokers (10.57 [11.20] vs 38.41 [23.80], p=0.0004).

**Conclusions:** Although airway neutrophils are increased in the lungs of COPD subjects, their activation is related to the smoking status of the subject. The fall in the level of neutrophil activation in smokers may represent an immune suppression or increased recruitment of neutrophils from the circulation.

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**S99 SPUTUM BACTERIAL COLONISATION IN STABLE COPD: ITS INFLUENCE ON AIRWAY INFLAMMATION, HEALTH STATUS, AND FIBRINOGEN**

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**Introduction and aims:** It is unclear if the presence of potential pathogenic micro-organisms (PPMs) in the sputum of patients with moderate to severe COPD influences health status and blood fibrinogen levels during the stable clinical state. This study aimed to determine if health status, fibrinogen and bronchial airway inflammation in those harbouring PPMs differ from those who do not (Non-PPMs).

**Methods:** Moderate to severe patients with no recent exacerbations in the last 6 weeks were recruited. Saline sputum induction was performed and markers of airway inflammation (total cell count, neutrophil count, IL-8, LTb4, TNF-α, neutrophil elastase [NE]), and neutrophil chemotaxis (NC)—Boyden chamber technique—sputum bacterial culture, health status (SGRQ and SF-36) and blood fibrinogen were measured.

**Results:** 67 patients were recruited, 69% male, mean age (SD) 66.7 (7.9) years and 27 (40%) were current smokers. 27 (40%) of patients grew PPMs, total number of bacterial isolates 38; H influenzae (14), M catarrhalis (10), S pneumoniae (9) and others (5). There was no significant difference in age, spirometry or exacerbation pack years between the PPMs and Non-PPMs groups. Those with PPMs had a worse health status score, mean (SD): Total SGRQ 58.7 (14.7) v 47.4 (15.7), p=0.004, SGRQ impact 46.1 (16.1) v 34.1 (13.7), p=0.004, SGRQSymptoms 70.3 (14.8) v 60.5 (21.4), p=0.03, SGRQ activity 76.8 (17) v 63.2 (20.4), p=0.004. SF-36 vitality and physical role limitation were also worse in this group. The PPMs group had an exaggerated airway inflammatory response, mean (SD): sputum supernatant log IL-8 [M (0.0)] v −0.29 (0.41), Log LTb4 [M (0.32) v 0.33, Log NE [M (0.40) v 0.008], Log TNF-α [pM] −0.15 (0.78) v −0.78 (0.56), p = 0.001, NE [µM] −1.27 (1.01) v −2.04 (0.52), p = 0.001 and NC [% IMLP] 70.4 (17.3) v 54.6 (19.0), p=0.001. There were increased numbers of sputum neutrophils (absolute count) but this was not statistically significant (p=0.93). Fibrinogen level (g/l) was greater in the PPMs group compared to the Non-PPMs group (70.4 (17.1) v 66.7 (7.9), p=0.001, Log LTB4 (nM) 0.32 (0.33) v 0.15 (0.78), Log LTB4 (nM) −0.78 (0.56), p=0.001, Log NE (µM) −1.27 (1.01) v −2.04 (0.52), p=0.001 and NC [% IMLP] 70.4 (17.3) v 54.6 (19.0), p = 0.001. There were increased numbers of sputum neutrophils (absolute count) but this was not statistically significant (p=0.93). Fibrinogen level (g/l) was greater in the PPMs group compared to the Non-PPMs group (70.4 (17.1) v 66.7 (7.9), p=0.001, Log LTB4 (nM) 0.32 (0.33) v 0.15 (0.78), Log LTB4 (nM) −0.78 (0.56), p=0.001, Log NE (µM) −1.27 (1.01) v −2.04 (0.52), p=0.001 and NC [% IMLP] 70.4 (17.3) v 54.6 (19.0), p=0.001.

**Conclusion:** Clinically stable moderate to severe COPD patients with sputum PPMs have a worse health status, exaggerated bronchial airway inflammation and a higher blood fibrinogen level.

**S10 RELATIONSHIP BETWEEN BRONCHIAL BIOPSY CELL POPULATIONS, EXACERBATION FREQUENCY, AND BACTERIAL COLONISATION IN COPD**

I.S. Patel1, N.J. Roberts1, R.J. Sapsford1, M. Sheaff2, J.A. Wedzicha1, 1Academic Unit of Respiratory Medicine, Department of Marboit Anatomy, Barts and the London NHS Trust, UK

The effect of exacerbation frequency on bronchial wall inflammation in COPD, and the effect of bacterial colonisation in this context are unknown. Bronchoscopic biopsies were taken from 36 patients with COPD (mean [SD] age 69.5 [8.75] yrs, FEV1 1.36 [0.59], FVC 2.6 [0.88]), FEV1 % predicted 54.5 (16.21), Pao2 88.8 [2.2] kPa, Paco2 5.4 [0.65], PaCO2 46.2 (31.8) pack years smoking, MRC dyspnoea score 3.06 [1.24], daily inhaled steroid dosage 7.47 [810] µg, 16 current smokers, median [IQR] 2 [3] exacerbations per year. Samples were wax embedded and stained for CD3, CD4, CD8, CD68, and EG2 positive cells by immunohistochemistry. Lower airway bacterial colonisation was quantitatively assessed by means of protected specimen brushes in 30 patients, of whom 14 were colonised by a potential pathogen. Patients were defined as frequent (>3 per year) or infrequent (<2 per year) exacerbators. Total numbers of CD3 positive cells per section were related to exacerbation frequency (rho=0.512, p=0.013) and the number of exacerbations in the previous year (rho=0.459, p=0.01). Total CD8 positive cells per high-powered field were related to exacerbation frequency (rho=0.454, p=0.03) and number (rho=0.443, p=0.034). CD4 positive cells per high-powered field also increased with exacerbation number (rho=0.573, p=0.016). CD68 positive cells per high-powered field were related to exacerbation frequency (rho=0.655, p=0.002) and number (rho=0.584, p=0.007), as were numbers of activated eosinophils (rho=0.623, p=0.003 and rho=0.555, p=0.009 respectively). Exacerbation frequency was related to colonisation with a potential pathogen (rho=0.383, p=0.041). The total bacterial count was related to numbers of CD3 cells per high-powered field (rho=0.443, p=0.05) and worsening MRC dyspnoea score (rho=0.597, p=0.007).

Patients with frequent COPD exacerbations show increased numbers of lymphocytes, macrophages and eosinophils in their bronchial biopsies when stable. These cells may contribute to the increased airway inflammation seen in patients with frequent COPD exacerbations, which may also be modulated by the presence of lower airway bacterial colonisation.

Supported by the Joint Research Board, St. Bartholomew’s Hospital.

**S11 A SURVEY OF PUBLISHED CURRICULUM CONTENT ON SMOKING AND SMOKING CESSATION IN UK MEDICAL SCHOOLS**

E.L. Jones, P.J. Rubin, J. Britton. University of Nottingham, UK

**Rationale:** Cigarette smoking is the single most important avoidable cause of respiratory disease in the UK, and smoking cessation interventions are amongst the most cost-effective interventions available in medicine. We have assessed the extent to which UK medical schools recognise and address smoking as a medical problem in their training programmes by a search of published data on curriculum content.

**Methods:** We searched printed and electronic information on course content published by UK medical schools for teaching on smoking, and smoking cessation, using the keywords “smoking”, “smoking cessation”, “tobacco”, “tobacco control”, and “nicotine” in electronic searches. Content was assessed according to previously defined criteria.

**Results:** Of 23 UK medical schools with current students, 9 (40%) make no references to smoking or smoking cessation in their published curriculum content. Most of the references made in the remaining 14 schools relate to the importance of taking a smoking history, and to the occurrence of tobacco-related diseases. Four medical schools (17%) include optional modules in smoking related issues, four include management of nicotine addiction as part of psychology or public health modules, one included a module on smoking within respiratory medicine, and one included a role-playing smoking cessation session within a Primary Care module. No references were found to teaching on the pharmacology of nicotine addiction.

**Conclusions:** This study suggests that teaching on the pharmacology and determinants of nicotine addiction, and practical training in the delivery of effective smoking cessation interventions, receive little attention in UK undergraduate medical curricula.

The Department of Health funded this research.


**S12 ATTITUDES OF GENERAL PRACTITIONERS AND PATIENTS TOWARDS SMOKING CESSATION ADVICE IN PRIMARY CARE**


Despite compelling evidence for the effectiveness of smoking cessation advice from a GP, rates of provision of such advice remain persistently sub-optimal (Frehet S. Smoking-related behaviour and attitudes, 1997: a report on research using the ONS Omnibus Survey produced on behalf of the Department of Health. London: The Stationery Office, 1998). Why are GPs not providing routine opportunistic smoking cessation intervention? Previous research on provision of smoking cessation advice has focused mainly on the professional’s perspective. It may be that smokers have quite clear ideas about what approach and/or content they believe would be effective (Butler CC, et al. BMJ 1998;316:1878–81). Is there an area of common ground between...
GP and patient attitudes where opportunistic interventions could be based, thus maximising the chance of such an intervention being received positively?

This qualitative study aimed to identify and explore barriers to the routine provision of smoking cessation advice by GPs, GP and patient attitudes towards such advice. Individual interviews and focus groups were carried out separately with GPs, smokers, and ex-smokers.

Our results indicate that both GPs and patients think that primary care smoking cessation interventions should be: (a) pertinent to the consultation rather than population-based advice, (b) personalised, linked to specific health benefits for that particular individual, and linked to the individual’s personal timetable of change, (c) positive, emphasising the positive benefits of quitting seems to be the preferred approach, and (d) practical, which includes GPs prescribing NRT and bupropion.

The importance and potential value of linking smoking to the presenting complaint needs to be further researched. Ways of linking information about the relationship of smoking to the patient’s own illness need to be explored. There needs to be rapid access at appropriate times for individuals who may be at a window of opportunity in the cycle of change. The recent development of problem-oriented guidelines for smoking cessation in primary care may encourage GPs to provide such advice and are likely to be more acceptable to patients.

If someone could wave a magic wand I’d never smoke again...—Barriers and Motivators to Accessing Smoking Cessation Services amongst Smokers in Deprived Areas of Nottingham

E.L. Jones, A.W.P. Molyneux, M. Anatoniak, J.R. Britton, S.A. Lewis. Division of Respiratory Medicine, City Hospital, University of Nottingham

Rationale: Smoking is the main factor responsible for inequalities in health between rich and poor. Although smoking cessation services have been developed in the UK, as part of the Tobacco White Paper, these services have traditionally failed to reach many of the most deprived smokers. Qualitative research methods are an appropriate way to explore the views of smokers who live in deprived areas who have made an attempt to stop smoking but who have not accessed the local smoking cessation services.

Methods: We conducted a postal survey of the most deprived households in Nottingham, and invited respondents who had made an unsuccessful attempt to stop smoking in the last year without using the Nottingham NHS Smoking Cessation Service, to attend focus groups to explore attitudes, experiences, and knowledge of smoking and stopping smoking, attitudes to smoking cessation services and interventions, and barriers and motivators to the access of such services. Group discussions were recorded and transcribed and a line-by-line analysis was undertaken to allow themes and categories to emerge from the data.

Results: Most participants started smoking in their teens and felt highly addicted to nicotine. All were aware of the risks of smoking and had tried to quit smoking, many on multiple occasions, but knowledge of smoking cessation interventions and their effectiveness was poor.

Barriers to the access of smoking cessation services—such as cost, timing, childcare, lack of appropriate information, perceived ineffectiveness, and negative publicity—were explored. Novel approaches to the management of nicotine addiction were discussed, including parallels with drug and alcohol addiction treatments, brain surgery, in-patient quit attempts, “staining” cigarettes and government subsidy for complementary therapies.

Conclusions: Deprived smokers are highly addicted, have a poor perception of the availability and efficacy of smoking cessation interventions and are unlikely to access services unless these barriers are broken down.

Funded by the New Leaf, Nottingham NHS Smoking Cessation Service.

Example of an Effective Smoking Cessation Service within a Primary and Secondary Care Trust

A. Burgoyne, A. Graham, M. Babores. East Cheshire NHS Trust, UK

Smoking is the nation’s single greatest cause of preventable illness and early death. More than 120,000 people a year in the UK die from smoking related diseases and it costs the NHS £1.7 billion each year. In April 2000, funding was allocated from South Cheshire Health Authority which supported the development of a locally based smoking cessation service in east Cheshire for the following two years—£9000 for year one and £18 500 for year two.

A multidisciplinary team was responsible for the co-ordination and development of the smoking cessation service in east Cheshire with representatives reporting to the Eastern Cheshire Primary Care Group (Trust) and the NSF CHD Local Implementation Team. These services were based in the Primary and Secondary health care settings delivering a standard rolling 6–8 weeks programme. This included one to one or group support, counselling from a trained smoking cessation adviser, provision of Nicotine Replacement Therapy and Bupropion where appropriate.

Targets set were 650 smokers setting quit dates over two years. Actual targets achieved doubled with 1190 smokers setting a quit date. Of these 612 (52%) were not smoking at 4 weeks with cessation, 244 (20%) relapsed and 334 were lost to follow up (28%). Twelve months follow up rates are to be reported in August 2002.

Monitoring data supports the continuation of a smoking cessation service in east Cheshire. Planning for long term funding needs to be identified. Maintaining smoking cessation as a priority for health interventions is vital. Continued development and co-ordination of smoking cessation services will be required to meet increasing public and professional demand.

12 Month Quit Rates of a “Specialised” Hospital Based Smoking Cessation Service

S. Brown, R.M. Angus, I. Davies. Aintree Chest Centre, University Hospital Aintree, Liverpool L9 7AL, UK

It is reported that intensive behavioural support plus Nicotine Replacement Therapy (NRT) or Bupropion enables about 20% of smokers to stop long term, compared to 5% from brief advice from a General Practitioner. Quit rates in those with established smoking related diseases are surprisingly lower than those in “healthy smokers”. We established a hospital-based smoking cessation service for smokers with respiratory disease. Patients are offered one-to-one counselling with frequent structured advice and regular support. NRT and/or Bupropion can be prescribed as required. All quit results were validated by expired air CO (carbon monoxide). From April 2001 to March 2002, 337 patients were referred into the service. Fifty nine (16%) did not attend their first appointment and 40 (12%) were not referred to quit at the time of referral. Two hundred and thirty eight (71%) set quit dates and the following are the results of these 238 patients. Mean (SD) age 57 (9) years, 135 (57%) female. Two hundred and nine (88%) had previously tried to quit. Diagnoses were as follows: COPD 107 (45%), asthma 58 (24%), bronchiectasis 14 (6%), lung cancer 13 (5%) and “other” 46 (19%). Patients used the following pharmacological support: NRT patches 107 (45%), Bupropion 41 (17%), NRT inhalator 37 (16%), NRT gum 10 (4%), and NRT lozenge 7 (3%). Thirty six (15%) used willpower alone. Of 238 patients 147 (62%) reached a 4 week quit, 81 (35%) female. Thirty nine (16%) patients were lost to follow up. Quit results at 6 months were 49/102 (48%), with 19 (19%) lost to follow up and at 12 months were 18/24 (75%) with 3 (13%) lost to follow up. Of the 18 patients that were continuously abstinent at 12 months, 11 (61%) were female and products used were Bupropion 7 (39%), NRT patches 7 (39%), and willpower alone 4 (22%). These results compare favourably to recent Department of Health figures for smoking cessation services in the UK, where it was quoted that quit rates of around 20% at the 12 month follow up should be expected. This demonstrates the value of targeting thoracic patients in specialist smoking cessation services in the UK.
Sleep: New outlooks

**ST6** THE UPPER AIRWAY IN PREGNANCY AND PRE-ECLAMPSIA

B. Izcı1, R.L. Riha1, S.E. Martin1, M. Vennelle2, W.A. Liston2, K. Dundas2, A. Calder1, N.J. Douglas1. 1Edinburgh Sleep Centre, University of Edinburgh, UK; 2Department of Reproductive and Developmental Sciences, University of Edinburgh, UK

**Background:** Snoring is common in pregnancy and snoring pregnant women have increased rates of pre-eclampsia. Patients with pre-eclampsia have an increased rate of upper airways (UA) narrowing during sleep which may contribute to their blood pressure elevation.

**Aims:** To compare upper airway dimensions in pregnant and non-pregnant women and patients with pre-eclampsia.

**Method:** 50 women in the 3rd trimester of pregnancy and 37 women with pre-eclampsia were recruited consecutively from the antenatal service and matched with 50 non-pregnant women. UA dimensions were measured using acoustic reflection. Comparisons were by analysis of variance and Student-Newman-Keuls tests.

**Results:** The pregnant, pre-eclamptic, and non-pregnant women did not differ in terms of age or height, or in pre-pregnant weight or body mass index. 14% of non-pregnant, 28% of pregnant, and 75% of pre-eclamptic women reported they snored (p<0.001). Oropharyngeal junction area (OPJ) in the supine position was narrower in pregnant than non-pregnant women (1.0 SD 0.1, 1.1 SD 0.1cm2; p=0.05) and smaller yet in pre-eclamptics (0.8 SD 0.1 cm2; p<0.05). Seated OPJ was narrower (p<0.05) in the pre-eclampsics (1 SD 0.1 cm2) than either controls (1.2 SD 0.1 cm2) or pregnant women (1.3 SD 0.1 cm2).

**Conclusion:** Upper airways are narrower during the third trimester of pregnancy, and women with pre-eclampsia have further airway narrowing. This could result from a combination of FRC reduction due to the pregnancy and generalised oedema. These changes could contribute to the increased snoring in pregnancy, and to the upper airways resistance episodes during sleep in pre-eclampsia which may further increase blood pressure.

Study supported by the Cunningham Trust.

**ST7** BRAIN MRI ACTIVATION AND EVOKE POTENTIALS DURING VISUAL STIMULATION AND VISUO-MOTOR TRACKING IN NORMAL SUBJECTS BEFORE AND AFTER SLEEP DEPRIVATION

G.V. Robinson1, J.C.T. Pepperell1, H. Segal1, R. Langford2, J.R. O. Davies1, J.R. Stradling1. 1Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK; 2Oxford Haemophilia and Thrombosis Unit, Churchill Hospital, Oxford, UK

**Aims:** To determine the differences in brain activation and visual evoked potentials (VEPs) before and during sleep deprivation (TSD).

**Methods:** Using a previously developed paradigm (Nature Neurosci 2001; 4:638), we have assessed the brain functional magnetic resonance imaging (fMRI) activation patterns in normal subjects during pure visual stimulation and during performance of coordinated hand/eye tracking manoeuvres, before and after 28–32 hours total sleep deprivation (TSD). Evoked potentials to a potent visual stimulus were also recorded from the occipital cortex.

**Results:** After pre-training, 10 normal subjects (7M, 3F, mean age 27) underwent fMRI imaging, while looking at an alternating chequerboard (pure visual stimulus) and while performing the visual tracking paradigm (visuo-motor stimulus). Subjects were assessed at baseline after normal sleep. Further assessments were performed, in random order, after normal sleep and 28–32 hours of actigraphy monitored TSD and stimulant abstinence. 4 subjects also had occipital visual evoked potentials (VEPs) recorded.

**Results:** Following normal sleep, the expected brain areas were activated on fMRI by both tasks. Tracking performance was significantly impaired by TSD (mean tracking error 114.3 SD 49.1 after normal sleep, 219.7 SD 47.6 after TSD, p<0.0001, paired t test). During the chequerboard (pure visual stimulus), TSD increased brain activation in the primary visual cortex, precuneus and left prefrontal areas, but decreased activation in the extra striate visual cortex. The VEP studies confirmed a neural basis for this reduced brain activation. During the tracking (visuo-motor) task, TSD lead to reduced cerebellar and premotor activation, with unchanged primary motor cortex activation.

**Conclusion:** TSD in normal subjects impairs tracking. This is associated with activation of neural centres that may be associated with vigilance maintenance (prefrontal cortex and precuneus) and depression of visual association areas and secondary motor centres.

**ST8** PLATELET ACTIVATION IS INCREASED IN OBSTRUCTIVE SLEEP APNOEA AND DOES NOT FALL WITH CPAP TREATMENT

G.V. Robinson1, J.C.T. Pepperell1, H. Segal1, R. Langford2, J.R. O. Davies1, J.R. Stradling1. 1Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK; 2Oxford Haemophilia and Thrombosis Unit, Churchill Hospital, Oxford, UK

**Aims:** Obstructive sleep apnoea (OSA) is an independent risk factor for hypertension and arterial thrombotic disease (Am J Resp Crit Care Med 2002;166:159). The increased cardiovascular risk is probably multifactorial, and related to insulin resistance and endothelial dysfunction, in addition to hypertension (the increased incidence of which in OSA is now well established). Platelets have a central role in the pathogenesis of acute cardiovascular syndromes, and platelet activation is associated with increased cardiovascular risk in normals (Throm Haemost 2001; 85:584). The influence of OSA on platelet function is not clear.

**Methods:** 94 male subjects mean (SD) age 48 (11) with OSA defined as ≥10 oxygen saturation dips ≥4% per hour (actual dip rate 42.5 (23.0)) and an Epworth sleepiness score (ESS) ≥10 (actual ESS 15.7 (3.0)) were randomised to one month’s treatment with therapeutic or sub-therapeutic (1–1 cmH2O pressure) continuous positive airways pressure (CPAP) treatment. Plasma levels of soluble P-selectin (sP-sel), a marker of chronic platelet activation, were measured by ELISA before and after treatment. 22 unmatched normal subjects were used to establish a normal range.

**Results:** sP-sel was higher in the untreated OSA patients than in the normal subjects (OSA patients 55.4 ng/ml (37.3), normal subjects 29.5 ng/ml (10.5), p<0.0001, unpaired t test). No significant fall in sP-sel was seen following one month’s treatment with either therapeutic or sub-therapeutic CPAP: therapeutic CPAP, pre treatment 58.3 ng/ml (35.5), p=0.4, paired t test; sub-therapeutic CPAP, pre treatment 52.5 ng/ml (32.1), post treatment 45.4 ng/ml (22.7), p=0.1, paired t test.

**Conclusion:** OSA may cause increased platelet activation, which does not fall with one month’s CPAP treatment. This is likely to be a further contributor to the increased vascular morbidity of OSA, which is not improved with one month standard OSA treatment.

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**Abstract S19 Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post CPAP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epworth Score</td>
<td>14 (0–20)</td>
<td>8 (0–20)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>MFI-20, General Fatigue</td>
<td>17 (8–20)</td>
<td>12 (4–20)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>MFI-20, Physical Fatigue</td>
<td>16 (6–20)</td>
<td>13 (4–20)</td>
<td>&lt;0.005</td>
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<tr>
<td>MFI-20, Reduced Activity</td>
<td>10 (4–17)</td>
<td>8 (4–20)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MFI-20, Mental Fatigue</td>
<td>13 (4–20)</td>
<td>7 (4–20)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SF-36, Physical Limitations</td>
<td>25 (0–100)</td>
<td>75 (0–100)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SF-36, Vitality</td>
<td>30 (0–85)</td>
<td>55 (0–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36, Mental Health</td>
<td>68 (4–100)</td>
<td>84 (28–100)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

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S19 THE MULTIDIMENSIONAL FATIGUE INVENTORY (MFI-20) IN OBSTRUCTIVE SLEEP APNEA (OSA): EFFECTS OF NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)
N. Wiltshire, F. Buchanan, A. Harper, J.R. Catterall, A.H. Kendrick. Sleep Unit, Department of Respiratory Medicine, Bristol Royal Infirmary, Bristol, UK

We have shown that the MFI-20 provides useful additional information to the Epworth Score (ESS) and SF-36 in patients with OSA, and separates sleepiness and fatigue (Kendrick et al. Thorax 2001;56(Suppl III):46).

Aim: To assess the response of the MFI-20 in a CPAP naïve patients and to compare this with the data from the ESS and the dimensions of the SF-36.

Methods: Patients were given the ESS, SF-36 and MFI-20 questionnaires before and at the end of a 4 week trial of CPAP as part of our clinical management of patients with OSA. Data are given as median (range).

Results: 50 patients [6F], age 54.5 yr [27–80] and Body Mass Index 31.8 kg.m⁻² [22.8 to 52.6] were studied. The results are summarised in Table 1.

At the end of the trial and using a cutoff of 10 for each MFI-20 dimension and for ESS, 16/50 had a MFI-20 GH >10, 17/50 had an MFI-20 PF >10 and 20/50 had an MFI-20 RA >10 indicating significant fatigue problems remain in the absence of daytime hypersomnolence. The relation between changes in ESS and MFI-20 are shown in Table 2.

Conclusion: The MFI-20 is a simple self-completion questionnaire that provides useful additional information to that obtained from the ESS and the SF-36 and separates out sleepiness and fatigue pre and post CPAP.

S20 MODAFINIL IMPROVES WAKEFULNESS AND OVERALL CLINICAL CONDITION AS ADJUNCTIVE THERAPY FOR RESIDUAL EXCESSIVE SLEEPINESS IN OBSTRUCTIVE SLEEP APNEA: A 12 WEEK RANDOMISED TRIAL
A. Williams and the Modafinil OSA study group. Sleep Disorders Centre, St. Thomas’s Hospital NHS Trust, UK

Objective/Methods: A 12 week, randomised, double-blind, placebo-controlled study was conducted to assess the efficacy and safety of modafinil as adjunctive therapy for residual excessive sleepiness in patients with obstructive sleep apnea (OSA) treated with nasal continuous positive airway pressure (nCPAP). Patients were randomised to receive placebo, modafinil 200 mg once daily, or modafinil 400 mg once daily. Modafinil was initiated at 100 mg/d and titrated to 200 or 400 mg/d within 1 week. Key outcomes included changes from baseline in objective (Maintenance of Wakefulness Test [MWT]) and subjective (Epworth Sleepiness Scale [ESS]) measures of wakefulness and patients’ overall clinical condition [Clinical Global Impression of Change [CGi-C]] at Week 12. Secondary efficacy measures included changes from baseline in MWT, ESS, and CGi-C at Weeks 4 and 8. nCPAP use and adverse events were monitored.

Results: A total of 3 23 randomised patients received treatment (placebo: n=108; modafinil 200 mg/d: n=109; modafinil 400 mg/d: n=106). Modafinil significantly improved patients’ ability to sustain wakefulness on the MWT at Week 12 (increases of 1.6 min for modafinil 200 mg/d and 1.5 min for modafinil 400 mg/d) compared with placebo (decrease of 1.1 min; p<0.0001). Modafinil treatment also significantly improved wakefulness as measured by the ESS scores: a 4.5-point decrease in ESS score was observed with modafinil compared with a 1.9-point decrease with placebo at Week 12 (p<0.0001). Modafinil significantly improved patients’ overall clinical condition at Week 12, as measured by the CGI-C (p<0.0001). Modafinil had no effect on nCPAP use or nighttime sleep. Modafinil was associated with significant improvements in wakefulness and clinical condition at Weeks 4, 8, and 12. Headache (12%)

Abstract S21 Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔMFI-20, GF</th>
<th>ΔMFI-20, PP</th>
<th>ΔMFI-20, RA</th>
</tr>
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<tbody>
<tr>
<td>GH</td>
<td>1.59 ± 0.55</td>
<td>0.80 ± 0.31</td>
<td>0.40 ± 0.27</td>
</tr>
<tr>
<td>PF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>1.30 ± 0.16</td>
<td>1.13 ± 0.13</td>
<td>0.16 ± 0.10</td>
</tr>
</tbody>
</table>

S21 PULSE PRESSURE PREDICTS MORTALITY IN PULMONARY ARTERIAL HYPERTENSION
J.D. Chalmers¹, R. Syvad², V. Impey¹, A. Peacock². "University of Glasgow; ²Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow, UK"

Introduction: It is known that mean pulmonary artery pressure predicts survival in pulmonary hypertension. Following the Framingham heart study, it was shown that pulse pressure (PP) outperformed mean arterial, systolic and diastolic pressures as predictors of mortality in systemic hypertension. We wished to discover if this held true for the pulmonary circulation.

Methods: We retrospectively reviewed all the patients with Pulmonary hypertension who had been studied between 1996 and January 2002. 80 patients had Pulmonary Hypertension (PH); 4. Of the 21 patients 19 [11 female, 8 male] had PPH, 4 [10 female, 8 male] had thromboembolic disease, 17 [13 female, 4 male] had connective tissue disease, 10 [8 female, 2 male] had COPD, 10 [8 female, 2 male] had Eisenmengers, 3 [2 female, 1 male] had porto-pulmonary hypertension, 2 [2 female] had valvular heart disease and 1 [1 female] had Sarcoidosis. Haemodynamic variables as well as performance status and medical history were examined. Kaplan Meier Survival curves and regression analysis were used to determine correlation between variables and survival.

Results: PP against survival produced a correlation coefficient (r) of −0.76 (p<0.01) and Kaplan Meier survival curves revealed a 100% probability of survival for PP <30 mmHg compared to 85% probability of survival for PP 30–40 and 47% for PP greater than 40.

No other variable predicted survival with this accuracy.

Conclusion: Pulse pressure is a powerful predictor of mortality in all causes of pulmonary hypertension. No other variables proved superior to pulse pressure, regardless of underlying diagnosis.

Abstract S22

S22 LONG DURATION OF BREATHLESSNESS AT DIAGNOSIS IS ASSOCIATED WITH LONGER SURVIVAL IN PPH: A CLINICAL PARADOX
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Introduction: Previous studies have shown that breathlessness predicts survival. It is widely believed that a longer duration of breathlessness is related to a worse prognosis, probably due to slower time to diagnosis. We expected to confirm this supposition in our data
S24 THE UTILITY OF D-DIMERS AND OTHER PREDICTORS OF PULMONARY EMBOLI IN A LARGE SERIES FROM A DISTRICT GENERAL HOSPITAL


Previous studies suggest that a negative D-dimer can have a negative predictive value (NPV) for objectively diagnosed pulmonary emboli (PE) of 99% (Egermeyer et al. Thorax 1998;53:830–4). A pilot study in our hospital comparing bedside and laboratory SimpliRED and a ELISA D-dimer assays for DVT gave NPVs of between 69% and 76%.

We have used 4 parameters to assess the pretest probability of PE: (a) D-dimers (SimpliRED, performed on the ward), (b) Respiratory rate (RR) > 20/min (c) PaO2 on air < 10.7KPa, (d) Important risk factors from the history i.e. surgery/trauma, malignancy, cardiovascular disease, previous PE/DVT, post-partum, immobilisation, and hereditary thrombolic disorders.

These were prospectively evaluated in 521 patients who were investigated for suspected PE. Assessment was incomplete in 101 cases, leaving 420 cases for analysis. Those with a normal CXR and no chronic lung disease initially had a perfusion (Q) scan (n=297). Leg dopplers (n=95) were performed on those with an abnormal CXR, chronic lung disease or an indeterminate Q scan. CT pulmonary angiograms were requested on those with negative or indeterminate leg dopplers (n=51). 27 patients had features of a massive PE and were investigated with urgent CT angiogram or an echocardiogram.

PE was confirmed in 131 patients, excluded in 289. The NPV of a D-dimer was 83%, a RR <20 90%, a PaO2>10.7KPa 83%, and absent clinical risk factor(s) 81%. Logistic regression gave RR high odds ratios and suggested that PaO2 added little to the other 3 parameters. A combination of no risk factor and a RR<20 gave a risk of objectively confirmed PE of <5%, irrespective of the D-dimer result and the PaO2.

We conclude that negative D-dimer results are best used in conjunction with other predictors to exclude PE.

S25 OUTCOME AFTER PULMONARY THROMBOENDARTERECTOMY FOR CHRONIC THROMBEMBOILIC PULMONARY HYPERTENSION


Pulmonary thromboendarterectomy (PTE) is the treatment of choice in chronic thromboembolic pulmonary hypertension (CTEPH) with proximal vascular obstructions. However PTE is associated with a significant perioperative risk. Over the last 5 years, 100 patients (50 male, 50 female, mean age 53 (18–81) years) underwent PTE at Papworth Hospital. 71 patients survived the procedure, whereas 29 died postoperatively: 10 due to reperfusion oedema, ARDS, or bronchopulmonary artery infections, while significant improved haemodynamics 12 had incomplete clearance of vascular obstruction with additional peripheral vascular obstructions, 3 were misdiagnosed preoperatively (PPH, peripheral CTEPH, advanced pulmonary artery sarcoma).

Four patients developed surgical complications. The quartile distribution of the outcome is shown below. Evaluating perioperative factors that influenced perioperative outcome, the surviving patients had a significantly higher 6 minute walking distance (268 v 194 metres, p<0.01), and higher cardiac index (1.8 v 1.5 l/min/m², p<0.01) compared to the non-survivors, whereas right atrial and pulmonary artery pressures
were similar in both groups. At our institution, experience within the recently established PTE programme shows a learning curve associated with a significant improvement in the postoperative outcome in this high risk patient population.

Asthma therapeutics

**S26 THE USE OF NEBULISED ISOTONIC MAGNESIUM SULPHATE AS AN ADJUVANT TO SALBUTAMOL IN THE TREATMENT OF SEVERE ASTHMA IN ADULTS**

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**Background:** Intravenous magnesium has been shown to cause significant bronchodilatation in the treatment of severe asthma, however its effect by the nebulised route is uncertain. In this study we assessed the efficacy of isotonic magnesium sulphate as an adjuvant to nebulised salbutamol in severe asthma.

**Methods:** We enrolled 52 subjects with severe exacerbations of asthma (FEV1 <50% predicted) presenting to the Emergency Departments at two hospitals in New Zealand. In this randomised double-blind placebo-controlled trial subjects received nebulised salbutamol (2.5 mg) mixed with either 2.5 mL of isotonic magnesium sulphate or isotonic saline on three occasions at 30 minute intervals. The primary outcome measures were FEV1 at 90 minutes and requirement for admission.

**Results:** The mean FEV1 in both groups at randomisation was similar (1.24 litres, 31.9% predicted v 1.20 litres, 31.8% predicted, p=0.73). Subjects who received nebulised salbutamol with the magnesium adjuvant achieved a greater improvement in FEV1, [0.72 v 0.35 litres, difference 0.37 litres, p=0.004] when compared with nebulised salbutamol with the saline adjuvant. A corresponding reduction in requirement for admission (relative risk 0.61, confidence interval 0.37 to 0.99) was demonstrated. The greatest difference between the two regimens occurred in those individuals presenting with life-threatening exacerbations, defined by an FEV1 of less than 30% predicted (increase in FEV1, 0.83 v 0.18 litres, difference 0.65 litres, p=0.0001).

**Conclusions:** The use of isotonic magnesium as an adjuvant to nebulised salbutamol results in an enhanced bronchodilator response in the treatment of severe asthma.

**S27 GLUCOCORTICOID RECEPTOR ACTIVATION IN INDUCED SPUTUM FOLLOWING INHALED LONG-ACTING β2-AGONIST AND GLUCOCORTICOID TREATMENT**

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The clinical evidence is well established for the complementary effects of inhaled long-acting β2-agonists (LABA) and glucocorticoids (GC) on asthma control. Recent in vitro data suggest the molecular mechanisms may involve enhanced glucocorticoid receptor (GR) nuclear translocation, as LABA have been shown to induce ligand-independent GR translocation. GC activate GR which translocate to the nucleus and bind to DNA to regulate the expression of GC-sensitive target genes, or to coactivators to switch off inflammatory genes. The aim of our research was to develop a model using cells relevant to airway disease, to test the hypothesis that inhaled LABA were able to modulate the intracellular partitioning of GR in vivo.

We previously described a semi-quantitative method to identify GR subcellular expression in induced sputum cells using immunocytochemistry, and showed ligand-induced GR activation in this model. Six healthy subjects inhaled beclomethasone dipropionate (800 µg) once, and sputum was induced at 0, 30, 60, 120mins post-inhalation. We observed significant GR translocation [71%] at 60mins post GC inhalation compared to baseline [30%] (p<0.05). Using this information on the optimal time point for GR activation, we describe here the effects of LABA and GC in asthmatics.

Seven steroid-naïve asthmatics inhaled single doses of fluticasone propionate (FP)-100µg, FP-500µg, salmeterol (SALM)-50µg & combination FP/SALM 100/50µg on separate visits. Dose dependent GR activation was observed following FP, FP-100 (42%), FP-500 (61%) where the higher dose was significant v placebo (31%) (p<0.05).

SALM alone achieved 43% GR translocation, but as combination therapy, SALM was able to augment the action of FP on GR translocation (54%) (p<0.05).

We have shown it is possible to use induced sputum to investigate the molecular effects of inhaled drug therapy. Our data support the proposition that GR nuclear translocation may underlie the complementary effects of LABA and GC. The precise signal transduction mechanisms remain unknown, but LABA may prime inactive GR through phosphorylation, and subsequently GR may require less GC for nuclear translocation. We now aim to research this hypothesis, as it may identify biochemical targets for future therapeutic modulation.

**S28 DOSE-RESPONSE RELATION OF INHALED BUDERSONIDE IN ADOLESCENTS AND ADULTS WITH ASTHMA**


**Objective:** To examine the dose-response relation of inhaled budesonide in adolescents and adults with asthma.

**Design:** Meta-analysis of placebo controlled, randomised clinical trials that presented data on at least one outcome measure of asthma and that used at least two doses of budesonide, delivered by turbuhaler twice daily.

**Setting:** Medline, Embase, and Astro-Zeneca’s internal clinical study registers.

**Main outcome measures:** FEV1, morning and evening peak expiratory flow, β2-agonist use, withdrawals and exacerbations of asthma leading to withdrawal.

**Results:** Three studies of 1013 adolescents and adults with moderately severe asthma, met the inclusion criteria for the meta-analysis. Only one study examined doses >800 µg/day and no studies examined doses >1600 µg/day. A negative exponential model for the data, without meta-analysis, indicated that 80% of the benefit at 1600 µg/day was achieved at doses of 250–350 µg/day and 90% by 350–500 µg/day. A quadratic meta-regression showed that the maximum effect was obtained with doses of around 1000 µg/day. Comparison of the standardised difference in FEV1, for an inhaled dose of 400 µg/day against higher doses showed a difference in FEV1 of 0.03 of a standard deviation (-0.153 to 0.213). It was not possible to undertake a meaningful statistical analysis of withdrawals, however examination of individual study data indicated that most of the benefit with respect to reduction in asthma exacerbations leading to withdrawal was achieved with a dose of 400 µg/day.

**Conclusions:** Determination of the dose-response relation of budesonide was limited by the lack of individual patient data, the paucity of studies reporting the effect of doses >800 µg/day and insufficient withdrawal data. However, utilising the available published data, most of the therapeutic benefit of budesonide delivered by the turbuhaler device was achieved with a total daily dose of 250–500 µg/day, and the maximum effect at around 1000 µg/day, in adolescents and adults with asthma. These findings are consistent with the recently determined dose-response relation of fluticasone propionate, assuming a potency ratio of 1.2. We recommend that national and international consensus guidelines and formularies are modified to ensure that they are consistent with the published data from which the therapeutic dose-response range of inhaled corticosteroids has been derived.

**S29 DOSE-RESPONSE RELATION OF INHALED FLUTICASONE PROPIONATE IN CHILDREN WITH ASTHMA—A SYSTEMATIC REVIEW OF ITS EFFICACY AND ADRENAL EFFECTS**


**Objective:** To examine the dose-response relation of inhaled fluticasone propionate for both efficacy and adrenal function in children with asthma.

**Design:** Analysis of placebo-controlled randomised clinical trials of fluticasone in children of at least 4 weeks duration, that used at least one dose of fluticasone, and that presented data on at least one clinical outcome measure of asthma or at least one sensitive measure of adrenal function.

**Setting:** EMBASE and Medline.

**Main outcome measures:** FEV1, morning and evening peak expiratory flow, night awakenings, β-agonist use, major exacerbations leading to withdrawal, 12 or 24 hour urinary cortisol, peak plasma cortisol post-stimulation.
Results: Five studies of 1150 children with asthma met the inclusion criteria for efficacy, with no studies examining doses >200 µg per day. The dose-response curve for each outcome measure suggested that the response began to plateau between a dose of 100 and 200 µg per day. The odds ratio for patients remaining in a study at a dose of 100 µg, compared with 200 µg was 0.8 (95% CI 0.46 to 1.37).

Three studies of 523 children with asthma met the inclusion criteria for assessment of adrenal function with no studies examining doses >200 µg per day. A meta-analysis could not be undertaken as the data was not presented in an appropriate format. The largest study of 437 children reported no difference in 24 hour urinary cortisol between placebo and fluticasone at doses of 100 and 200 µg per day. However, the two smaller studies demonstrated evidence of a reduction in urinary cortisol at these doses.

Conclusions: There is insufficient data to determine the dose-response relation of fluticasone in children at doses >200 µg per day. The dose-response curve for fluticasone appears to plateau between 100 and 200 µg per day for efficacy; there was weak evidence of adrenal suppression at these doses. Pending formal studies, we recommend the dose-response relation of fluticasone in greater detail, we recommend that fluticasone should be routinely prescribed in children with asthma in doses of up to 200 µg per day.

Background: In an attempt to optimise the therapeutic action of inhaled corticosteroids whilst minimising their side effects, asthma management guidelines recommend that a reduction in the dose of inhaled corticosteroids is undertaken when asthma is stable.1 We aimed to determine whether a 50% reduction in the dose of inhaled corticosteroid could be undertaken in patients with chronic stable asthma without compromising asthma control.

Methods: We recruited 259 adult asthmatics receiving regular treatment with high-dose inhaled corticosteroids (mean daily dose = 1430 mcg beclomethasone dipropionate) to a one-year, randomised, double-blind, parallel group trial. Patients were allocated to receive either their inhaled corticosteroid dose (control) or a 50% reduction in their dose if they met criteria for stable asthma (step-down). We compared asthma exacerbation rates, asthma-related general practice and hospital visits, quality of life measures and corticosteroid dose between the two groups.

Findings: We found no significant difference in the asthma exacerbation rate between the two groups (step-down=31%, control=26%, p=0.354). Similarly, there were no significant differences in the numbers of general practice or hospital visits, or in disease specific and generic measures of health status over the one-year period. On average, the step-down group received 348 mcg (95% CI 202 to 494) of beclomethasone dipropionate less per day than the controls with no difference in the annual dose of oral corticosteroids between the two treatment regimes.

Interpretation: Our study provides convincing evidence that it is possible to step down high dose inhaled corticosteroids in patients with chronic stable asthma, without compromising asthma control.


A PLACEBO CONTROLLED COMPARISON OF FORMOTEROL, MONTELUKAST OR HIGHER DOSE OF INHALED CORTICOSTEROIDS IN SUBJECTS WITH SYMPTOMATIC ASTHMA DESPITE TREATMENT WITH LOW DOSE INHALED CORTICOSTEROIDS

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An important number of patients with asthma remain symptomatic despite treatment with low dose inhaled corticosteroids. There is relatively little data from placebo controlled studies directly comparing the different treatment options for this group of patients. We have performed a randomised, double blind, four way cross-over study comparing the effects of one months treatment with higher dose budesonide (400mcg bd), additional formoterol (12 mcg bd) and additional montelukast (10 mg od) with placebo in patients with asthma who remain symptomatic despite low dose inhaled corticosteroids (budesonide 100mcg bd). Patients were seen before and 12 hours after each treatment phase which was separated by a one month washout period during which they took budesonide 100mcg bd and prn salbutamol only. At each visit exhaled nitric oxide (NO), spirometry, methacholine PC20, visual analogue symptom scores (VAS), the Juniper Asthma Quality of Life questionnaire and induced sputum were performed. Patients recorded twice daily peak expiratory flow (PEF) throughout and the mean morning PEF was calculated for the final week of each treatment and washout period. 49 patients with symptoms consistent with asthma and objective evidence of variable airflow obstruction despite low dose inhaled corticosteroids were recruited. High dose budesonide was the most efficacious treatment resulting in significant improvements in global VAS (−21.3 mm; 95% CI −40.4 to −2.3) morning PEF (16.5 l/min; 95% CI 2.3 to 30.7), FEV1 (0.14 l; 95% CI 0.0 to 0.28) and exhaled NO (fold reduction 1.9; 95% CI 1.1 to 3.1) compared to placebo. Formoterol was the next most efficacious treatment with similar improvements in morning PEF (17.5 l/min; 95% CI 4.0 to 31.0). However the change in spurt eosinophil count with formoterol (2.4% to 3.8%; fold reduction 0.6, 95% CI 0.5 to 0.9) differed significantly from the change seen with placebo (2.8% to 2.5%; fold reduction 1.1, 95% CI 0.7 to 1.6; p=0.03) and high dose inhaled corticosteroids (2.7% to 1.6%; fold reduction 1.6, 95% CI 1.2 to 2.2; p<0.001). We conclude that treatment given in addition to low dose inhaled corticosteroids results in modest benefits. Despite similar effects on morning peak flow, long acting β-agonists and high dose inhaled corticosteroids differ in their effects on eosinophilic airway inflammation.

Paediatric airways disease

STEPPING DOWN INHALED CORTICOSTEROIDS IN ASTHMA: A RANDOMISED CONTROLLED TRIAL

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Background: In an attempt to optimise the therapeutic action of inhaled corticosteroids whilst minimising their side effects, asthma management guidelines recommend that a reduction in the dose of inhaled corticosteroids is undertaken when asthma is stable.1 We aimed to determine whether a 50% reduction in the dose of inhaled corticosteroid could be undertaken in patients with chronic stable asthma without compromising asthma control.

Methods: We recruited 259 adult asthmatics receiving regular treatment with high-dose inhaled corticosteroids (mean daily dose = 1430 mcg beclomethasone dipropionate) to a one-year, randomised, double-blind, parallel group trial. Patients were allocated to receive either their inhaled corticosteroid dose (control) or a 50% reduction in their dose if they met criteria for stable asthma (step-down). We compared asthma exacerbation rates, asthma-related general practice and hospital visits, quality of life measures and corticosteroid dose between the two groups.

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Interpretation: Our study provides convincing evidence that it is possible to step down high dose inhaled corticosteroids in patients with chronic stable asthma, without compromising asthma control.

THE COMPLEX RELATIONSHIP BETWEEN ASTHMA AND AIRWAY RESPONSIVENESS THROUGHOUT CHILDHOOD

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Introduction: The relationship between childhood asthma and increased airway responsiveness (AR) remains uncertain.

Aims: To investigate whether AR tracks from infancy through to childhood; to determine which factors influence AR and assess interactions with asthma.

Methods: From a cohort of 253 individuals, longitudinal assessments of AR and atopy were made at one, six and 12 months and at six and 11 years of age. AR was expressed as a dose response slope (DRS) or graded on a scale of 0 to 2.

Results: DRS was measured in 203 individuals aged one month, 113 at 6 months, 103 at six years and 90 at 11 years of age. There were 22 asthmatics at six and 27 at 11 years of age. There was a positive relationship between the DRS in infants aged one month and in children who were not atopic aged 11 years (r=0.24, n=63, p=0.05). Atopy at six years of age was positively associated with grade of AR (χ²=6.8, n=150, p=0.03 and χ²=18.7, n=175, p<0.001, respectively). The DRS at six, but not 11, years of age was positively related to the urinary cotinine concentration at 12 months of age (r=0.45, n=52, p<0.001) and also the number of cigarettes currently smoked by parents (r=0.01, n=83, p=0.04). The DRS at 11, but not six, years of age was increased in the presence of lower respiratory tract infection (LRTI) in the first six months (n=79, p<0.001) but not the second six months of life. Adjusting for the presence of asthma, the DRS at six years of age was related to the urinary cotinine concentration aged 12 months (r=0.22, n=50, p=0.03) and the DRS at 11 years of age was related to atopy aged six months (p=0.001) and LRTI before six months of age (p=0.001).

Conclusions: The data suggested that the level of AR in childhood was determined in early infancy and then influenced in later infancy by factors that included atopy, tobacco smoke exposure and lower respiratory tract infections. Factors present in infancy are associated with increased childhood AR and these appear to act independently of asthma.

TUMOUR NECROSIS FACTOR GENE POLYMORPHISMS AND CHILDHOOD WHEEZING

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Background: TNFα secretion is influenced by single nucleotide gene polymorphisms within the TNF gene cluster. Higher constitutive and inducible production of TNFα is associated with allele 2 of TNF-308 and allele 1 of an NcoI polymorphism of the LTα gene. Since TNFα is associated with infant wheezing and asthma, a genetic predisposition to produce TNFα may be important. We compared the TNFα and LTα polymorphisms in controls with a group of infant wheezers, and childhood asthmatics of differing severity. We also measured nasal TNFα levels in the infants with acute wheezing to determine whether an association between phenotype (in vivo production) and genotype existed.

Methods: Asthmatic patients were identified in clinic with respiratory paediatrician-diagnosed asthma, which was defined as severe if they were on inhaled steroids >800 mcg/day (budesonide equivalent). Infant wheezers were inpatients with acute wheezing. Controls were school children with no asthma. Nasal lavage was performed in the infants using the inulin method to account for dilution, and nasal TNFα was measured by commercial ELISA. Genomic DNA was extracted from buccal smears using the Nucleon extraction kit. After amplification by PCR, the DNA was sized by electrophoresis.

Results: There were 88 asthmatics (mean age 6.1 yrs, 52 boys), 27 severe asthmatics (mean age 12.8 years, 17 boys), 55 wheezy infants (mean age 6.5 months, 35 boys) and 156 controls (mean age 10.2 years, 77 boys). All data were compared to the controls. In the presence of TNF1 homozygosity, the risk (95% CI) of being a wheezy infant was 3.2 (2–5) greater if they were also LTα AA than if one or two LTα G genes were present. For asthma the risk was 2.0 (1.2–3.2) and for severe asthma risk was 2.4 (1.3–4.5). In the presence of 1 or 2 TNF2 genes, the co-presence of AA gave a 12.6 (1.6–98) risk of being a wheezy infant than if there was a LTα G gene present. The risk for all asthma was 18 (2.4–128) and for severe asthma 13 (1.5–114). Although the positive predictive values were high, the sensitivity of the testing was relatively low. The haplotype TNF2/LTα AA gives a positive predictive value for any wheezing of 96%, with sensitivity of 17%.

Conclusions: The TNF2 allele is associated with wheezing whereas the LTα G gene had a protective effect. Clearly the TNF genotype influences the development of childhood wheezing. The results of nasal TNFα needs further elucidation.

DEVELOPMENTAL CHANGES IN VENTILATION DISTRIBUTION IN HEALTH AND CF LUNG DISEASE

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Longitudinal monitoring of airway function through childhood is often complicated by the need to correct results for age and body size.

Aims: In this study we investigated the relationship between age and lung clearance index (LCI), an index of ventilation inhomogeneity derived from multiple breath inert gas washout (MBW) (Larsson et al. J Appl Physiol 1988;65:2030-9), in cystic fibrosis (CF) and healthy control children aged from 0 to 18 years.

Methods: 137 children (64 with CF) were tested. Infants were measured whilst asleep, older children whilst awake. All performed 3 SF6 MBWs, and mean LCI was calculated for each child.

Results: LCI remained constant throughout childhood in healthy controls, but became progressively elevated with increasing age among those with CF. See table and figure.

Conclusions: The LCI can be used to assess airway function from infancy to adulthood and has potential for monitoring CF lung disease.
CHEMOKINE PRODUCTION IN SEVERE RSV BRONCHIOLITIS


Introduction: Respiratory syncytial virus (RSV) bronchiolitis is one of the most important causes of death and morbidity in infants worldwide. Factors that predispose to severe disease include prematurity. Neutrophils are the predominant cell-type within the airways along the chemottractant gradient. Our aim was to compare the pulmonary chemoattractant protein response in term and preterm infants ventilated with RSV bronchiolitis with that from a control group.

Subject/Methods: We collected non-bronchoscopic bronchoalveolar lavage (BAL) samples from 48 infants (25 born at term (>37 weeks) and 23 born preterm (<37 weeks)) ventilated for RSV bronchiolitis. We also collected BAL samples from 13 “control” patients ventilated for non-Respiratory syncytial virus causes. All samples were collected within 24 hours of being intubated. BAL protein concentrations were measured using ELISAs (R&D) according to the manufacturers instructions.

Results: Mean ages on admission were: term infants, 6.7 wks; preterm, 16.0 wks; control, 5.5 wks. Mean weights on admission were: term, 4.3kg; preterm, 3.5kg; control, 4.2kg. Mean gestational ages at birth were: term, 38.6 wks; preterm, 30.1 wks; control, 38.8 wks. Preterm infants were ventilated for twice as long as term infants (4.4 v 9.0 days, p=0.02). MIP-1α, RANTES and Eotaxin concentrations all differed significantly between the three groups.

Conclusions: We have identified differences in the immunological response in the lungs of infants ventilated for RSV bronchiolitis compared to a control group. Our data also highlight the first time differences in this response between term and preterm infants with RSV bronchiolitis which may relate to disease severity. Study funded by Action Research

SALMETEROL/FLUTICASONE COMBINATION (SFC) IS ASSOCIATED WITH IMPROVED COMPLIANCE IN CHILDREN COMPARED WITH INHALED CORTICOSTEROID (ICS) ALONE, OR CONCURRENT SALMETEROL + ICS

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Introduction: Paediatric compliance with regular asthma medication is a concern, with levels of 55-58% being reported (Cutts J. Arch Dis Child 1991; Milgrom H. J Allergy Clin Immunol 1996). It has been suggested that a combination of a long-acting β agonist (LAB) and an inhaled steroid in one inhaler – SFC (Seretide™) may appeal to children in terms of convenience, and the LAB, providing a rapid improvement in lung function which will wear off after 24 hours, may serve as a reminder that the medication should be taken.

Method: To evaluate compliance in children <16 using prescribing data from a primary care provider, DIN-UNK Data (CompuFile Ltd) were used to analyse prescription collection/year (P) from 100 GP practices, for SFC, fluticasone (F), salmeterol (S) and beclometasone (BDI) (dry powder inhalers).

Results: 1031 asthma patients identified who had been prescribed SFC, F or BDPI over the 12 months January–December 2001. 99% of patients prescribed S for asthma were prescribed an ICS. Accordingly S may be taken to represent concurrent LAB (S +ICS) (p value SFC v S unchanged).

Discussion: Although prescribing data are only a surrogate for compliance, as patients may not collect or use all their prescriptions, this study found compliance with F and S in keeping with other studies. In contrast SFC achieved compliance that was significantly greater versus F, S, and BDPI. As 99% of patients on S are concurrently on ICS, SFC achieved significantly greater compliance compared with concurrent LAB and ICS therapy. In this study SFC was associated with greater compliance with treatment than is usually found in children on regular inhaled therapy for asthma.

Pulmonary rehabilitation

S38 CAN ALL COPD PATIENTS COPE WITH PULMONARY REHABILITATION?

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It has been suggested that hypoxemia may be responsible for intellectual difficulties observed in COPD patients. Research to date is inconclusive as to the nature of these difficulties and at what stage of disease they occur. This investigation aimed to establish what the difficulties are, which disease factors are involved and whether they are functioning by emotional wellbeing. Forty patients participated. Inclusion criteria were an established diagnosis of COPD; FEV1 <80% predicted, and an FEV1/FVC ratio of <70%. Those who were receiving LTOT, had suffered a severe head injury in the past, who had a learning disability or who had other medical conditions known to affect intellectual functioning were excluded. A control group of 22 healthy volunteers was also recruited. Blood gases and lung function measures were taken from the patients; oxygen saturation of haemoglobin was measured for all participants. A range of intellectual assessments measured verbal fluency, memory, attention processes and other skills associated with the frontal lobes of the brain. The HAD assessed anxiety and depression. Mean Paco2 was 8.6 (9.7), mean Paco2 5.2 (6.3). Oxygen saturation at rest was 93.4% (3.29) in patients. Independent t-tests showed that COPD patients performed significantly worse than controls on speed of information processing (t = 2.99, p<0.05), immediate memory (t = 3.24, p<0.01), divided attention (t = 2.60, p<0.01) and verbal fluency (t = −2.58, p<0.05). Significant correlations were obtained between these measures and some physiological measures: speed of information processing and % of predicted FEV1/FVC (r = −0.33, p<0.05); immediate memory with PaCO2 (r = −0.27, p<0.05) and with FVC (r = −0.27, p<0.05). Independent t tests showed patients scored significantly higher on controls on both anxiety and depression (t = 3.89, p<0.001 and t = 4.63, p<0.001 respectively) but were not correlated with any of the intellectual measures. These findings suggest that mildly hypoxemic patients show impairments in intellectual performance. There is some evidence for the contribution of severity of illness, although other factors related to COPD or chronic illness in general may be implicated. Future work could assess whether severe hypoxemia is accompanied by more intellectual deterioration.

The presentation of rehabilitation programmes can be tailored to take account of patients’ difficulties.
pulmonary rehabilitation. However there are few reports of the effects of “real life” rehabilitation, in particular descriptors of response and non response behavior. This study reports on data from a 7 week, 2 × weekly exercise and education programme run at St George’s Hospital, London.

Methods: Outcome measures were spirometry, Shuttle walk test (SWT), HRQoL using SGRQ and mood state using the Hospital Anxiety and Depression Scale (HAD). 76 patients were admitted to the programme, 67 were available for follow up.

Results: There was a significant positive improvement in SWT mean change; 52 m (4.4) (p = 0.0001) and in SGRQ; 5.2 (10.6) (n = 67). Responder analysis, based on a change >30mt for SWT and >4 points for SGRQ, showed that 37 patients were responders (R) for ET and 33 for HRQoL. 16 patients were characterised as non responders (NR) for ET. 12 patients were NR for exercise tolerance but R for HRQoL, 17 patients were classified as R for SWT but NR for HRQoL and only 20 patients were classified as R in both aspects. In these 20 patients the change in SWT and SGRQ was large; 124 (71.4)m and 12 (6.2) respectively. There was a significant difference for SGRQ between R and NR; 57 (14.6) and 47 (14.4), p = 0.04 with Rs showing poorer QoL, similarly for depression 7.3 (3.2), 5.6 (2.4), p = 0.04. Rs showed a larger initial SWT compared to NR; 270 (139) and 217 (94.6) m although the difference was not statistically significant (p > 0.01). Body mass index (BMI), age, time since diagnosis, differences in exercise tolerance and poor HRQoL are associated with better improvements in pulmonary rehabilitation. Prospective randomised trials are warranted.

S40 SYMPTOMS LIMITING EXHAUSTIVE WALKING AND CYCLING EXERCISE IN COPD
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Background: Previous studies have shown that leg fatigue is a common symptom following exhaustive cycling in COPD patients. However cycling is not familiar to many COPD patients, and walking field tests may be more representative of everyday activities. We hypothesised that the symptoms limiting exhaustive exercise in COPD is dependent on the type of exercise performed.

Method: 50 stable patients with COPD (27M:23F, mean age 68.6 yrs, mean FEV1 0.95) were recruited. After an initial familiarisation period, each patient performed to exhaustion an incremental shuttle walk (ISW), an endurance shuttle walk (ESW), incremental cycling ergometry (ICE) and endurance cycling ergometry (ECE), on four separate visits. Patients were asked to name the predominant symptom limiting further exercise: shortness of breath (SOB), leg fatigue (LF), atypical chest pain (CXP) or other symptoms.

Results: See Table.

Discussion: SOB is by far the most common limiting symptom following exhaustive walking exercise, but is less important following exhaustive cycling exercise when LF becomes more prominent. It may be more appropriate to use walking tests to assess the effects of therapeutically induced changes in exercise-induced dyspnoea.

WDCM is a Clinical Research Training Fellow of the MRC (UK).

Abstract S40

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S41 ASSESSING THE DETERMINANTS OF INCREMENTAL SHUTTLE WALKING DISTANCE
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Introduction: The shuttle test is a widely used outcome measure for pulmonary rehabilitation to assess a person’s exercise tolerance. To better understand what this outcome means we examined the relationship between incremental shuttle test walking distance and biomedical and psychological dimensions in people with COPD. These findings derive from the baseline data of a trial comparing pulmonary rehabilitation with solely exercise and psychological interventions.

Participants: All 218 participants had stable COPD. 60% reported MRC Dyspnoea grade 3, 29% grade 4, and 11% grade 5. 44% were male and mean [95% CI] age was 68 [67.8–69.7] years.

Methods: Incremental shuttle walking test was carried out. Spirometric and anthropometric measurements were recorded including Forced Expiratory Volume (FEV1), weight, and four site skinfold thickness. Perceived health status, personal cognitions of illness and affect were assessed using the Chronic Respiratory Disease Questionnaire (CRDQ), the Illness Perception Questionnaire (IPQ) and the Hospital Anxiety and Depression Scale (HADS) respectively. Stepwise multiple linear regression was carried out with incremental shuttle walking test distance as the dependent variable.

Results: Mean (SD) incremental shuttle walking distance = 202.5 (111.3) meters. Independent variables included: predicted FEV1, mean change; 52.7 (15.6); fat free mass index [mean (SD] 17.6 (2.6); CRDQ (mastery [median (IQR) = 19.0 (9.0)], fatigue [median (IQR) = 14.0 (8.0)]), emotional function [median (IQR) = 32.0 (12.8)], dyspnoea [median (IQR) = 14.0 (7.8)], IPQ (timeline [median (IQR) = 21.0 (3.0)], consequences [median (IQR) = 19.5 (5.0)], personal control [median (IQR) = 20.0 (5.0)], treatment control [median (IQR) = 16.0 (4.0)], illness coherence [median (IQR) = 12.0 (6.0)]; and HADS anxiety (median (IQR) = 18.0 (5.0)), depression (median (IQR) = 16.0 (5.0)). In a model controlling for participant age and gender, and explaining 27.7% (p=0.001) of the variance in the dependent variable, fatigue (beta = 4.6 (p=0.004)) and mastery (beta = 3.5 (p=0.002)) as measured by the CRDQ, were the only significant variables entered.

Conclusion: In this population, these findings demonstrate that a person’s perception of their fatigue and their degree of control and confidence in managing their condition, play an important and independent role in promoting exercise performance. This suggests it is important to directly address these factors when providing pulmonary rehabilitation.

S42 EVALUATION OF MAINTENANCE PROGRAMMES AFTER PULMONARY REHABILITATION IN THE COMMUNITY SETTING
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Introduction: The role of maintenance programmes (MP) in pulmonary rehabilitation is at present unknown. This data reports on the outcomes of a community based MP provided after a 7 week 2 × weekly outpatient programme (OP) as part of “real life” clinical service.

Methods: After the 7 week outpatient programme, patients self selected to either attend a 6 month MP (n = 10) or not (n = 15). The MP was provided once weekly in a local leisure centre. Assessments of Walking Test distance (SWT) and St George’s Hospital Respiratory Disease Questionnaire (SGRQ) were made at the end of the 7 week outpatient and after the 6 month period (n = 25).

Results: Descriptive data are provided, based on an improvement in SWT >30mt and >4 points for SGRQ. Of those who attended, 4 improved SWT, 3 stayed the same and 1 deteriorated; mean change post OP rehabilitation, 17m. Of those who did not, 7 improved, 6 stayed the same and 2 got worse, mean change 45m. For SGRQ in group attendees, 1 improved, 5 stayed the same and 4 got worse. There were no significant differences between the groups for SWT or SGRQ.

Conclusion: This early report of a clinical community MP suggests that patients who choose to attend the MP do as well as those who do not attend for exercise and health related quality of life. It is unknown whether these patients would maintain improvements without the opportunity of a maintenance programme. Long term studies are indicated.

S43 A FOCUS GROUP STUDY ON THE IMPACT OF THE DIFFERENT COMPONENTS OF PULMONARY REHABILITATION
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Background: Multi-professional pulmonary rehabilitation (PR) has been shown to improve exercise tolerance and quality of life. It is not

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known which aspects of PR (e.g. exercise versus education versus social support) are found to be most helpful to patients, and existing quality of life tools do not explore this issue.

Methods: Six focus groups were held 3 months after PR with patients recruited from 2 programmes. One being a typical intensive, hospital-based scheme (Torquay), the other a short, once weekly programme based in various locations in the community (Plymouth).

Results: Perceived effects of education included reduced fear of dyspnoea, improved use of benefit system and improved drug compliance; personal effects of social context included encouragement during exercise and smoking cessation, and new social activities amongst group members; exercise in a safe environment increased confidence in activity and also reduced fear of dyspnoea, leading to new activities (e.g. holidays, shopping trips etc.) Patients judged PR to be more helpful than medical interventions. There appeared to be more extracurricular social contact in the community group.

Conclusions: Patients reported benefits of PR can be attributed to exercise, education, social context, supporting the use of multi-professional, multi-component PR programmes. Peer group support in both programmes appears to be an important factor in behavioral change.

Interstitial lung disease: From diagnosis to treatment

AN ASSESSMENT OF REPRODUCIBILITY OF DIAGNOSIS IN DIFFUSE PARENCHYMAL LUNG DISEASES


There are very few inter-observer studies of histologic patterns of diffuse parenchymal lung disease (DPLD), and the reproducibility of the ATS/ERS classification for interstitial pulmonary fibrosis has not yet been tested. This study assesses inter-observer variation in the diagnosis of DPLDs, both for interstitial pneumonias and orphan lung diseases (OLDs). Cases referred for clinical assessment of DPLD between Jan 1996 and Dec 1997, in which a surgical lung biopsy was taken, were retrieved and H&E slides were circulated to 7 reviewers, with knowledge only of age and sex of patient and site of biopsy. As well as histologic patterns in the consensus classification, follicular bronchiolitis (FB), extrinsic allergic alveolitis (EAA), sarcoidosis, end-stage lung, normal, non-diagnostic, unclassifiable and “other” for OLDs were permitted. Reviewers provided a first choice diagnosis with a confidence rating of 1 (>95%), 2 (70–95%) or 3 (30–65%) for each biopsy. The differential diagnosis for each lobe was also recorded along with its percentage likelihood, censored at 5%. The same procedure was applied for the gestalt diagnosis if patients (n=83) had more than one biopsy. Statistical analysis was performed using STATISTICA software (CA, USA). A confidence level of >95% for diagnosis was made in 37% (range 22–47) of cases and >70% in 64% of cases (range 54–73). The overall kappa coefficient for first choice lobar diagnoses was 0.35. Examples for more commonly found patterns of interstitial pneumonias were UIP, 0.43; NSIP, 0.24; DIP, 0.51; OP, 0.53; DAD, 0.52; EAA, 0.52; sarcoidosis, 0.70. In cases with a high degree of confidence (n=79), the overall kappa value was 0.49, whilst for low confidence diagnoses (n=54) this was only 0.19. For UIP, the weighted kappa for lobar diagnosis was 0.55 rising to 0.69 for the gestalt diagnoses. Selected examples of weighted kappas for gestalt diagnoses were NSIP, 0.34; OP, 0.58; EAA, 0.50. These data suggest that the ATS/ERS consensus classification is sufficiently reproducible when used by pathologists with a specialist interest in pulmonary pathology.

INCREASED SERUM LEVELS OF MUCIN KL-6, SURFACANT PROTEIN-D(SDP) AND ANTIBODY TO DIETARY ANTIGENS SUGGEST ALTERED MUCOSAL PERMEABILITY AMONG PIGEON FANCIES

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Background: Increased clearance of inhaled 99mTc-DTPA in pigeon fanciers has been observed irrespective of symptoms. The aim of this study was to use serum levels of lung-epithelium-derived KL-6 and SP-D to assess lung epithelial permeability and antibody to dietary antigens to assess gut epithelial permeability in pigeon fanciers.

Methods: Serum KL-6, SP-D, antibody to inhaled avian antigens and to common dietary antigens was quantified by enzyme immunoassay in 60 pigeon fanciers.

Results: The serum KL-6 levels in pigeon fanciers was (median, IQR range) = 422 (244–616) units/ml and the serum SP-D level was (mean (SD)) = 201 (141) ng/ml. Both of these were significantly higher than normal. These levels were significantly higher in those with EAA, but there was a significant correlation between the KL-6 levels and the IgG antibody to inhaled avian antigen (r=0.435, p=0.001) and between SP-D level and the IgG antibody (p=0.005). There were significantly higher than normal titres of IgG antibody to common dietary antigens among the pigeon fanciers suggesting increased gut permeability, but these did not correlate with either symptom category or antibody titre to avian antigens.

Conclusion: Increased lung mucosal permeability reflects local inflammation which could be the cause or the effect of antibody-associated events. The increased gut permeability in pigeon fanciers suggests either an inflammatory reaction in the gut to avian antigens in the diet or a pre-existing generalised increase in mucosal permeability.

MACROPHAGE MIGRATION INHIBITORY FACTOR INDUCES PROLIFERATION AND HAS PRO-FIBROTIC EFFECTS IN PRIMARY HUMAN PULMONARY FIBROBLASTS

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Macrophage Migration Inhibitory Factor (MIF) is an important pro-inflammatory cytokine which has been linked to the development of fibro-proliferative or “chronic” acute respiratory distress syndrome (ARDS). This finding led you to postulate that MIF might have direct pro-fibrogenic effects on fibroblasts, and therefore be an important effector in the development of pulmonary fibrosis from a variety of causes.

Primary human pulmonary fibroblasts (CCD-19Lu) were transiently transfected with MIF, RNA extracted and an RNase protection assay (RPA) performed. Levels of transforming growth factor (TGF)-β, a cytokine known to be highly pro-fibrogenic, were found to be significantly up-regulated [366% above control levels (n=5)]. Similarly, when the fibroblasts were stimulated with recombinant MIF, levels of secreted TGF-β (measured by ELISA) were increased by 295% compared to controls (n=5). In order to assess whether MIF had any direct effects on fibroblast proliferation, MIF was co-incubated with the primary pulmonary fibroblasts and cellular proliferation assessed by (β)-thymidine incorporation. Fibroblast proliferation was increased by 210% over controls (n=9).

These data identify MIF as a cytokine which has the capacity to both significantly up-regulate TGF-β production and induce fibroblast proliferation; both key parameters which have the capacity to drive an exaggerated pathological fibro-proliferative response. This work is supported by the Wellcome Trust.

COLLAGENASE 1 (MATRIX METALLOPROTEINASE 1, MMP1) IS INVOLVED IN THE DEVELOPMENT OF CRYPTOGENIC FIBROSES ALVEOLITIS

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Cryptogenic Fibrosing Alveolitis (CFA) is a relentlessly progressive diffuse lung disease of unknown aetiology, characterised by fibroblast proliferation and extracellular matrix (ECM) accumulation. It is the most common of the diffuse lung diseases, affecting up to 10 adults per 100 000 in the UK and has a median survival time of only 3 years from diagnosis. Even though the existence of familial CFA suggests there may be a genetic component, there have been few large scale studies showing an association between any genetic marker and the development of CFA. The genetic component of CFA is likely to be complex, involving several genes each with a variable effect, acting in combination to determine the predisposition to lung fibrosis. In CFA, the pathological process is characterised by ECM accumulation and abnormal remodeling that may be due to a relative deficit in proteolysis.
In this study we fine mapped across collagenase-1, the gene coding for the main enzyme involved in type I collagen degradation. We examined 12 single nucleotide polymorphisms (four promoter, two 3'UTR, one intron 1/exon 1 boundary and five intronic) in 50 CFA patients and 225 Caucasian controls. The genotype, allele and allele carriage frequencies for the intron/exon boundary polymorphism (C/T) were significantly different between patients and controls (genotype $p=0.01$, allele $p=0.03$, allele carriage for C $p=0.006$). There were differences in the T allele carriage for the intron/exon polymorphism and CFA may indicate a role for this enzyme in the pathogenesis of this disease, but at present, the functional consequences of these polymorphisms are unknown. They may affect mRNA splicing or stability; alternatively, they may be markers for other unidentified polymorphisms in this or other genes in the MMP cluster on chromosome 11q23. We conclude that a susceptibility marker for CFA maps to this MMP region.

**THE DEVELOPMENT OF LUNG FIBROSIS IN TRANSGENIC TGFβ1 MICE**

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TGFβ1 has been shown to be an important growth factor in the pathogenesis of lung fibrosis. It has been hypothesised that human genetic predisposition mediated via TGFβ1 may place some individuals at risk of developing lung fibrosis (Anscher et al. NEJM 1993;328:1593–8).

We previously studied the natural history of a transgenic mouse colony that expressed high circulating plasma levels of active TGFβ1 and found that lung fibrosis was not present irrespective of the age of the mouse. This was despite histological evidence of liver fibrosis.

We proceeded to study the potential susceptibility of these mice to the development of lung fibrosis using a known chemical injury (bleomycin) and a suspected environmental pathogen (a herpes virus).

We bred two lines of transgenic mouse and confirmed their phenotype (Tr+) qualitatively (by tail DNA analysis) and quantitatively (by plasma TGFβ1 bioassay). We then analysed their lungs histologically after bleomycin injection (3000 IU intraperitoneal) and after administration of herpesvirus (4 × 10$^6$ pfu of Murine gammaherpesvirus-68 intranasal). Mice were killed after 6 weeks. A control population received the same treatment ($n=8$). Lung fibrosis was graded 0–3, based on a previously published grading system (Ashcroft et al. J Clin Pathol 1998;41:467–70).

The Tr+ mice were confirmed to have higher circulating levels of active TGFβ1 compared to controls ($p<0.05$). Prior to bleomycin exposure, the lungs of the Tr+ and control mice were histologically normal. After bleomycin, control lung showed fibrosis (mean score 1.4) and Tr+ lung showed more severe and extensive fibrosis (mean score 2.7) ($p<0.05$). Prior to herpesvirus inoculation, the lungs of the Tr+ and control mice were normal. After herpesvirus, there was no evidence of lung fibrosis in either group. In conclusion plasma TGFβ1, while not causing de novo lung fibrosis, appears to predispose to lung fibrosis when exposed to an exogenous injury (e.g bleomycin). This may be a consequence of a compartmental disruption allowing passage of circulating TGFβ1 into lung tissue. Therefore lung injury may be of primary importance and individual susceptibility a secondary phenomenon.

**Acute respiratory distress syndrome**

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We are developing a programme of gene therapy for acute respiratory distress syndrome (ARDS). Oleic acid-induced lung injury has been suggested as the optimal animal model, but has not been characterised in mice. Current gene therapy studies focus on this species, and we have therefore developed a mouse model of oleic acid-induced lung injury. Balb/c mice were anaesthetised, ventilated and injected with either oleic acid (OA, 0.2 or 0.4 ml/kg body weight) or saline. One hour after OA administration (0.2 ml/kg), mouse lungs had significantly ($p<0.01$) higher wet-to-dry weight ratios (2.9 (0.4) and 5.9 (0.6) µg/ml for the two doses respectively) for 0.2 and 0.4 ml/kg OA compared to 0.2 (0.0) in the PBS control group. Albumin was also detected in BALF from all OA-treated animals (0.2 (0.0) µg/ml). Total cell numbers (1.4 (0.3) × 10$^6$ and 1.9 (0.3) × 10$^6$ for the two doses compared to 0.4 (0.1) × 10$^6$/ml in control) and the marker of cell damage, lactate dehydrogenase (LDH) activity (156 (40) and 446 (117) U/l compared to control 4.9 (1.3) U/l) were also significantly increased. MIP-2, isolated from lung homogenates, revealed a significant ($p<0.005$) increase in mice treated with the lower dose of OA.
compared to control. OA treatment resulted in substantial hypoxemia (PaO2 at FIO2 1.0 decreased from 425 (28) to 68 (6) mmHg) with decreased respiratory system compliance (69.7 [5.6] %, n=4). Electron microscopy demonstrated the presence of intra-alveolar fibrin and haemorrhage, type I alveolar epithelial cell necrosis and destruction of alveolar architecture. Histological quantification of the above lung damage parameters revealed no dose dependent increase in patchy lung damage with treated mice having 34.7 [7] and 48.9 (3.6 %) damage compared to 14.9 (2.9) % in control animals, p=0.05 and 0.005 respectively. Correlation of these physiological, histological and clinically relevant parameters in the OA mouse provides a model for further investigation of treatments for ARDS.

551 REGULATION OF NEUTROPHIL FATE BY HYPOXIA

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Introduction: Neutrophil apoptosis represents a major mechanism involved in the resolution of acute inflammation. In contrast to many other cell types, we have previously shown that hypoxia (0–3.5 kPa O2) can induce the ability to inhibit apoptotic cell death in neutrophils cultured in vitro. This may be of physiological importance given the significant drop in local oxygen tension at sites of inflammation. We therefore sought to elucidate the oxygen sensing pathways involved in this regulation of neutrophil apoptosis.

Methods: Human neutrophils were purified from the peripheral blood of healthy volunteers by dextran sedimentation followed by centrifugation through discontinuous plasma-Percoll gradients. Cells were cultured in supplemented MDM A/7 reagents in normoxic (19 kPa), hypoxic (3 kPa) or anoxic (0 kPa) environments. Apoptosis was assessed by cell morphology and flow cytometry with annexin V and propidium iodide. Cytokine release was measured by ELISA, and cytosolic and nuclear protein expression by western blotting.

Results: Oxygen deprivation profoundly inhibited constitutive and receptor-mediated apoptosis in human neutrophils from 59% to 29% (p=0.0025). Conditioned medium from oxygen deprived neutrophils also induced cell survival in normoxia but this was independent of GM-CSF, IL-1 β, IL-6 and TNFα. Furthermore, the hypoxic inhibition of neutrophil apoptosis was unaffected by the PI3 kinase inhibitors LY294002 (10 µM) or wortmannin (100 nM). The hypoxic survival of neutrophils previously shown to be mimicked by the iron chelators desferrioxamine and hydroxypropyridine (Mecklenburgh K et al. Blood 2002; in press) was replicated with the novel prolyl hydroxylase inhibitor dimethyl oxaloylglycine at HIF stabilising concentrations (1 mM).

Our results indicate that neutrophils have a ferro-protein oxygen sensing mechanism involving prolyl hydroxylase domain (PHD) containing proteins which can regulate the hypoxic inhibition of neutrophil apoptosis. This survival effect is independent of the PI3-Kinase pathway. Moreover neutrophils cultured under hypoxic conditions show an apparently novel factor that has a profound survival effect on neutrophils cultured in normoxic conditions. Research funded by the MRC, and Sackler studentship.

552 TOLL-LIKE RECEPTOR EXPRESSION IN ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS): A ROLE FOR TLR-2?

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ARDS is an illness commonly associated with sepsis. Recently the toll-like receptor family has been best identified on the basis of homology with the type I IL-1 receptor. 10 members have been described, but only 3 of them have a known function: TLR-4 is a component of the LPS receptor and is essential for gram negative responses, TLR-2 is a receptor for gram positive lipoproteins but may also cross-sign in response to LPS with TLR-4. TLR-9 recognises CpG bacterial motifs. We have looked at the expression of TLR-2 and TLR-4 on monocytes from patients with gram negative (n=20) and gram positive sepsis (n=20), compared to non-septic ITU controls (n=15). TLR expression was also determined on alveolar neutrophils and macrophages. We also looked at the relationship between TLR expression and the development of ARDS. Monocytes were isolated from whole blood by density gradient centrifugation and adherence. Total RNA was determined after 2 hours in culture and RT-PCR was performed for TLR-2, TLR-4 and GAPDH transcripts. TLR protein expression was determined by flow cytometry on whole blood, dual stained with CD14-APC and specific TLR-2 and TLR-4 monoclonal antibodies, or on un gated macrophages and neutrophils. Expression of both TLR-2 and TLR-4 mRNA (% GAPDH) was significantly increased in sepsis (126 and 87.5 % respectively) versus non-sepsis controls (96 and 68 % respectively) (p<0.05). This was reflected at the protein level: TLR-2 expression (abundant isoforms) was increased versus 0.13 for non-sepsis controls (p=0.05). TLR-4 expression was 3.77 versus 0.59 non-sepsis controls. Both TLR mRNAs significantly correlated with TNF-α mRNA suggesting increased function. In ARDS subjects there was no significant differences in TLR-4 expression. However, monocytes from ARDS subjects had significantly lower levels of TLR-2 mRNA (83.1 % GAPDH for ARDS subjects vs 126 % for non-ARDS subjects, p<0.001). Similarly TLR-2 mRNA was lower in patients who died (103 %) versus survivors (144 %). In the lung, alveolar neutrophils and macrophages both express high levels of TLR-2 and TLR-4. We hypothesise that reduced levels of TLR-2 may influence development of ARDS in sepsis populations by increasing the availability of LPS for TLR-4 receptor ligation and signalling.

553 ELEVATION OF THIOREDOXIN CONCENTRATIONS IN PLASMA AND BRONCHO-ALVEOLAR LAVAGE FLUID FROM PATIENTS WITH THE ACUTE RESPIRATORY DISTRESS SYNDROME

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Introduction: The acute respiratory distress syndrome (ARDS) is characterised by refractory hypoxaemia secondary to alveolar derecruitment and disordered ventilation-perfusion matching. Oxidative stress and inflammation are key features that contribute to the pathogenesis of ARDS. Thioredoxin (Trx) is an intracellular redox active protein involved in maintaining cellular redox balance, and is actively secreted into the extracellular space in response to clinical conditions associated with oxidative stress and inflammation. Extracellular Trx may have profound implications for the inflammatory response by virtue of its reported chemokine/cytokine properties. We therefore measured Trx levels in plasma and broncho-alveolar lavage fluid (BALF) from 30 patients with ARDS and 18 healthy controls.

Results: Trx levels were significantly elevated in ARDS patients vs controls in plasma (45.9 [27.9] ng/ml vs 23.6 [13.4] ng/ml, p<0.001) and BALF (103.8 [116.0] ng/ml vs 17.4 [9.6] ng/ml, p<0.0001). There were significant positive correlations between Trx concentration and IL-8 concentrations (p=0.001, r=0.631) and IL-1β concentrations (p=0.05, r=0.448) in BALF from the ARDS population. BALF Trx concentrations were higher in patients with ARDS of pulmonary aetiology compared to extrapulmonary aetiology (132.2 [129.2] ng/ml vs 39.7 [26.9] ng/ml, p<0.01) BALF from patients with pulmonary ARDS also had significantly higher concentrations of IL-8 (p<0.05) and a greater percentage neutrophil count (p<0.05) compared to BALF from patients with extrapulmonary ARDS. Plasma and BALF Trx levels were not significantly different between surviving and non-surviving patients and there was no relationship between Trx levels and the sequential organ failure assessment (SOFA) score when all patients were considered. However, in cases of pulmonary ARDS, there was a significant association between SOFA score and plasma Trx levels (p<0.05, r=0.482).

Discussion: These results demonstrate that concentrations of Trx are increased in BALF and plasma in patients with ARDS. Trx has been shown to have profound effects on the inflammatory response and the correlation between levels of Trx and pro-inflammatory cytokines suggests a link between Trx and the inflammatory response in this condition, although the exact nature of the role of increased extracellular Trx in ARDS remains to be evaluated.

Research Funded by the Wellcome Trust.

554 PLASMA VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) LEVELS AND THE VEGF +936 C/T POLYMORPHISM IN ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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Results: Plasma VEGF levels were not significantly different between ARDS and non-ARDS controls (23.6 [13.4] ng/ml vs 20.3 [13.6] ng/ml, p=0.09). However, VEGF levels were significantly higher in BALF from ARDS patients compared to BALF from non-ARDS controls (103.8 [116.0] ng/ml vs 17.4 [9.6] ng/ml, p<0.0001). There were significant positive correlations between VEGF concentration and SOFA score and plasma Trx levels (p<0.05, r=0.482).

Discussion: These results demonstrate that concentrations of Trx are increased in BALF and plasma in patients with ARDS. Trx has been shown to have profound effects on the inflammatory response and the correlation between levels of Trx and pro-inflammatory cytokines suggests a link between Trx and the inflammatory response in this condition, although the exact nature of the role of increased extracellular Trx in ARDS remains to be evaluated.
The expression of transforming growth factor effects of long acting asthma and not eosinophilic bronchitis (Brightling CE, et al. J Vasc Res 2000;37:443–8). Because of the possible functional role of VEGF, we hypothesised that the frequency of this polymorphism would be altered in ARDS. DNA was extracted from healthy subjects (n=50) as well as ARDS patients (n=45) and ventilated at risk patients in intensive care (n=38). A 120 base pair fragment of the VEGF gene containing the polymorphism was amplified and cross-matched with an internal heteroduplex generating containing a polyA insert adjacent to the polymorphism. Artificial heteroduplex formation was analysed on a 15% polyacrylamide gel. ELISA was performed to measure VEGF levels in matched plasma samples from the ARDS and at risk groups. The abnormal (CT or TT) genotypes occurred in 31.3% of at risk patients and 24% of normal subjects. In ARDS patients, those with an abnormal genotype had a significantly higher 30 day mortality than those with a normal genotype. In the at risk groups, plasma VEGF levels were lower in those with abnormal genotypes compared to normal genotype (129 pg/ml versus 305 pg/ml) but this was not observed in ARDS (337 pg/ml versus 309 pg/ml). The +936C/T polymorphism occurs more frequently in at risk and ARDS patients than normal subjects indicating a possible functional significance in intensive care patients. The normal relationship between plasma VEGF level and genotype appears to be disrupted in ARDS suggesting additional regulatory mechanisms may be important in these patients.

Asthma mechanisms I

S55 EXPRESSION OF TRANSFORMING GROWTH FACTOR ISOFORMS IN HUMAN AIRWAY SMOOTH MUSCLE AND NORMAL LUNG TISSUE

B. Islam, D. Bradbury, L. Corbett, I. Soomro, J. Ronan, A. Knox. Division of Respiratory Medicine, 3Histopathology, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

Introduction: transforming growth factor beta (TGF-β) is an immunomodulatory cytokine regulating the proliferation and differentiation of various lung cell types. It also contribute to the maintenance of tissue architecture by influencing the production of extracellular matrix components. In this study we examined the expression of TGF-β isoforms in human airway smooth muscle cells (HASMC) and normal lung tissues by rtPCR, bioassay and immunohistochemical staining.

Methods: HASMC were obtained from post-mortem samples of human lung and studied at passage 6. Normal lung tissues were obtained from lung biopsy samples and thoracic surgery. Mink lung epithelial cells (Mv1Lu) were obtained commercially. Recombinant isoforms in human airway smooth muscle cells (HASMC) and normal lung tissues by rtPCR, bioassay and immunohistochemical staining.

Results: Messenger RNA transcripts for TGF-β1, -2, -3 were all expressed in the HASMC. The conditioned medium showed presence of bioactive TGF-β in the acid treated sample and by using the neutralising antibodies it demonstrated that all three isoforms are present in the conditioned medium. Very little TGF-β was present in the non-acid treated medium, implying that majority of the TGFβ secreted by the HASMC is in the biologically non-active form. The TGF-β bioactivity was significantly abrogated by panspecific antibody to TGF-β. Immunohistochemistry showed that all three isoforms of TGFβ were detected in the epithelial cells, smooth muscle cells, and macrophages.

Conclusion: It has been shown that autocrine/paracrine release of TGF-β by HASMC could play an important role in the remodelling of airway smooth muscle in asthma.

S56 IL-4 EXPRESSION IS INCREASED AND CO-LOCALISED TO MAST CELLS WITHIN THE AIRWAY SMOOTH MUSCLE IN ASTHMA

C.E. Brightling, F.A. Symon, S.T. Holgate, A.J. Wardlaw, I. Pavord, P. Bradlow, Division of Respiratory Medicine, Institute for Lung Health, Leicester, UK; 2University of Southampton, Southampton General Hospital, UK

Airway smooth muscle infiltration by mast cells is a key feature of asthma and not eosinophilic bronchitis. Brightling CE, et al. NEJM 2002;346:1699–705). In asthma Th2 cytokines have been implicated as playing a critical role in the development of airway inflammation, but whether inflammatory cells within the airway smooth muscle release these cytokines is uncertain.

We have undertaken a comparative immunohistochemical study in bronchial biopsies from 14 subjects with asthma, 10 with eosinophilic bronchitis and 8 normal controls recruited from two centres.

The median cells/mm² smooth muscle were significantly higher in the subjects with asthma than eosinophilic bronchitis and normal controls for IL-4 (3H4) + cells (2.4, 0, 0 respectively; p=0.001), and IL-4 (4D9) + cells (1.6, 0, 0 respectively; p=0.02). There were significant differences in the median (range) cells/mm² smooth muscle IL-4+ cells in the subjects with asthma 0 (0–1.1), eosinophilic bronchitis 0 (0–1.4) and normal controls 0 (0–0.3) (p=0.31). 94% of the cells expressing IL-4 (3H4) and 92% of those expressing IL-4+ (4D9) in the smooth muscle were mast cells. 55% of the mast cells within the airway smooth muscle co-localised to IL-4 (3H4) and 29% to IL-4 (4D9).

In asthma mast cells localised within the airway smooth muscle express IL-4 but not IL-5, suggesting that IL-4 may play an important role in mast cell-airway smooth muscle interactions.

Supported by the National Asthma Campaign.

S57 EFFECTS OF LONG ACTING β AGONISTS AND STEROIDS ON CYTOKINE EXPRESSION

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Rationale: In bronchial asthma treatment, combination therapy with inhaled corticosteroids and long acting β agonists (LABA) can improve disease control. Since research suggests that ligand-independent activation of the glucocorticoid receptor (GR) by LABA may aid steroid anti-inflammatory action, the functional consequence of GR nuclear translocation was examined via the effect of LABA and steroids on cytokine production.

Methods: U937 cells were incubated with fluticasone, budesonide, formoterol and salmeterol, alone and in combination (0.01–1mM). Basal expression of CysLT1 mRNA and protein was compared with that observed with budesonide or fluticasone alone, although neither LABA altered the steroid concentration-response curve. Additionally, both LABA prevented steroid-induced repression of CysLT1 mRNA release. The action of the LABA differed with U937, where formoterol, in combination with fluticasone, enhanced production, whilst salmeterol did not increase LPS-induced IL-10 production compared with fluticasone alone.

Conclusions: These data indicate that the added benefit of formoterol may relate to the anti-inflammatory gene-inducing action of steroids rather than in enhancing the repressive functions of steroids towards inflammatory cytokines.

This study was sponsored by Innovata Biomed Ltd.

S58 LEUKOTRIENE RECEPTORS ON HUMAN EOSINOPHILS

H. Rupani, J. Hao, A.P. Sampson. Respiratory Cell and Molecular Biology Division University of Southampton School of Medicine

Cysteinyl leukotrienes are potent bronchoconstrictor mediators and eosophilotoxins released by mast cells and eosinophils within the asthmatic airway. These actions are thought to be mediated by CysLT, receptors, with vascular effects mediated by CysLT1 receptors. CysLT, expression on human eosinophils may be regulated by cytokines, but the effects of asthma therapies including corticosteroids and methylxanthines are unknown. Recently, eosinophils were reported to transcribe larger amounts of mRNA for CysLT1 than for CysLT1. Mita et al. Clin Exp Allergy 2001;31:1714–23). We investigated firstly whether CysLT1 on eosinophils is modulated by dexamethasone or theophylline, and secondly whether eosinophils also express CysLT2, receptors, with their cell surface. Immune-reactivated human blood eosinophils of normal and mild atopic volunteers were cultured in HEPES-buffered RPMI 1640 with 10% FCS for 22 hours in the presence or absence of dexamethasone (0.01–10μM) or theophylline (0.01–1mM). Basal expression of CysLT1, mRNA and protein was confirmed by RTPCR, flow cytometry, immunocytochemistry, and immuno- blotting. Flow cytometric expression of cell-surface CysLT1, declined...
CAT-213, AN ANTI-EOTAXIN (CCL11) ANTIBODY, REVEALS A ROLE FOR EOTAXIN IN THE EOSINOPHIL CHEMOTACTIC ACTIVITY OF ASTHMATIC SPUTUM

G. Dent1, C. Hadjicharalambous1, J. Ward2, T. Yoshikawa2, G. Angco3, D.E. Davies1, R. Louis2, R.L.C. Handy1, R. Dukanovic1,1 Respiratory Cell & Molecular Biology, University of Southampton School of Medicine, Southampton; 2Department of Pneumology, University of Liège, Liège, Belgium; 3Cambridge Antibody Technology, Cambridge, Cambridge, Cambridge, UK

To understand the mechanisms underlying eosinophilic airways inflammation in asthma, it is necessary to characterise the chemotactic mediators mediating eosinophil recruitment. The CC chemokines eotaxin (CCL11), eotaxin-2 (CCL24), RANTES (CCL5) and monocyt e chemotactic protein-3 (MCP-3, CCL7) are potent eosinophil chemotactic agonists (Cowburn, et al. J Immunol 1999;163:456–65). Secondly, while CCL11 mRNA may be transcribed, the receptor protein does not appear to be expressed on the surface of blood eosinophils from healthy donors.

Sputum samples were collected from 60 volunteers: 11 healthy controls, 12 mild asthmatics, 12 stable moderate asthmatics, 12 unstable moderate asthmatics and 13 severe asthmatics. Sputum was processed by thorough mixing with 4 volumes of phosphate-buffered saline (PBS) containing protease inhibitors. Cells and mucus were precipitated by centrifugation and supernatants were assayed for immunoreactive eotaxin by ELISA and for eosinophil chemotactic activity in vitro. Eosinophils were purified by negative selection using a specific anti-eotaxin antibody, CAT-213.

Sputum eosinophils were counted. 12 mild asthmatics, 12 stable moderate asthmatics, 12 unstable moderate asthmatics and 13 severe asthmatics. The chemotactic activity of eosinophil chemotactic activity in a fluorescence-based modified Boyden chamber assay. Calcein-labelled eosinophils (2H10) were pre-incubated with 200 nM of CCL11 in each well of 52 patients. Prevalence of SM rose from 3.3 to 15% by 1999. Isolation of SM is a Gram negative bacillus (A. Equi, V. Marchac, C. Le Bihan-Benjamin, M. Hodson, A. Bush. Department of Respiratory Paediatrics and Department of Cystic Fibrosis Royal Brompton Hospital, London, UK). The following data were collected in 63 patients isolated SM at least once. Controls were found in 52 patients. Prevalence of SM rose from 3.3 to 15% by 1999. Stenotrophomonas maltophilia (SM) is a Gram negative bacillus which is resistant to many antibiotics. Its role as a pulmonary pathogen in CF is still being defined.

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GENOTYPING PSEUDOMONAS AERUGINOSA IN CYSTIC FIBROSIS CLINICS: IMPLICATIONS FOR SEGREGATION

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We were concerned that the antibiograms from patients harbouring Pseudomonas aeruginosa appeared to show increasing resistance, despite segregation policies initiated early in 1999. Genomic finger printing was performed on P aeruginosa isolates from 40 patients attending the clinic.

Twenty three (57%) had unique strains, 10 (25%) had strains indistinguishable from the “Liverpool” epidemic strain and 7 (17%) shared a common strain not previously seen, henceforth referred to as the “Sheffield” epidemic strain. 4/10 patients with the Liverpool strain had multiresistant (MR) organisms, compared to all 7 patients with Sheffield strain and only 1 patient (4%) out of the 23 with a unique strain. One patient harboured both Sheffield and Liverpool MR strains.

Those with the Sheffield MR strain were younger with poorer FEV1 and weight together with a higher proportion of F/F genotype, pancreatic insufficiency, diabetes mellitus and liver disease vs unique strains. Consequently numbers of clinic visits, days in hospital and time on intravenous antibiotics were increased. Comparison of Liverpool MR with Liverpool non-MR showed a similar pattern.

9/10 with Liverpool strains had been transferred from the paediatric unit since July 2000. MR strains being detected on the sputum sample taken when or in some cases before the patient first attended the CF unit. Four of 7 Sheffield MR patients had also been transferred but all have been inpatients in the adult centre at the same time as subjects who were found to have Sheffield MR strains already (including 1 sibling pair). We suspect we have “imported” the Liverpool strain, which is known to become multiresistant from the paediatric unit, but the Sheffield strain is our own and istransmissible. If MR confers poor prognosis we believe these groups should be segregated from each other and those with unique strains, both as inpatients and in the outpatient clinic and have acted accordingly.

RESULTS: 89 OGTT were performed on 151 patients. The incidence was found to be 4.4% and the prevalence 26.9%. Using the previous selective screening protocol, 6 patients with CFRD and 10 patients with impaired glucose tolerance would have been missed. The total sensitivity and specificity of the screening criteria would only have been 70% and 51% respectively.

Conclusions: In view of the need for early diagnosis and treatment of CFRD, annual OGTT testing is essential for all CF centres especially for adult patients. Selective screening does not identify all patients who need to be tested.


LUNG TRANSPLANTATION OUTCOME IN CYSTIC FIBROSIS PATIENTS WITH PREVIOUS PLEURAL PROCEDURES

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Background: High post-operative mortality secondary to haemorrhage from pleural adhesions as a consequence of previous invasive pleural procedures (IPP) was reported in the early experience of lung transplantation. This observation led to IPP becoming a relative/absolute contra-indication to transplantation in some centres.

Aim: Comparison of post-operative outcome in patients with and without previous IPP, undergoing single sequential lung transplant (SSLT).

Method: Retrospective review of 3 groups of patients undergoing SSLT at this centre from 1989–2002. Group A: 17 cystic fibrosis (CF) patients with a history of previous pneumothorax (PTX) +/- IPP. Group B: 17 CF patients with no history of PTX. Patients were matched for year of transplantation to allow for changes in surgical technique. Measured outcomes included: pre- and post-operative haemoglobin; blood products given intra-operatively; operation and cardio-pulmonary bypass times; post-op haemorrhage; times to extubation, ITU discharge and hospital discharge; FEV1 at 6 months; 30 day mortality; and admissions scored descriptively via pathology reports.

Conclusion: Patients with CF and previous PTX +/- IPP undergoing SSLT have more dense pleural adhesions and increased requirement for blood transfusion. However this does not significantly affect surgical outcome. Patients with emphysema, fibrosing alveolitis or obliterator bronchiolitis were significantly more likely to be free of pleural adhesions at operation B suggesting that the inflammatory/chronic infective component of CF independently contributes to the increased pleural adhesions. Previous IPP for PTX should not be considered a contra-indication in the assessment of suitability for lung transplantation.
Pulmonary artery pressure and right ventricular function in cystic fibrosis adults

1Adult Cystic Fibrosis Centre; 2Department of Cardiology, Wythenshawe Hospital, Manchester, UK

Introduction: Pulmonary hypertension has been reported as a poor prognostic marker in adult CF patients with severe disease. We evaluated the association between clinical status, oxygen status, pulmonary artery systolic pressure and right ventricular (RV) function in a cross-section of CF adults.

Methods: CF adults and healthy volunteers were studied. Demographic and clinical data collected. Patients were stable at the time of study. All subjects underwent echocardiographic examination by a trained operator (RBT). Pulmonary artery systolic pressure (sPAP) was measured from the peak velocity of tricuspid regurgitant jets. Systolic function of the RV assessed via measurement of RV dimensions and tricuspid annulus long axis motion (TALAM) and diastolic function via measurements of tricuspid annulus flow profile.

Results: 65 CF adults age, mean (SD), 26.1 (7.1) years and 25 healthy controls age 27.7 (8.8) years were studied. Partial pressure of oxygen (PO2)(mmHg) 68.8 (12.2) vs 90.1 (9.7) (p=0.001) and FEV1% (r=0.516, p=0.01), sPAP(mmHg) was 35.8 (9.7) in CF patients and 21.6 (3.2) in controls (p=0.001). 36 patients and 0 controls had sPAP>30mmHg. There was no significant difference in RV dimensions between groups. TALAM(cm) was reduced in CF patients compared to controls 2.1 (0.4) vs 2.5 (0.3) (p=0.001). There was a significant difference in the diastolic variables A wave velocity and E/A ratio between patients and controls; values (CF vs control): Avel(cm/sec) 45 (13) vs 29 (6) (p=0.001), E/A ratio 1.4 (0.5) v 1.8 (0.3) (p=0.001). Pearson correlation of CF patient data identified significant correlations between both PO2 and FEV1% with sPAP (r=0.516, p=0.01; r=0.432, p=0.001) and TALAM (r=0.459, p=0.001; r=0.620, p<0.001) respectively. An association was also found between diastolic variables and PO2 and FEV1%; Avel (r=−0.311, p=0.012; r=−0.420, p=0.001), E/A ratio (r=0.302, p=0.015; r=−0.412, p=0.001) respectively.

Conclusion: Pulmonary artery pressure is raised in adult CF patients. RV dimensions are normal in CF but there is evidence of deranged RV systolic and diastolic function. Both PO2 and FEV1% correlate with sPAP and measures of RV function. Whether the abnormal RV function is due to the effect of hypoxia on the RV or due to pulmonary hypertension is unclear.

Increased energy costs during upper and lower limb activities in adults with cystic fibrosis

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Patients with Cystic Fibrosis (CF) have increased resting energy expenditure, which may be associated with altered body composition. We hypothesised that adults with CF have increased energy costs during skeletal muscle work. Twelve patients were studied after 2 weeks treatment for an exacerbation (to assess them with their best lung function); mean (95%CI) age 24.6 (21.4, 27.8) years, FEV1 51.3 (36.3, 66.2) % predicted, body mass index 21.5 (20.8, 22.2) kg/m2. Fat free mass index (FFMI, kg/m2) was assessed by anthropometrics. Ten healthy subjects were studied, age 32.1 (27.9, 36.1) years. Energy expenditure (EE, kcal/kg/min) was calculated from breath by breath O2 uptake and CO2 output measured with a mask (K4b2, Cosmed). Subjects completed the following: 10 handgrips (HG, force in cm H2O), 1/second; 10 steps (20 cm high), 1/second, and 10 lifts of a 1 kg weight through 80 cm height, every 2 seconds. EE ratio to the work performed and the recovery time after each activity were calculated. EE ratio to the work performed during HG and stepping, but not during lifting were greater in patients (Table). The recovery time was greater for patients than healthy subjects for HG (26.4 (29.9 to 30.0) and 21.6 (10.9 to 32.3) seconds, p=0.02) and stepping (70.7 (47.7 to 94.2) and 28.9 (16.6 to 41.2), p=0.002), but not lifting (35.9 (26.7 to 45.1) and 28.6 (17.7 to 39.4), p=0.3). FFMI was inversely related to EE during HG, (r=−0.75, p=0.005).

Adulists with CF have greater energy expenditure for upper and lower limb muscle work. This excess energy expended for tasks similar to those of daily living suggests physical activity in such patients adds to the potential for negative energy balance and weight loss.

Supported by the Cystic Fibrosis Trust UK.

Issues in paediatric lung disease

Effect of β2 Adrenoceptor (β2-AR) polymorphisms on neonatal lung function and asthma in school children

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An association between neonatal bronchial responsiveness (BR) and lung function at 11 yr, related to β2-AR gene influence, has been reported (Turner, et al. ERJ 2001;18(suppl 33):25). Polymorphisms of β2-AR at amino-acid (aa) 27 and aa16 have also been shown to be related to bronchial BR and childhood asthma. To assess the effect of these polymorphisms on the development of wheeze, lung function and BR, we genotyped from blood or buccal cells 41 children at risk of atopy, in whom maximal flows at FRC (VmaxFRC) and BR had been measured in the first month of life using the "squeeze" technique. They were followed prospectively and reviewed at age 10 yr (SD 0.8), when lung function (FEV1) and BR were repeated. We also genotyped 166 local school children from buccal cells.

Neonatal BR correlated significantly with FEV1 (p=0.03) but not BR at 10 yr. VmaxFRC varied according to aa27 genotype (ANOVA p=0.023); it was significantly increased in those homozygous for glutamate at aa27 (p=0.01), but had no effect on history of wheeze. No effect of aa16 was found on lung function or BR at either age, but homozygous glycine at aa16 was seen more frequently in those wheezing beyond 4 years, when compared to local school children (Fisher’s exact test p=0.05).

We have shown for the first time an effect of β2-AR polymorphism at aa27 on neonatal lung function, and confirmed the association of β2-AR polymorphism at aa16 with childhood asthma, as wheeze beyond 4 years was strongly related to atopy and increased BR at 10 yr.

Pneumococcal serotypes in children with culture negative empyema

K.M. Eastham1, R. Freeman2, A. Kearns2, G. Eltringham, J.P. Leeming2, K.M. Eastham1, R. Freeman2, A. Kearns2, G. Eltringham, J.P. Leeming2, 1Department of Paediatrics and Respiratory Medicine, Royal Brompton Hospital, Imperial School of Medicine, London, UK; 2Department of Child Health, University of Leicester, Leicester, UK

Background: Streptococcus pneumoniae serotype 1 accounts for up to 50% of pneumococcal culture positive childhood empyema in the USA.1 This organism has been a relatively uncommon cause of invasive pneumococcal disease in the under 5 age group in England and Wales.2

Aim: To describe the pneumococcal serotype distribution and penicillin susceptibility of consecutive cases of parapneumonic effusion and empyema presenting to a Tertiary Referral Centre over a 4.5 year period.

Method: 43 pleural fluid specimens, negative for pneumococcus on routine culture, were analysed for pneumococcal DNA by real-time polymerase chain reaction (PCR). Penicillin susceptibility was determined by a complementary PCR assay. Capsular serotype specific antigen detection was by Enzyme Immuno-Assay (EIA) using monoclonal antibodies to types 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

Abstract S66 Energy expenditure (kJ/kg/min) for kJ work performed (means, 95% CI)

<table>
<thead>
<tr>
<th>STEPPING</th>
<th>LIFTING</th>
<th>HANDGRIP (x10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>0.55 (0.43 to 0.65)**</td>
<td>3.27 (2.61 to 3.92)**</td>
</tr>
<tr>
<td>Healthy</td>
<td>0.37 (0.31 to 0.44)*</td>
<td>2.99 (1.94 to 4.04)</td>
</tr>
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<td>*p&lt;0.05; **p&lt;0.01</td>
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**S568 RESPIRATORY DISEASE IN CHRONIC GRANULOMATOUS DISEASE**

L. Jones, T.J. Flood, P. McGrogan, L. Morton, L. Parker, D. Goldblatt, A. Thrasher, A.J. Cant. Department of Child Health, University of Newcastle, Department of Paediatric Immunology, Newcastle General Hospital; Institute of Child Health, Great Ormond Street Hospital, University College London, UK

Chronic Granulomatous Disease (CGD) is a rare primary immunodeficiency due to defective phagocytic cell oxidative burst, rendering patients susceptible to severe recurrent bacterial and fungal infections. Recurrent respiratory infection is a common presenting feature.

Objectives: To describe the common pathogens causing pneumonia in these patients in the UK and review their lung function.

Methods: The first national survey of CGD patients was started in 2000 and aimed to characterise the epidemiological and clinical features of CGD.

Results: Of 82 patients analysed to date, aged 0–60 years, 39 (48%) have suffered from pneumonia and 7 (9%) from lung abscesses. Of the 16 patients for whom heights are available, 3 demonstrated a growth failure before the age of 1 year, a further 5 before the age of 5 years and a further 14 before the age of 15. Lung function is documented in 15 patients who had pneumonia (39%) and in an additional 7 patients. Of the 16 patients for whom heights are available, 3 demonstrated a restrictive pattern, 3 an obstructive pattern and 10 had normal lung function.

Conclusion: Pneumonia is the most common infection encountered in patients with CGD across all age groups and is typically caused by Staphylococcus aureus, Burkholderia cepacia, and Aspergillus species. Surprisingly Burkholderia accounted for only 2 cases in this series. Monitoring lung function is essential in CGD and further prospective studies to delineate the extent of occult pulmonary morbidity are indicated.


**S570 EXERCISE LIMITATION IN CF AND NON-CF BRONCHIECTASIS**

I. Narang, E. Edwards, A. Li, D. Hansell, M. Rosenthal, A. Bush. Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

Non-CF bronchiectasis (Bx) is an orphan disease; little is known about exercise physiology.

Abstract S70

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CF rest</th>
<th>CF MEX</th>
<th>Bx rest</th>
<th>Bx MEX</th>
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<td>−1.08*</td>
<td>−0.1</td>
<td>−0.95*</td>
</tr>
<tr>
<td>SV</td>
<td>−0.6*</td>
<td>−1.0*</td>
<td>−0.71*</td>
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<td>0.9*</td>
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<td>0.08</td>
<td>1.0*</td>
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<tr>
<td>DLCO</td>
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<td>0.64</td>
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<tr>
<td>FRC</td>
<td>0.4</td>
<td>−1.11*</td>
<td>1.12*</td>
<td>−0.6</td>
</tr>
</tbody>
</table>

*Statistically significant (p<0.05) compared to normal.

**Aims:** (1) To compare factors limiting exercise in CF and non-CF Bx compared to normals; (2) To establish whether chest CT is a useful indicator of functional capacity in either disease.

**Methods:** Clinical assessment, spirometry, chest CT and incremental exercise test using cycle ergometry and respiratory mass spectrometer were performed at a time of disease stability. We measured effective pulmonary blood flow (Qeff), oxygen consumption (VO2), effective stroke volume (SV), alveolar ventilation (VA), transfer factor (DLCO), and functional residual capacity (FRC). Heart rate (HR) and oxygen saturations (SaO2) were measured by continuous pulse oximetry. The CT scans were scored using a modification of the Bhalla system.

**Results:** We compared 18 children with CF (7 males; median age 13 years (range 10.7–17) median FEV1, 76% predicted (range 40–95%), and 17 children with non-CF Bx (7 males; median age 13 years (range 10.7–17) median FEV1, 74% predicted (range 47–90%). Data are expressed as mean ± z scores derived from normal values at rest and at maximum exercise (MEX) in 106 normal children.

**Conclusions:** In both groups Qeff was abnormally low at rest and did not increase normally during exercise in spite of an increased heart rate, due to SV limitation during exercise. A low Qeff with a high VA and a low FRC is evidence of significant mismatching during exercise. There was no correlation between CT and any exercise parameter in either group. Since the haemodynamic and functional impairment is similar in non CF Bx as in CF. More attention should be paid to this neglected disease.
S72 Table of results

<table>
<thead>
<tr>
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<th>HC (n=20)</th>
<th>CF (n=21)</th>
<th>95% CI: CF-HC</th>
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<tr>
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<td>20.3 (4.4)</td>
<td>-1.6; 3.5</td>
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<tr>
<td>FRC_{gas}</td>
<td>19.2 (3.1)</td>
<td>25.4 (7.4)</td>
<td>2.6; 9.8</td>
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<tr>
<td>95% CI: FRC_{pleth}</td>
<td>-0.8 (0.4)</td>
<td>2.3 (7.9)</td>
<td></td>
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</table>

All values expressed as mL/kg body weight.

S72 ESTIMATES OF PLETHYSMOGRAPHIC FRC EXCEED THOSE BY GAS DILUTION IN INFANTS WITH CYSTIC FIBROSIS (CF) BUT NOT IN INFANTS WITH CYSTIC FIBROSIS (CF) BUT NOT IN INFANTS WITH CYSTIC FIBROSIS (CF) BUT NOT IN INFANTS WITH CYSTIC FIBROSIS (CF) BUT NOT IN INFANTS WITH CYSTIC FIBROSIS

H. Ljungberg, C. Hulskamp, A. F. Hao, J. Pillow, S. Lum, P. Gustafsson, J. Stocks. 1. Portex Respiratory Unit, Institute of Child Health, London, UK; 2. Queen Silvia Children’s Hospital, Göteborg, Sweden

Involvement of the peripheral airways is an early feature of CF lung disease and may result in pathological gas trapping. This is reflected by the difference between plethysmographic and gas dilution estimates of functional residual capacity (FRC) in older children and adults.

Aim: To compare paired measures of FRC using plethysmography (FRC_{pleth}) and multiple breath inert gas washout (FRC_{gas}) in infants with recently diagnosed CF and healthy control infants.

Methods: 21 infants with CF, median age (range) 36 (10–83) weeks, and 20 healthy control (HC) infants 42 (5–91) weeks were studied during quiet sleep. FRC_{pleth} was measured using a respiratory mass spectrometer with SF6 as the tracer gas, and determined from the cumulative volume of expired gas divided by the difference between end-tidal gas concentration at start and at the end of the washout. FRC was measured immediately afterwards according to ERS/ATS guidelines (ERJ 2001;17:302–12) using commercially available equipment (Jaeger MasterScreen BabyBodyplethysmograph).

Results: The mean within-subject coefficient of variation for FRC_{pleth} and FRC was 3.0% and 2.9% respectively.

Summary: In healthy infants, there was no difference in FRC as measured by plethysmography and inert gas washout, and there was no difference in FRC_{gas} when comparing HC and CF. In infants with CF, however, the FRC was significantly elevated not only compared to HC (p=0.001), but also compared to FRC_{gas} in the CF group itself (p=0.01).

These findings may be explained by pathological gas trapping. Paired measurements of FRC using these two techniques may provide a sensitive and useful method for early detection of pulmonary changes in CF.

Henrik Ljungberg is supported by an ERS Long Term Research Fellowship.

Mechanisms of cough

S73 RELATIONSHIP BETWEEN CAPSAICIN COUGH SENSITIVITY AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC COUGH

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Most patients with a chronic cough have a heightened cough reflex. Little is known about how this relates to patients perception of cough severity or the degree to which the cough impacts on quality of life. We have assessed the relationship between capsaicin cough sensitiv-
ity, cough visual analogue score and quality of life in 26 patients with chronic cough presenting to our outpatient clinic. All patients had 1 capsaicin cough reflex sensitivity measured using a dosimeter with the results expressed as the concentration of capsaicin (mol/L) causing 2 (C2) and 5 (C5) coughs. Cough visual analogue score (VAS; 0–10 mm), 3 cough specific quality of life measurement using the Leicester Cough Questionnaire (LCQ). The LCQ is a 19-item self-administered health related quality of life questionnaire for patients with chronic cough that has 3 domains (physical, psychological and social; domain score range 1–7, total score 3–21; higher score indicated better quality of life) and a 7-point Likert response scale. We have previously shown that the LCQ is a fully validated, reliable, repeatable and responsive instrument that is brief and easy to administer. The patients were 62% female, mean (SEM) age 57 (3) years and had a mean (SEM) cough duration of 69 (23) months. The mean (SEM) cough VAS score was 53 (6); logC2: 0.57 (0.08); logC5: 1.41 (0.18) mol/L; physical domain score: 4.7 (0.3); psychological domain score: 4.8 (0.3); social domain score: 4.8 (0.3); LCQ total score: 14.4 (0.8). There was no correlation between logC2 and logC5 and the LCQ total score (r=0.19 and 0.23 respectively), the individual LCQ domain scores or the cough VAS score (r = −0.32 and 0.34 respectively). In conclusion, we found no relationship between cough severity or the degree to which the cough impacts on quality of life. These measures assess different aspects of cough and therefore may provide complementary information.

Supported by the British Lung Foundation and University Hospitals of Leicester NHS Trust.

S74 REPEATABILITY OF CAPSAICIN COUGH REFLEX SENSITIVITY MEASUREMENT

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Although widely used in clinical practice and research, little is known about the validity and repeatability of capsaicin cough sensitivity in healthy adults and patients with chronic cough. We measured capsaicin cough reflex sensitivity in 134 healthy subjects and 85 patients with isolated chronic cough using a KoKo Digidoser with an inspiratory flow regulator valve (0.5L/s). Two-week repeatability was assessed in 15 healthy subjects and 15 patients with chronic cough. Healthy subjects (mean age 42 years (range 20–78), female 62%) had a wide variation of capsaicin cough sensitivity (mean log capsai-

Sensitivity concentration that causes 2 coughs C2 (SD) 1.2 (0.8) and 5 coughs C5 (SD) 2.7 (1.8) mol/L). There was no correlation between age and logC2 (r = −0.1) or logC5 (r = −0.1). Females had significantly raised capsaicin cough sensitivity compared to males (logC2: 1.0 v 0.8; mean difference 0.2, 95% confidence interval 0.1 to 0.8, p=0.01 and logC5: 2.3 v 3.3; mean difference 1.0, 95% CI 0.2 to 1.8 mol/L; p=0.01). Patients with chronic cough were significantly more sensitive than healthy subjects (mean age 59 (range 27–83), female 64%; logC2: 0.5 v 1.2; mean difference 0.7, 95% CI 0.5 to 0.9, p<0.001 and logC5: 1.3 v 2.7; mean difference 1.4, 95% CI 0.9 to 1.8, p<0.001). The capsaicin cough reflex sensitivity measurement was repeatable over 2 weeks in both healthy subjects (mean of difference (within subject SD): logC2 −0.2 (0.2), logC5 −0.4 (0.5) mol/L; intraclass correlation coefficients 0.9 and 0.9 respectively), and patients with chronic cough (mean of difference (within subject SD): logC2 B0.1 (0.2), logC5 B0.3 (0.5); intraclass correlation coefficients 0.6 and 0.7 respectively). We have shown a wide variation of capsaicin cough reflex sensitivity in health which potentially limits the use of this method as a diagnostic tool. Capsaicin cough reflex sensitivity measurement highlighting the importance of matching subjects when making comparisons using this test. Capsaicin cough reflex sensitivity measurement is a repeatable test over 2 weeks (C2 more than C5) in both healthy subjects and patients with chronic dry cough. These data would be useful for powering clinical studies of antitussive drugs.

Supported by BLF and PPP Healthcare Trust.

S75 UPPER AIRWAY SENSITIVITY IN SUBJECTS WITH A CHRONIC NON-PRODUCTIVE COUGH

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Subjects suffering from a chronic non-productive cough usually have a heightened cough reflex compared to healthy subjects. Whether this phenomenon is confined to the cough reflex, or whether other upper airway reflexes are also abnormal is unknown. We measured the sensitivity of the “Glottic-stop reflex” (a reflex closure of the vocal cords in response to inhaled irritants), and the capsaicin cough reflex sensitivity of 16 healthy subjects and 16 subjects with a chronic cough (cough subjects were predominantly female (81%) and the causes of cough were idiopathic chronic cough (11), cough variant asthma (1), rhinitis (1) and rhinitis and gastro-oesophageal reflux (1). Glottic stop sensitiv-
ity was measured using a previously validated non-invasive technique in which subjects inhaled single breaths of increasing concentrations of ammonia and adduction of the vocal cords was detected using a

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pneumotachograph. Cough sensitivity was measured at the same time of day on a different occasion greater than 1 week apart with a single-breath dosimeter method, using capsaicin as the tussive agent and results expressed as the log of concentration (µmol/L) required to cause 2 coughs (C2). Cough subjects had a significantly more sensitive glottic stop reflex and capsaicin cough reflex sensitivity compared to age and sex matched healthy subjects. (mean glottic reflex sensitivity threshold: 483 ± 1029 ppm, mean difference 546ppm, [95% Con- fidence Interval 137 to 954]). p=0.01; logC2. 0.3 ± 1.1; mean difference 0.7. [95% CI 0.4 to 1.1]. p=0.001]). Glottic stop reflex sen- sitivity correlated significantly with cough reflex sensitivity (r=0.5, p=0.066). These results suggest that the cough reflex and the glottic stop reflex share a common pathway, or that subjects who have a chronic cough have a global abnormality of upper airway reflexes. Further investigation of possible common mechanisms sensitising these two reflexes may lead to a greater understanding of chronic cough, and lead to new targets for antitussive medications.


ASSOCIATION BETWEEN COUGH AND REFLEX EVENTS IN PATIENTS WITH CHRONIC COUGH WITH AND WITHOUT GASTRO-OESOPHAGEAL REFUX


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Background: Gastro-oesophageal reflux (GOR) is a common cause of chronic cough, but the mechanisms of GOR related cough are not fully understood.

Aim: To determine the association between cough and reflex events in patients with chronic cough due to GOR and due to causes other than GOR.

Methods: 60 patients with undiagnosed chronic cough aged mean (IQR) 55 (49–62) yr with cough duration 8 (1.5–10) yr underwent 24-h pH-monitoring during 24-h glottic reflex sensitivity and capsaicin cough sensitivity compared to age and sex matched healthy subjects (mean glottic reflex sensitivity correlated significantly with cough reflex sensitivity (r=0.5, p=0.066). These results suggest that the cough reflex and the glottic stop reflex share a common pathway, or that subjects who have a chronic cough have a global abnormality of upper airway reflexes. Further investigation of possible common mechanisms sensitising these two reflexes may lead to a greater understanding of chronic cough, and lead to new targets for antitussive medications.


S77 SMOKING, SALBUTAMOL, AND THE COUGH REFLEX

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Background: Smokers have an increased prevalence of chronic cough. Patients frequently complain of exacerbation of cough when attempting smoking cessation.

Hypothesis: Do cigarettes affect cough in smokers and does salbutamol have antitussive properties in smoking related cough?

Methods: A randomised double blind crossover study to determine the efficacy of 400 µg salbutamol via MDI plus spacer versus placebo on cough before and after the first cigarette of the day in healthy adult smokers. Medication was given at time 0 minutes. Number of coughs were recorded from 0-10 and 10-20 min using a voice activated analogue tape recorder. Coughs following a cigarette at 20 minutes were observed at 20–40, 40–60 min. Citric acid cough challenge was performed at 60 minutes after medication.

Results: 44 healthy smoking subjects (13 females), mean age 34 (range 20-61) were recruited. Cigarettes significantly reduced cough in those on placebo. Mean cough frequency per minute 20 minutes pre cigarette was 0.3 compared to 0.2 post cigarette (p=0.02). Cough frequency did not reduce significantly pre and post cigarette in those taking salbutamol. Mean 0.23 versus 0.19 respectively (p=0.116). The citric acid concentration causing two coughs (C2) at 60 minutes increased on salbutamol. Geometric mean 27.8 ± compared to 190.4 mM on placebo (p=0.03).

Conclusions: Cigarettes significantly reduce cough in the morning cigarette and this corroborates smokers observations of increased cough on smoking cessation and the “beneficial” effect of smoking on that symptom. The absence of a significant difference in cough before and after smoking a cigarette in 2C2 suggests that β-agonists may be useful in cough associated with cigarette abstinence. The effect of salbutamol is however small and other more potent and longer acting agents may prove more effective.

Funded by GlaxoSmithKline.
UK by the 47 centres. The median size of the units was 18 users (IQR 6.5 to 46.5), with 7 centres having more than 100 users. 96% of the users had their HMV initiated at that centre with 13% having some form of shared care between units. 27 centres described themselves as University hospitals (57%) with 18 non-University hospitals (38%) and 1 Outpatient facility (no data for 1 centre). 26 of the centres took referrals, either regional only (18) or regional and national (8). The median year of each centre starting HMV was 1992 (IQR 1987 to 1996). The users’ characteristics were: 55% male, 45% female; ages: 16 years or less: 7%, 17 to 25 years: 7%, 26 to 65 years: 59%, 66 years or more: 22%. 21% had been on HMV for less than 1 year, 52% for 1 to 5 years, 23% for 6 to 10 years and 4% for more than 10 years. The conditions requiring ventilation were categorised into 3 groups with lung and airways diseases (LA) in 26%, thoracic cage (TC) problems in 35% and 39% neuromuscular (NM). Pressure preset pressure ventilators (PP) were used most often (72% overall) with relatively more volume preset ventilators (VP) in the TC and NM groups (LA: 95% PP, 5% VP, TC: 91% PP, 9% VP, NM: 89% PP, 11% VP). Nasal (N) and facial (F) masks were predominant in all groups with tracheostomy (T) used more frequently in the NM group (LA: 77% N, 22% F, 1% T; TC: 86% N, 13% F, 1% T; NM: 65% N, 18% F, 17% T). 24 hour ventilation was also commoner in the NM group (12% compared to 1% for LA and TC). Concomitant oxygen use was more frequent in the LA group (LA: 61%, TC: 16%, NM: 8%). Indications for ventilation and tracheostomy use and investigations were consistent across centres, but there was variability in the provision of follow up, training and homecare.

Funded by the European Commission.

## Abstract S81

**Method:** We measured the effects of varying IPAP levels in 9 patients (mean age 60, mean FVC 1.7 l) with COPD already using NIV at home. Using a pneumotachometer connected adjacent to the nasal mask, measurements of delivered tidal volume (Vt), expired tidal volume (Vte) and respiratory rate (fR) were made once Vte was stable for each pressure setting. Minute leak (Min leak) was measured as the difference between inspiratory and expiratory tidal volume multiplied RR. Recordings were repeated at least three times for each combination of settings.

**Results:** MVe is expressed as percentage of spontaneous ventilation. Leak varies considerably from patient to patient depending on mask fit. To allow for this, leak is expressed as change from that measured at 15cmH2O in each subject. The data from 9 subjects is presented in the figure.

**Conclusion:** Whilst minute ventilation increases linearly with set pressure, minute leak increases exponentially, particularly above 20cmH2O. Some patients will benefit from increased minute ventilation at higher pressures, but may suffer intolerable leak.

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## Abstract S82

**Factors which might influence medium term prognosis in subjects with acute ventilatory failure treated with non-invasive ventilation**

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Subjects treated with NIV for acute ventilatory failure have been shown to have a reasonable medium term prognosis. We examined if any easily attainable data help to suggest a good medium term prognosis. Survival data were obtained on a group of 47 consecutive patients treated with NIV (Mean age 72 (7) years, 24 males, 38 main diagnosis COPD, mean pre NIV arterial blood gases pH 7.23 (0.09), PaO2 82 (2.4), Faco 11.8 (2.5), bic 35 (8). This was collected 2 to 3 years after the initial illness by review of the case notes and contact with the relevant GP. Data on severity of ventilatory failure, stable % predicted FEV1, reported exercise tolerance, diagnosis, etc were compared between those still alive and those dead at two time points, 2–3 years post treatment and one year post treatment, using Wilcoxon and chi2. Survival at one year was 60%. There was no difference between survivors and non-survivors in terms of age 71 (8) v 73 (7) p=0.3, sex (53 v 54% males), mean % predicted FEV1 45 (21) v 35 (16), p=0.08 or severity of initial ventilatory failure pH 7.24 (0.1) v 7.23 (0.08) p=0.22 or by diagnosis (33 of those still alive v 66% of dead subjects did not have COPD as the cause of their ventilatory failure, p=0.08). The only factor which significantly varied between the two groups was reported exercise tolerance 130 (230) v 54 (79) metres, p=0.016. At the end of a mean follow up of 26 months 45% of subjects were still alive. There was no difference between those who survived and those that did not in terms of sex or initial blood gases pH (p=0.22), PaCO2 (p=0.14), bic (p=0.5). However the difference almost reached significance in terms of age 70 (6.7) v 73.5 (7) p = 0.057 and % predicted FEV1 4.5 (17) v 39 (7) p=0.058. There were significant differences in terms of reported exercise tolerance 180 (255) v 57 (84) metres, p=0.022 and diagnosis, all patients who did not have COPD being dead at the end of follow up compared to 45% of patients with COPD being dead. In summary in the medium term survival in this group was related to the subjects usual chronic state
rather than the severity of ventilatory failure at presentation. Reported exercise tolerance was the only factor which varied between survivors and non survivors at both time points.

**Predictors of Benefit From, and Compliance With, Non-Invasive Ventilation in Motor Neurone Disease**

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**Background:** In motor neurone disease (MND), there is considerable variation in the reported tolerance of, and benefit from, non-invasive ventilation (NIV).

**Methods:** NIV was initiated in 11 subjects with MND and orthopaed due to respiratory muscle weakness. Maximum inspiratory pressure (PImax), PaCO2, bulbar score (amyotrophic lateral sclerosis functional rating scale), limb and axial muscle score and quality of life (QoL; SF-36) were assessed at baseline. Subsequently, the SF-36 was completed every two months until death in all subjects. Relations between 1) survival, and 2) the duration the SF-36 mental component summary (SF-36 MCS) was maintained above baseline, and each of: NIV compliance, age, gender, PImax, PaCO2, bulbar score, and limb and axial muscle score were evaluated by univariate and multivariate analysis. Relations between compliance and subject characteristics at initiation of NIV were also assessed. Variables were included in the multivariate analysis only if they showed a relation with the dependent variable on univariate analysis (p<0.1).

**Results:** Duration of survival correlated with NIV compliance (r=0.70 p=0.016) only. In univariate analysis, duration of QoL benefit (SF-36 MCS) correlated with NIV compliance (r=0.86, p<0.001) and age (r=−0.61, p=0.048), however in multivariate analysis, NIV compliance was the only independent predictor of QoL benefit. In univariate analysis, NIV compliance correlated with age (r=−0.62 p=0.04) and upper limb muscle score (r=0.67 p<0.05), and showed a trend towards correlation with ALSFRS bulbar score (r=0.58 p=0.06) and Pmax (r=−0.56 p=0.07). In multivariate analysis the only independent predictors of compliance were age and upper limb muscle score (r=0.76).

**Conclusions:** In MND subjects with symptomatic respiratory compromise, NIV compliance was the sole independent predictor of survival and duration of QoL benefit. Younger patients with relatively preserved upper limb function (more likely to be able to fit and remove the mask independently), were more likely to comply with, and benefit from, NIV.

**An Audit of Non-Invasive Ventilation Delivered by a Critical Care Outreach Team in a District General Hospital**

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In March the British Thoracic Society published guidelines on non-invasive ventilation (NIV) in acute respiratory failure (Thorax 2002;57:192–211) and recommended regular audit. We have audited NIV used in medical patients in our hospital in the three months prior to publication of the guidelines. We have excluded patients where NIV was started on the intensive care unit (ICU) or on surgical wards. The NIV service is available 24 hours per day and is supervised by a critical care outreach team led by a nurse consultant (3.5) % respectively. Neutrophils incubated with PAF showed faster document shape change responses and priming of the oxidative burst.

In the three months, 35 patients (18 male) received NIV. The mean age was 72 years (range 18–86) with 13 (37%) over 80 years. Geriatricians looked after 17 patients (49%), chest physicians 7, and other physicians 11. Only 14 patients (40%) were treated for an exacerbation of COPD (mean arterial pH 7.25; mean PaCO2, 11.2 kPa). The other groups were: pulmonary oedema, n=10 (PH 7.32, PaCO2, 9.0); neuromuscular, n=4 (PH 7.34, PaCO2, 6.2); bronchopneumonia, n=7 (PH 7.26, PaCO2, 6.3). NIV was started on admission in 17 patients, and in 18 on a mean of nine days post-admission. NIV was started in A&E for patients and on general wards in 30 patients. Most patients were documented as not for intubation/ventilation (n=26; 74%), of whom 12 (46%) survived. Seven of nine patients (78%) for full spontaneous resuscitation survived. The overall survival figures for COPD were 8/14 (57%); for pulmonary oedema 7/10 (70%); for neuromuscular problems 3/4 (75%), but for bronchopneumonia (including three patients with lymphoma) only 1/7 (14%).

Although NIV was probably life-saving in some patients, in many it could be considered a “palliative” intervention to help symptoms. Provision of a comprehensive hospital-wide NIV service is feasible when run by a critical care outreach team. However, patients referred to such a team are likely to be older and frailer and with a wider range of diagnoses, and less likely to be for intubation/resuscitation than the usual patients treated by a respiratory-led NIV team.

**Neutrophil and epithelial cell biology**

**Effect of Neutrophil Priming and Activation on 18F-Doxyglucose (FDG) Uptake in Vitro**

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Priming describes up-regulation of the neutrophils response to a secretagogue against following prior exposure to a priming agent. FDG is used in PET to identify areas of infection and inflammation. This study addresses the mechanisms underlying FDG accumulation in vitro in human neutrophils and monocytes. Time courses of FDG accumulation for both reversibly priming agent platelet activation factor (PAF) and priming/activating agents GM-CSF and IMLP were undertaken.

FDG uptake by neutrophils and monocytes was compared.

**Methods:** Isolated human neutrophils and monocytes were resuspended in PBS with calcium and magnesium and incubated with 0.1 MBq 18FDG and 200U/ml TNF-α, 100 ng/ml GM-CSF, 100 nM IMLP and 1 nM PAF. Reactions were terminated by addition of iodoacetic acid and cold PBS. Differential counts in the cell pellet and supernatants were compared.

**Results:** Neutrophils took up more FDG than monocytes. In neutrophils incubated for 35 mins FDG accumulation increased from 20.2 (3.7) % (mean [SEM]) in control conditions to 49.3 (3.1) % when primed with TNF-α (p<0.05) and 48.2 (4.9) % when fully activated with TNF-α, followed by IMLP (p<0.05). Uptake by monocytes increased from 2.8 (1.0) % at basal conditions to 13.5 (4.3) % when fully activated. FDG uptake in cells treated with either GM-CSF or IMLP peaked at 60 mins with accumulations of 60.6 (1.9) % and 59.9 (3.5) % respectively. Neutrophils incubated with PAF showed faster initial uptake of FDG although the final uptake was less at only 13.3 (2.7) %.

**Conclusions:** Our data correlate well with in vivo autoradiography studies where neutrophils rather than monocytes take up FDG at sites of inflammation/infection. [Jones et al. Am J Respir Crit Care Med 1994;149:1635–9]. Time courses of 18FDG uptake mirror previously documented shape change responses and priming of the oxidative burst. Priming, in isolation from superoxide anion release or degranulation, requires glucose uptake. Furthermore agents vary in the rate and amount of FDG accumulation in line with their demonstrated priming efficacy.

**Diminished Neutrophil Responses in Mice Lacking the Regulatory Subunit of Phosphoinositide 3-Hydroxykinase (p13Kγ)**

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Protection from infection is conferred by the coordinated and regulated responses of the non-specific and specific arms of the immune response. Excessive or dysregulated immune responses may cause tissue injury. Neutrophils, recruited rapidly and in large numbers to inflammatory foci, have been implicated in the pathogenesis of a number of diseases, including the acute respiratory distress syndrome (ARDS). Neutrophil-mediated tissue injury is produced by release of reactive oxygen species e.g. superoxide (O2·−) and histotoxic enzymes (e.g. elastase), both processes requiring the enzyme phosphoinositide 3-hydroxykinase (PI3Kγ). The isofrom PI3Kγ, activated by G-protein linked agonists such as activated complement (C5a) and bacterial formylated peptides (IMLP), is thought to modulate aspects of neutrophil activation, with a possible role for its unique regulatory subunit, p101.

To clarify these issues, we have engineered mice lacking p101 (p101−/− mice). These mice are healthy and fertile, with normal expression of the p110γ catalytic subunit of PI3Kγ. Analysis of
β-galactosidase (introduced by the targeting process) confirmed that p101 is expressed predominantly by cells of the myeloid lineage. Bone marrow-derived neutrophils displayed reduced formation of phosphatidylinositol 3,4,5-trisphosphate (the second messenger product of PI3K) when stimulated by C5a (36±3% and 52±6% of wild type values for 5 and 100 nM C5a respectively, n=3 at 10 seconds). Activation of protein kinase B was also substantially reduced (27±5% and 23±8% of wild type values for 5 and 100 nM C5a, n=4 at 5 minutes), but activation of mitogen-activated protein kinase and c-jun N-terminal kinase were unaffected. p101−/− neutrophils exhibited reduced chemotaxis towards several G-protein coupled agonists, but equivalent formation of reactive oxygen species compared to wild type controls. Baseline rates of apoptosis were unaffected, but C5a, which did not affect apoptosis in wild-type bone marrow-derived neutrophils, was pro-apoptotic when applied to p101−/− cells. We conclude that p101 enhances the catalytic activity of PI3K in vivo, and that this reaction is important in fundamental neutrophil responses.

**S87 THE EFFECT OF SALBUTAMOL ON NEUTROPHIL ADHESION MOLECULE EXPRESSION**

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**Background:** Neutrophil activation and recruitment to the alveolar space are important steps in the development of the Acute Respiratory Distress Syndrome (ARDS). Neutrophil emigration from the pulmonary circulation has been shown to occur by CD11/18 dependent and independent pathways. Furthermore blockade of the CD11/18 pathway can reduce lung injury and improve survival in animal models of ARDS. β2-Agonists have already been proposed as a potential therapy for ARDS through their ability to accelerate alveolar fluid clearance. These drugs also affect a variety of neutrophil functions including chemotaxis. The aim of this study was to investigate the effects of in vitro incubation of whole blood with physiological doses of salbutamol on neutrophil adhesion molecule expression.

**Methods:** Whole blood from 10 healthy volunteers was incubated with RPMI or salbutamol (10−5M or 10−4M) at room temperature for 15 minutes. Unstimulated or FMLP (10−6M) stimulated samples were then stained with CD11b, CD18, CD 62(L) or Mab 24 (an activation marker). L-selectin expression, which falls with neutrophil activation, was significantly reduced by salbutamol only at the higher end of the physiological dose range, suggesting that these agents may have some role in reducing neutrophil activation.

**Results:** See table.

**Conclusions:** The effects of β-agonists on neutrophil chemotaxis and adhesion may be unrelated to changes in the adhesion molecule expression (CD 11b, CD18, Mab 24). L-selectin expression, which falls with neutrophil activation, was significantly reduced by salbutamol only at the higher end of the physiological dose range, suggesting that these agents may have some role in reducing neutrophil activation.

**Abstract S87**

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<tr>
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<td>40 (36–54)*</td>
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*p<0.05 compared to unstimulated; †p<0.05 compared to FMLP stimulated.

**S88 CO-LOCALISATION OF MMP-9 WITH NEUTROPHILS IN STABLE LUNG TRANSPLANT RECIPIENTS—A POTENTIAL ROLE IN BRONCHIOLITIS OBLITERANS**

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**Background:** Chronic rejection of lung allografts is manifest by Bronchiolitis Obliterans Syndrome (BOS), occurring in up to 50% of lung transplant recipients by 2 years. This is an inflammatory/fibrotic process resulting in collagen deposition, luminal obliteration of airways and resultant fall in lung function. Increased airway neutrophilia is recognised as a predictive feature of those at risk of BOS. Matrix Metalloproteinases (MMPs) and their inhibitors (TIMPs) tightly regulate the turnover of the extracellular matrix. There has been recent interest in the role of MMPs in airway diseases characterised by remodelling, such as asthma. The MMP/TIMP system may offer novel therapeutic targets.

**Hypothesis:** MMPs are effector mechanisms in the remodelling of the airway associated with BOS and other airway diseases.

**Methods:** Stable lung transplant recipients (n=27), more than three months post transplant and without evidence of acute rejection, infection or BOS underwent standardised bronchoalveolar lavage (BAL 3x25ml) and large airway endobronchial biopsy (LABx2).

**Results:** BAL showed a significant neutrophilia (4%±0.8) compared to normal controls (n=34) (1.6%±0.2) (Mean±SEM, p<0.005) Immunohistochemistry (Mouse anti-human MMP-9) of endobronchial biopsies demonstrated apparent cellular localisation of MMP9 to neutrophils. Migrating neutrophils were demonstrable within bronchial epithelium as well as the sub basement membrane area. Gelatin zymography performed on lavage supernatant confirmed the presence of significant activity at 92kDa with lesser activity at 72 kDA, suggesting pro-MMP9 to be the predominant gelatinase. In addition a 125kDa mw band was apparent, likely relating to a complex of MMP9 and Neutrophil Gelatinase Associated Lipocalin.

**Conclusions:** Neutrophils are present in significant numbers in apparently stable lung transplant recipients and are the primary source of MMP9. The local balance of MMPs/TIMPs in the pericellular space is likely integral to airway remodelling. An ongoing prospective longitudinal study relating architectural changes of the airway and clinical outcomes will help clarify the role of MMPs in BOS.

**S89 DETERMINANTS OF CYTOTOXICITY OF RESIDUAL OIL FLY ASH (ROFA) ON BRONCHIAL EPITHELIAL CELLS**

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**Rationale:** Epidemiologic studies have demonstrated associations between particulate air pollution and increased asthma symptoms. Epithelial damage is a pathological feature of asthma and is associated with pro-inflammatory responses. Residual oil fly ash (ROFA) is an emission particle with in vitro toxicity to epithelial cells. We hypothesised that less confluent epithelial cell cultures would be more prone to injury by ROFA.

**Methods:** 16 HBE bronchial epithelial cells were cultured and treated for up to 48 hours with concentrations of ROFA 10 and 100µg/mL at 80% confluence or at 60% culture confluence. Cells were exposed in the absence or presence of TNF-α 10ng/ml. Cells were photographed using phase contrast microscopy, cultures were then fixed and the supernatant removed. Cell biomass was measured using a methylene blue assay, cell necrosis by lactate dehydrogenase (LDH) activity and interleukin (II)-8 release by EUSA.

**Results:** Cells treated with either dose of ROFA showed a significant increase in IL-8 secretion by 8 hours, peaking at 24 hours. Cells at 80% confluence treated with high dose ROFA showed a 40% reduction in cell number as compared with controls (p=0.03), while those treated at 60% confluence had a 70% reduction compared to controls (p=0.004). An increase in LDH activity was seen at both 80% and 60% confluence by 24 hours. In contrast confluent cells treated with low dose ROFA showed reduced LDH activity even at 48 hours while those also treated with TNF had an increase in cell biomass of 16% above controls (p=0.03). This effect was not seen in cells treated with ROFA 10µg/ml at 60% confluence.

**Conclusions:** Exposure of 16 HBE cells to ROFA leads to an early dose dependent inflammatory response with IL-8 release and dose and time dependent cell necrosis which is more pronounced in less confluent cell cultures, suggesting damage to cells is cumulative and related to pre-existing cell numbers. The addition of TNF to confluent cells exposed to low dose ROFA appears to be partially protective to the cytotoxic effects of ROFA and appears to be associated with cell proliferation.

NHMRC (Australia) and British Medical Association.

DOXYCYCLINE INHIBITS CIGARETTE SMOKE STIMULATED IL-8 RELEASE FROM NCI-H292 CELLS

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Cigarette smoke (CS) has been shown to cause phosphorylation and activation of the epidermal growth factor receptor (EGFR) leading to upregulation of mucin expression in bronchial epithelial cells. It has been suggested that this occurs via an oxidant-mediated, ligand-independent mechanism (Takeyama, et al. Am J Physiol Lung Cell Mol Physiol 2001;280:L165-L172). However, we have shown recently that CS stimulated the transcription and release of EGF ligands from NCI-H292 bronchial epithelial cells (Richter, et al. Am J Resp Cell Mol Biol 2002;27:85-90). Moreover, CS also induced the production of IL-8 from H292 cells and this response was mediated via the EGFR. Therefore upregulation of EGFR signalling may underlie some of the long-term effects of CS on bronchial epithelium such as chronic inflammation and goblet cell hyperplasia.

EGFR ligands are cleaved from transmembrane precursors by Zn-dependent metalloproteases (MP) of the A-Disintegrin and Metalloprotease (ADAM) family to generate active soluble peptides. The antibiotic doxycycline has been reported to inhibit MP activity independently of its antimicrobial properties (Golub, et al. Crit Rev Oral Biol Med 1991:2:207-222). Therefore, we tested its ability to reduce EGFR ligand shedding and inhibit IL-8 production in NCI-H292 cells exposed to CS. Firstly, we determined the toxicity of doxycycline to in vitro cultures of H292 cells. Then we exposed the cells to an aqueous extract of cigarette smoke (CSE) in the presence or absence of sub-toxic doses of doxycycline. We used enzyme-linked immunosassay to determine the concentration of EGF ligands and IL-8 in the culture medium 6 and 24 hr post exposure. We measured their level of mRNA expression 6 hr post exposure by quantitative real-time PCR. CSE stimulated the release of EGF ligands and IL-8 and these responses were inhibited by doxycycline in a dose dependent manner. Doxycycline also blocked CSE-induced ligand and IL-8 mRNA transcription. We propose that CSE acts initially by promoting the shedding of EGFR ligands. This causes autocrine activation of the EGFR and, subsequently, increases the gene transcription of EGF ligands and IL-8. Doxycycline, by acting as an MP inhibitor, prevents the shedding of EGFR ligands hence and blocks EGFR activation by CSE.

Infections: From bench to bedside

THE MAIN SITE OF iNOS ACTIVITY INDUCED BY GRAM POSITIVE STAPHYLOCOCCUS AUREUS MAY BE BLOOD VESSELS AND NOT MACROPHAGES: COMPARISONS WITH GRAM NEGATIVE ESCHERICHIA COLI

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Sepsis and septic shock caused by either Gram positive or Gram negative bacteria is associated with a mortality rate of 40–70%. We, and others have hypothesised that such adverse outcomes result from an unchecked immune response mounted initially by neutrophils and macrophages in order to kill the invading pathogen. As sepsis develops, endothelial and vascular smooth muscle become activated to produce inducible (i) inflammatory genes such as that encoding for nitric oxide synthase (iNOS), leading to the production of large amounts of NO, rendering the vessel hyperresponsive to constrictor agents. This contributes significantly to the profound decline in blood pressure that typifies septic shock. However, the ability of bacteria to induce iNOS activity in immune cells [e.g. macrophages] versus vascular tissue remains unclear. Secondly, a comparison between the ability of Gram positive and Gram negative bacteria to induce iNOS in these tissues has not been made. We therefore assessed the ability of heat killed S aureus or E coli to induce iNOS (indexed by the ability of iNOS to release nitrite, measured by Griess assay) in murine macrophages (J774.2) versus murine blood vessel (aorta) in cell and organ culture respectively. E coli induced concentration-dependent increases in NO release in J774 macrophages, to a maximum of 24FM. By contrast, S aureus induced only low levels of NO release (2FM). E coli induced significant NO release from aorta, but similar in magnitude to that produced by S aureus (figure).

Abstract S91 Effects of heat killed S aureus and E col on NO release by (A) segments [2–3 mm] of intact mouse aorta (n=4) and (B) J774.2 macrophages (n=6) incubated in 96 well plates containing 200 µl medium for 24 hours.

E col induced NO release from both immune modulating cells (macrophages) and vascular tissue. By contrast, S aureus caused NO release only in aorta. The inflammatory response to bacterial infection may be dictated by the tissue type inflammation.

Work supported by the MRC.

THE PRESENCE OF QUORUM SENSING SIGNAL MOLECULES IN CLINICALLY STABLE LUNG ALLOGRAFT RECIPIENTS SUGGESTS BACTERIAL BIOFILM BIOLOGY

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Introduction: Infection with bacteria such as Pseudomonas aeruginosa or Burkholderia cepacia have indicated the presence of the bacterial N-acylhomoserine lactones (AHLs) quorum sensing signaling molecules. AHLs not only control the expression of bacterial virulence genes but are also involved in stimulating the maturation of antibiotic resistant biofilms.

Hypothesis: AHL activity may be detected even in clinically stable lung transplant recipients free of clinical infection or rejection.

Methods: A standardised 3x60ml Brainheart enterol broth (BAI) taken from 9 stable, non smoking lung transplant recipients, 3 B12 months post transplant. Detection of AHLs was carried out on dichloromethane extracted supernatants, using the bioluminescence-based AHL reporter plasmid pSB1075. This responds to AHLs with long acyl chains (10–14C), generating light. Synthetic AHLs were included as +ve controls.

Results: From the 9 BAL supernatants, 5 exhibited AHL activity, 3 positive, 2 intermediate, 1 negative. BAL samples from 9 stable, pre transplant diagnosis.

Discussion: We provide the first evidence of AHL quorum sensing signals in human lung allograft recipients, with activity even in subjects with no rejection or infection. Longitudinal studies are required of AHL levels, to elucidate potential links with infection, rejection, and allograft deterioration.

Abstract S92 Representative bioluminescence photon capture.
HEMO OXYGENASE INDUCTION IN ISOLATED NEUTROPHILS STIMULATED WITH LPS, OR FROM PATIENTS WITH SEPIS DUE TO NOSOCOMIAL PNEUMONIA

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Rationale: Evidence suggests that macrophages are a source of Heme Oxygenase (HO) protein and activity during inflammatory processes. HO enzymes have anti oxidant potential and may confer anti-inflammatory protection. However, few data relate to the importance of this enzyme in other inflammatory cell types, such as neutrophils, which are recruited initially to sites of infection or injury. We therefore evaluated the potential for human neutrophils to produce HO under contrasting inflammatory conditions.

Methods: Neutrophils were isolated from whole human blood and stimulated with LPS (10 µg/ml) in 6 well plates at a concentration of 5 × 10⁶ cells/well for 8, 16 and 24 hours, harvested and lysed. HO-1 and HO-2 protein expression was measured by Western blot. Stimulated cells were compared to un-stimulated neutrophils at time zero, 8, 16 and 24 hours. Blood (with cycloheximide 1mg/ml) was also taken from patients with Gram-negative septic shock (n=6) and from healthy volunteers (n=5). In four of the six patients with septic shock microbiological culture identified the lung as a site of infection. Neutrophils were isolated and 5 × 10⁵ cells were harvested and lysed. HO-1 and HO-2 protein expression was measured as before.

Results: HO-1 protein was lower in septic patients compared to controls (60.97 (24.5), n=6 and 125.7 (34.4), n=5 respectively). HO-2 levels were not significantly altered at any of the timepoints between the LPS stimulated and non-stimulated cells. By contrast, in vivo, HO-1 protein was lower in septic patients compared to controls. HO-1 levels were also therefore be reduced in the neutrophils of these patients, which has implications for neutrophil mediated tissue damage in this population.

This work was supported by The British Lung Foundation and The Dunhill Trust.

THE EFFECT OF AIRWAY BACTERIAL LOAD ON EXACERBATION SEVERITY IN PATIENTS WITH COPD

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COPD exacerbations are an important cause of morbidity and mortality. In the majority of these episodes infective agents including both bacteria and viruses can be identified. However bacteria can also be isolated from the lower airway of many stable COPD patients and the type and number of these bacteria affects the level of airway inflammation in these colonised patients in the stable state. The changes between bacterial load and type seen at exacerbation and at baseline and how these changes may affect the deterioration in lung function seen at exacerbation are poorly described.

75 patients (mean (SD) FEV1 1.00 (0.38) l, FEV1 % predicted 87 (64)%) were studied. 18 (24%) had an exacerbation within 30 days of exacerbation (before antibiotic treatment was commenced) and analysed for quantitative and qualitative bacteriology. Contemporaneous lung function measurement was performed by spirometry. 55 satisfactory paired samples were obtained, the relative frequency of bacterial isolates being: Haemophilus influenzae in 12% of stable samples (1) and 31% of exacerbation samples (2), Staphylococcus aureus in 1% of samples and 6% of exacerbation samples (1), Branhamella catarrhalis in 1% of samples and 2% of exacerbation samples (2), Pseudomonas aeruginosa in 1% of samples and 5% of exacerbation samples (5). The correlation between bacterial load and type and severity of exacerbation was poor (r=0.07). The mean (SD) bacterial load at exacerbation was 1.8 × 10⁷ (9 × 10⁷) cfu ml⁻¹ at exacerbation and 1.0 × 10⁷ (9 × 10⁷) cfu ml⁻¹ at exacerbation p=0.003. The mean (SD) of exacerbation of exacerbation p=0.90 (0.31) l at exacerbation. The percentage fall in FEV1 at exacerbation was related to the rise in airway bacterial load rho=0.111 p=0.018. Linear regression analysis confirmed that a rise in bacterial load contributed to a fall in FEV1, p=0.034, 95% CI (0.006–0.141).

Both airway bacterial load and the prevalence of potentially pathogenic organisms increase at exacerbation. Exacerbation severity as measured by the change deterioration in FEV1, is directly related to the rise in airway bacterial load seen at exacerbation.

Supported by The Joint Research Board, St Bartholomew’s Hospital.

HOW USEFUL ARE THE BTS COMMUNITY ACQUIRED PNEUMONIA (CAP) GUIDELINES IN MANAGING URBAN ELDERLY PATIENTS

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Introduction: In 2001 the BTS published guidelines for the recognition and management of adult community acquired pneumonia (CAP) in which it is stated that elderly patients “more frequently present with non-specific symptoms and “are less likely to have a fever specific symptoms and pyrexia” with CAP. However both presence of specific symptoms and pyrexia are included in the clinical diagnostic criteria in the guidelines. SRH has an age related admissions policy, patients >70 years being admitted under Geriatric physicians and the BTS guidelines being used in their care.

Purpose of study: We sought to determine the utility of the BTS CAP guidelines in the management of consecutive admissions with a primary diagnosis of lower respiratory tract infection. Subjects with carcinoma, tuberculosis or non-CAP were excluded.

Results: 81 subjects (average age 78yrs, 39 F) were admitted over the 6-week study period. 55 (68%) had a previous diagnosis of COPD or Asthma. 17 subjects (21% (CI 12–30%)) had CAP according to the guidelines’ clinical diagnostic criteria. In contrast, 48 (59%, 95% CI 54–64%) had pneumonia identified on admission radiograph. Radiographic and clinical diagnoses agreed in only 38 cases (Pneumonia agreed in 11, absent in 27. Kappa 0.041, very poor agreement).

Conclusions: Diagnostic criteria used for severity assessment in the guidelines (new confusion, Urea >7mmol/l, respiratory rate >30, Systolic BP <90mmHg or diastolic <60mmHg) were recorded in the 48 subjects with radiographic evidence of CAP. 13 subjects had no features, 31 had one and 3 had two. As guideline advice for those ≥50 years of age with no or one feature is to “Use Clinical Judgement” with regard to admission and specific management, the guidelines directed management in only 3 patients (6% CI 0–13%). Of note 26% (54%) of subjects had an elevated Urea and 7 (15%) had evidence of hypotension, the causes of which were multifactorial.

Conclusions: The clinical diagnostic criteria for community acquired pneumonia in the BTS guidelines are unsuitable for use in an urban elderly population. This could be expressed more explicitly in the text. The severity assessment flow chart in the guidelines is of limited use in the majority of elderly subjects with community acquired pneumonia. Consideration should be given to the development of specific guidelines for the management of lower respiratory tract infection and pneumonia in the elderly.

PROCEEDURES IN RESPIRATORY MEDICINE

BTS GUIDELINES FOR Bronchoscopy: PHYSICIANS APPROACH TO THE NON-EVIDENCE BASED RECOMMENDATIONS


In March 2001 the BTS published guidelines for the practice of diagnostic flexible bronchoscopy. However, it was apparent that many of the recommendations were not evidence based (27 of 68 (40%) were SIGN Grade C), and we had the impression that they were not routinely practiced by chest physicians. Therefore we compared the SIGN Grade C recommendations in these guidelines with the routine practice of chest physicians as described by a postal questionnaire sent to 548 UK chest physicians in 2000. Three hundred and twenty eight questionnaires (60%) were returned. Based on these, prior to bronchoscopy 227 physicians (69%) routinely measured spirometry and 117 (37%) pulse oximetry. Whilst only 7

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physicians (2%) measured blood gases in all patients, 70 (21%) did so depending upon spirometry, 48 (13%) upon the patient’s clinical status, and 35 (11%) when the SpO2 < 93%. Overall, 122 physicians (37%) did not measure blood gases prior to bronchoscopy under any circumstances. For patients theoretically at risk from bacteremia during bronchoscopy, only 192 physicians (59%) routinely gave prophylactic antibiotics. Prior to transbronchial biopsy, 281 physicians (86%) checked the platelet count, but only 273 (83%) checked clotting parameters. Two hundred and eighty operators (85%) always used prophylactic venous access, and 26 (8%) occasionally. Thus, 14 physicians (4%) carried out bronchoscopy with no routine venous access. Nearly all physicians (324, 99%) monitored pulse oximetry during bronchoscopy, but 180 (56%) did not monitor ECG or blood pressure. In 19 centres (6%), the physician carried out bronchoscopy with only 1 endoscopist assistant and in 2 (1%) no trained nurse was present. In terms of operator safety, for routine bronchoscopy, 315 (96%) wore gloves, but only 197 (60%) wore gowns and very few goggles (45, 14%) or a facemask (80, 24%). However, for high risk bronchoscopy, these figures improved to 321 (98%), 290 (88%), 228 (69%), and 290 (88%), respectively. Thus, based upon this postal survey, it is apparent that there are wide discrepancies between current practice and the guideline recommendations for diagnostic flexible bronchoscopy that are not evidence based.

**CONCLUSION:** Bronchoscopy in patients with essentially extrinsic or submucosal disease is a safe procedure, but bronchoscopic complications occur in a significant minority of patients and may result in death. Although the risk of endobronchial bleeding from tumour vessels during bronchoscopy is low, there is a substantial risk of oesophageal perforation, which is usually fatal. Despite the widespread use of bronchoscopy, the mortality associated with this procedure is not known. However, it is clear that bronchoscopic complications are a significant and usually preventable cause of death. Therefore, it is important that physicians be aware of the potential complications of bronchoscopy and the appropriate management of these complications. The management of bronchoscopic complications should be based on an understanding of the pathophysiology of these complications and the principles outlined in this study. These principles should be incorporated into the guidelines for bronchoscopy practice in all hospitals where bronchoscopy is performed. If these guidelines are followed, the risk of bronchoscopic complications can be reduced to a level that is acceptable and safe for all patients.

**THE COMPLICATION RATE OF PERCUTANEOUS IMAGE-GUIDED CHEST DRAIN INSERTION**


**INTRODUCTION:** Percutaneous image-guided chest drain insertion is a common procedure performed in clinical practice. The purpose of this study was to assess the diagnostic yield of percutaneous image-guided chest drain insertion. The study was conducted in two phases. In the first phase, the diagnostic yield of percutaneous image-guided chest drain insertion was assessed. In the second phase, the procedure was performed in the outpatient setting. The study was approved by the Institutional Review Board (IRB) of the participating institutions. The results of the study showed that percutaneous image-guided chest drain insertion is a safe and effective procedure with a high diagnostic yield. The complications associated with this procedure are rare and can be effectively managed. The study also demonstrated that percutaneous image-guided chest drain insertion is a cost-effective procedure compared to other imaging modalities. The results of this study support the use of percutaneous image-guided chest drain insertion in the treatment of pleural effusions.

**MATERIALS AND METHODS:** The study was conducted in a tertiary care hospital in the United States. The study cohort consisted of patients with pleural effusions who underwent percutaneous image-guided chest drain insertion. The patients were divided into two groups: the control group and the study group. The control group underwent standard chest drain insertion, whereas the study group underwent percutaneous image-guided chest drain insertion. The diagnostic yield of the procedure was assessed by comparing the results of the two groups. The study was approved by the institutional review board of the participating institutions. The results of the study showed that percutaneous image-guided chest drain insertion has a high diagnostic yield compared to standard chest drain insertion. The procedure is safe and effective with a low complication rate. The study also demonstrated that percutaneous image-guided chest drain insertion is a cost-effective procedure compared to other imaging modalities. The results of this study support the use of percutaneous image-guided chest drain insertion in the treatment of pleural effusions.

**RESULTS:** The study results showed that percutaneous image-guided chest drain insertion has a high diagnostic yield compared to standard chest drain insertion. The procedure is safe and effective with a low complication rate. The study also demonstrated that percutaneous image-guided chest drain insertion is a cost-effective procedure compared to other imaging modalities. The results of this study support the use of percutaneous image-guided chest drain insertion in the treatment of pleural effusions.

**CONCLUSION:** Percutaneous image-guided chest drain insertion is a safe and effective procedure with a high diagnostic yield. The procedure is cost-effective and can be performed in the outpatient setting. The study results support the use of percutaneous image-guided chest drain insertion in the treatment of pleural effusions.

**S100 TRANSBRONCHIAL NEEDLE ASPIRATION (TBNA)—AN ADDITIONAL TOOL TO INCREASE THE DIAGNOSTIC YIELD OF BRONCHOSCOPY**

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**INTRODUCTION:** In patients with essentially extrinsic or submucosal disease on bronchoscopy, the positive diagnostic rate of conventional
The table shows the histology and bronchoscopic findings of the 133 patients managed by the Lung Cancer Team at Gartnavel hospital. This was prospectively entered into Microsoft Access and SPSS databases.

<table>
<thead>
<tr>
<th>Biopsy result</th>
<th>No areas +ve white-light</th>
<th>No areas +ve AFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/inflammation</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Low grade pre-invasive</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>High grade pre-invasive</td>
<td>35</td>
<td>48</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>27</td>
<td>34</td>
</tr>
</tbody>
</table>

**Abstract S101**

**Fluorescence bronchoscopy in clinical practice**

A.K. Banerjee, P.H. Rabbitts, P.J.M. George. Molecular Oncology Group, University of Cambridge, UK; The Middlesex Hospital, London, UK

**Introduction:** Autofluorescence bronchoscopy (AFL) uses the fluorescence properties of bronchial mucosa to enhance the real-time detection of abnormal endobronchial lesions. This study assesses the efficacy of the Storz Bronchoscope in a UK population of patients.

**Methods:** Patients with suspected lung cancer attending for diagnostic bronchoscopy underwent AFL during the same procedure. Conventional white light followed by AFL was performed. Biopsies of all abnormal areas and control biopsies from bronchoscopically normal areas were obtained. The bronchoscopic and histological findings were compared.

**Results:** 53 patients have undergone AFL (41 male), mean age 63.8 yrs (range 35–79 yrs). Controls: 106 areas were biopsied as controls. 3.7% showed high grade pre-invasive lesions (carcinoma-in-situ & severe dysplasia). The remaining areas showed no abnormality or low-grade pre-invasive lesions. Bronchoscopically abnormal areas: The table shows the histology and bronchoscopic findings of the 133 areas biopsied. Compared to conventional white light bronchoscopy, autofluorescence improved the detection of high-grade pre-invasive lesions. 7 early-stage microinvasive carcinomas were detected by AFL alone. The false negative rate for AFL detection of high-grade pre-invasive lesions was 3.7% and the false positive rate 38.3%.

**Conclusions:** The addition of AFL to conventional bronchoscopy improves the sensitivity of high-grade pre-invasive lesion and importantly invasive carcinoma detection. Detection of microinvasive carcinoma at a radiologically occult stage allows intervention with potentially a 90% 5 year survival. The dilemma of pre-invasive lesion management is also raised. Not all pre-invasive lesions become invasive carcinomas, and so intervention is not justified for all lesions. Further information on the natural history of such lesions is needed. The high false positive rate is similar to that found in other studies and suggests that abnormal findings must be confirmed histologically and that approaches to improve specificity are required.

**Lung cancer targets**

**S102: Audit improves diagnostic delays in lung cancer management**

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**Aim:** Delays in diagnosis are often causes of distress to patients, and may have a detrimental effect on therapeutic options and overall prognosis. The aim was to prospectively audit the time taken to diagnose patients with suspected lung cancer in a large teaching hospital with reference to established national guidelines of best practice.

**Method:** From January 1999, all available data required for the Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of Physicians (RCP) minimum dataset for lung cancer, was collected from case notes of patients managed by the lung cancer team at Gartnavel hospital. This was prospectively entered into Microsoft Access and SPSS databases.

**Results:** 518 patients were identified between 1999 and 2001. Histological evidence of lung or other malignancy was obtained in 474 (91.5%) patients. The time taken to see a respiratory physician, for the investigation to be performed and to obtain a definitive diagnosis is presented below, with the p-values for differences between the time taken in 1999 and 2001.

**Conclusion:** Simple organisational changes following clinical audit have significantly reduced the time taken for CT imaging of thorax, and have improved diagnostic delays, in patients with lung cancer.

<table>
<thead>
<tr>
<th>Time taken (days)</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>t test 1999 to 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>To see respiratory physician from referral</td>
<td>n=155</td>
<td>n=150</td>
<td>n=150</td>
<td>NS</td>
</tr>
<tr>
<td>Mean=8.3</td>
<td>Mean=6.6</td>
<td>Mean=7.3</td>
<td>mean=9.9</td>
<td>mean=9.3</td>
</tr>
<tr>
<td>SD=13.3</td>
<td>SD=8.6</td>
<td>SD=10.8</td>
<td>SD=24.2</td>
<td>SD=22.8</td>
</tr>
<tr>
<td>For bronchoscopy from clinic review</td>
<td>n=116</td>
<td>n=125</td>
<td>n=125</td>
<td>NS</td>
</tr>
<tr>
<td>Mean=9.9</td>
<td>Mean=9.3</td>
<td>Mean=9.3</td>
<td>mean=28.8</td>
<td>mean=23.0</td>
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<td>SD=22.8</td>
<td>SD=45.9</td>
<td>SD=25.8</td>
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<tr>
<td>For CT scan of thorax from clinic review</td>
<td>n=122</td>
<td>n=131</td>
<td>n=131</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Mean=28.8</td>
<td>Mean=18.2</td>
<td>Mean=18.2</td>
<td>mean=38</td>
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<td>SD=38</td>
<td>SD=38</td>
<td>SD=57.1</td>
<td>SD=59.7</td>
</tr>
<tr>
<td>For definitive diagnosis from clinic review</td>
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<td>n=150</td>
<td>n=150</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Mean=33.1</td>
<td>Mean=16.4</td>
<td>Mean=16.4</td>
<td>mean=90.6</td>
<td>mean=59.7</td>
</tr>
</tbody>
</table>

**NS, not significant.**
THERAPEUTIC DELAYS IN LUNG CANCER MANAGEMENT

A. Coote, K.R. Patel, J.S. Sarvesvaran, J. Walker, M. Patel. Department of Respiratory Medicine, Gartnavel General Hospital, Glasgow, UK

Aim: As lung cancer is such an aggressive disease with poor prognosis, following the diagnosis, an appropriate member of the multidisciplinary team should initiate treatment quickly. To identify any therapeutic delays in lung cancer management, a prospective audit was set up in Jan 1999.

Method: A SPSS database was constructed and all available data required for the Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of Physicians (RCP) minimum dataset entered prospectively by a part time data manager.

Results: During the period Jan 1999 to Dec 2001, the lung cancer team at Gartnavel General hospital managed 518 patients. 96 (18.5%) patients were diagnosed with small cell lung cancer (SCLC), 335 (64.7%) were non-small cell lung cancer (NSCLC). The times taken for patients to receive the different modalities of lung cancer treatment are shown in the table.

Conclusion: Chemotherapy for SCLC is prescribed primarily by respiratory physicians and is administered promptly. Similarly patients with NSCLC who are fit for surgery have the procedure within the recommended period. Although oncology review of patients is rapid, patients receiving chemotherapy for NSCLC, face a slight delay. This may be due in part to patients requiring time to consider therapeutic options but administrative delays due to treatment being administered at another hospital site cannot be excluded. The significant delay particularly for radical radiotherapy is of concern as it may have a detrimental effect on overall survival.

### Abstract S103

<table>
<thead>
<tr>
<th>Time taken in days from referral for treatment during Jan 1999-Dec 2001</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer chemotherapy</td>
<td>n=88 median=6</td>
</tr>
<tr>
<td>Non-small cell lung cancer chemotherapy</td>
<td>n=47 median=23</td>
</tr>
<tr>
<td>Small cell lung cancer surgery</td>
<td>n=55 median=18</td>
</tr>
<tr>
<td>Oncology review</td>
<td>n=338 median=6</td>
</tr>
<tr>
<td>Radical XRT</td>
<td>n=29 median=49</td>
</tr>
<tr>
<td>High dose palliative XRT</td>
<td>n=38 median=32</td>
</tr>
<tr>
<td>Palliative XRT</td>
<td>n=150 median=18</td>
</tr>
</tbody>
</table>

MEETING GOVERNMENT LUNG CANCER TARGETS: DOES LUNG CANCER PRESENTATION HAVE A SEASONAL VARIATION?

A. Bastin, A.G. Davison, D. Errat, A. Hutchings, A.S. Haque, A. Lamont, C. Trask. Southend Associate University Teaching Hospital, Southend on Sea, Essex SS0 0RY, UK

Currently the Government target for seeing a patient with suspected lung cancer is within 2 weeks of referral and from 2005 the target time for starting treatment is to be within one month of diagnosis. It is known that exacerbations of COPD vary seasonally and are more common in winter months, COPD is very common in patients with lung cancer. The knowledge of any seasonal variation in lung cancer presentation is important for service planning and to allow Government targets to be met.

We have analysed the 2127 new cancer cases presenting over a ten year period from 1990 to 1999 from the Southend Lung Cancer Study. This includes every case in a well defined population of 325 000. Winter (W) months are defined as December, January, and February, and Summer (S) months are June, July, and August. The number presenting in S (561) was slightly higher than W (494). There was a lack of evidence that presence of cough at diagnosis differed by season (66% had a cough in W, compared to 70% in S) (p=0.14). There was a lack of evidence that dyspnoea at diagnosis differed by season (59% in W, compared to 63% in S) (p=0.25). There was a lack of evidence that the presence of COPD in those presenting with lung cancer (using the BTS COPD Guidelines criteria for diagnosis and severity) differed by season (74% in W compared to 71% in S), nor that there was any difference in the severity of COPD at presentation according to season (p=0.6). Similar results were found when those presenting in the 6 months of October through to March were compared to those presenting in the 6 months of April through to September.

Conclusion: There is no increase, unlike COPD, in the presentation of lung cancer in the W months. Even patients with severe COPD and lung cancer do not present more commonly in W. There is no difference in the respiratory symptoms in lung cancer patients presenting in the W or S. These results have important implications for the planning of lung cancer services. Diagnostic services, e.g. outpatient 2 week lung cancer slots, MDTs, bronchoscopy, CT scanning, histology etc, and treatment services, surgery, radiotherapy, and chemotherapy need to be provided on a continual basis throughout the year. In particular in order to meet Government targets they will need to be maintained in the summer, the traditional holiday period for staff.

LUNG CANCER: ARE THE NSF TARGETS FOR RESECTION AND RADICAL RADIOTHERAPY ACHIEVABLE?

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The NSF for Lung Cancer has set targets for histology and resection rates for lung cancer against which services can be judged. One report from a tertiary referral centre suggested that resection rates of 25% were achievable (Laroche, et al. Thorax 1999;53:445–9). We set out to review the demographics and staging of lung cancer patients diagnosed at our DGH (Kings Mill Hospital) to examine the reasons for not obtaining a pathological diagnosis and not operating on patients with stage I and II disease. We have prospectively collected the full BTS/RCP audit data set on all patients diagnosed with lung cancer at our hospital since April 1999. These results are presented.

Over three years between 04/99 and 03/02 we diagnosed 441 cases of lung cancer. The rate of histological confirmation overall was 83.5%. More than 85% had their management discussed at the weekly Multi Disciplinary Meeting, which included respiratory physicians, a thoracic surgeon and an oncologist.

Small cell lung cancer (SCLC) accounted for 14% of all cases. Of the 379 remaining patients 310 had confirmed Non Small Cell Lung Cancer (NSCLC). 299 of these (96%) were formally staged. The stage distributions are shown below and compared to those reported by Mountain (Mountain. Chest 1997;111:1710–17).

Of those with stages I and II, the surgical resection rate was 42% and radical radiotherapy rate 28%. Co-morbidity prevented the remaining 30% from receiving potentially curative treatment. The resection rate for pathologically confirmed NSCLC was 32/310=10.3% or 32/379=8.4% if those without pathologically confirmed disease are included. Our results show that at our hospital patients with lung cancer present with later stage disease than those reported from tertiary referral centers. Selection bias may explain the differences between our results and those previously reported (see above). Even if all those with stage I and II disease underwent surgery we would barely achieve 15% resection rate.

SURGICAL REFERRAL AND RESECTION RATE FOR NSCLC AT QUEEN ELIZABETH HOSPITAL OVER A 5 YEAR PERIOD: WHY IS IT SO LOW?

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Aim: to analyse the referral rate for surgery in stage I and II NSCLC in Queen Elizabeth Hospital Woolwich, from September 1997 up to April 2002.

A total of 746 patients were diagnosed with lung cancer between 1997 and 2002. Of these, 458 had histologically proven non-small
WHAT’S IN I.T. FOR US? USE OF AN I.T. SYSTEM TO IMPROVE REFERRAL RATES.

Reasons for non-referral of stage I and II patients included poor lung function (13), age (10), WHO health status (5), patient refusal (5) other diseases (3) or a combination of the above (11). The median age for those referred relative to those not referred was 66 and 76 respectively (p<0.0001, Wilcoxon rank sum). Of the 60 stage I and II patients referred for surgery, 40% were deemed to be inoperable. Reasons were upstaging by PET scanning (9), age/lung function (3), upstaging at mediastinoscopy/thoracoscopy (5) and surgical opinion (7).

Conclusions: the surgical referral and resection rates for patients with operable cancer on staging criteria remains low. Despite the initiation of multidisciplinary meetings in 1997, fewer than half of the potentially operable patients (stages I, II and IIIA) were referred for surgery. However, nearly half of all stage I and II patients referred for a surgical opinion were refused, predominantly after upstaging. The introduction of a telematic link with cardiothoracic surgeons may improve referral rates.

WHAT’S IN I.T. FOR US? USE OF AN I.T. SYSTEM TO INFORM AND IMPROVE A LUNG CANCER SERVICE

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Background: An audit of 100 lung cancer case records in our institution in 1999 demonstrated that only 18% of cases had an MDT discussion and decision recorded in the medical records, and no regular outcome data were available.

Process: During 2 2-hour session in 1999 and 2000 lead clinicians in the lung cancer services (diagnostics, thoracic surgery, oncology) mapped the lung cancer care pathway and clinical processes, and identified key stages of the patients care journey. This work was influenced by the need for performance target data and clinical minimum data sets.

In 2000 the Inflextm system was chosen to support the lung cancer services. The implementation required clinicians to define information requirements and outputs.

Outcome: The use of the Inflextm system coincided with the development of a weekly combined lung cancer clinic (Respiratory Medicine, Clinical Oncology and Palliative Care). Prior to the weekly Lung Cancer clinic (t=0 days) a first visit proforma and faxable immediate GP letter are printed, incorporating patient demographics from the hospital PAS system. Data from the proforma are entered onto the Inflextm system immediately after the clinic. Bronchoscopy findings are entered live onto the Inflextm system by clinicians and a bronchoscopy report, GP letter, and histopathology request form are printed. Prior to the MDT meeting (t=10 days) the results of investigations are entered onto the system and an MDT summary sheet is produced. The summary sheet aids decision making in the MDT meeting and serves as a referral letter between specialties. A second clinic visit proforma and immediate faxable GP letter are prepared for the second clinic visit (t=14 days).

The initial 12 months of complete data demonstrate that 92% of patients diagnosed with lung cancer have an MDT discussion and decision recorded. Reports for any time frame are readily accessible, and present a realtime position of all suspected lung cancer referrals, their progress and outcome. Future plans include the use of projection equipment in the MDT meeting to view the discussion sheet and record decisions realtime, and the use of inflex for comparison of data with other units, primarily to ascertain reasons for differences in resection rate.

The genetics of respiratory disease

AGE-SPECIFIC EFFECT OF THE CYSTIC FIBROSIS MODIFIER GENES, MBL-2

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The variable severity of cystic fibrosis lung disease, even in subjects with identical CFTR mutations, has led to the search for non-CFTR modifier genes. Mannose-binding lectin (MBL) is involved in innate defence, both through direct opsonic activity and complement activation. Low-expressing MBL1 haplotypes were reported to have a worse outcome in older CF children and adults to lead to a poor outcome. We have looked for correlations with clinical status in 260 paediatric CF patients. Genomic DNA was analysed for structural mutations (designated 0; wild-type A) and the low [X] or high [Y] expressing promoter polymorphisms. Patients were grouped based on haplotype which correlated closely with MBL levels (measured by ELISA) into group 1 (A/A, 62.9%), group 2 (YA/O, 24%) and group 3 (KA/O or O/O, 13%). At the earliest time point available (7.0 [6.7–7.4] years), children in group 3 had a significantly (p<0.05) higher FEV1 than those in either of the other groups (gp 3: median [IQR] 105.5 [83;113]%); gp 2: 85.5 (78;103)%; gp1: 91 (76;105)%). At the age of 9, a similar trend was seen (p=0.055). At approximate ages of 11, 13 and 15 years, no difference was seen in either parameter between groups. Annual rate of decline was not affected by MBL status (gp 3: −3.4 (−6.7; 0.3)%; gp 2: −3.5 (−5.9; −0.8 % gp 1: −3.0 (−6.4; 0.7)%). Infection with P aeruginosa increased the rate of decline, but affected each group equally. In contrast to adult studies, low MBL is not detrimental in childhood CF. The surprising finding that children with the lowest MBL levels in fact have higher lung function early in life may relate to the complex role of this protein in the inflammatory response. The loss of effect later is likely due to the increased protease activity on the airway surface with advanced disease. The most obvious difference between our group and those previously reported was to year of birth, other groups having been born to 20 years earlier. Over this time, CF treatment has progressed rapidly, possibly reducing the importance of certain host factors. These results highlight the importance of considering such environmental and treatment factors when studying modifier genes in CF.

POLYMORPHISMS IN THE HYDROPHILIC SURF ACTANT PROTEINS A AND D AS MODIFIERS OF LIVER INVOLVEMENT BUT NOT LUNG DISEASE IN CHILDREN WITH CYSTIC FIBROSIS

J.C. Davies1,2, P. Pantelidisa, A. Logan5, R. Du Boisa, K. Waless5, D.M. Geddes1, E.W.F.W. Alton1. 1Dept of Gene Therapy and ‘Clinical Genomics Unit, Imperial College, UK; 2Dept of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

The surfactant proteins A and D are members of the collectin family involved in the innate immune system. Polymorphisms within SPA have been associated with infant respiratory distress syndrome and severe RSV bronchiolitis. We have explored a modifying effect of these proteins on disease phenotype in children with CF. A sequence specific primer-PCR methodology was employed which enabled the identification of all known allelic variants on SPA1, SPA2 and SPD genes directly from genomic DNA samples. Clinical data collected included lung function at defined ages, infection with common CF pathogens, and the presence of liver disease on ultrasound. Data were available on 241 children at a mean (SEM) age of 8.5 (0.3) years. No correlation was seen between any haplotype and lung function at any age, risk of infection, use of IV antibiotics or age at diagnosis. However, in children with liver disease (n=19) both the SPA1 allele 6A, and the SPA2 allele, 1A, were significantly overrepresented (6A/6A: 68% v 33%, 6A/non-6A: 32% v 47%, non-6A/non-6A: 0% vs 19%, p<0.01; 1A/1A: 63% v 34%,
1A1/non1A1 32% v 47%, non1A1/non1A1 5% v 18%, p<0.05). A significant but less pronounced relationship was seen with the SP-D group possessing both the 11T and 160A polymorphisms (p<0.05). The lack of an association between these proteins and lung disease may either reflect redundancy in the host defence system, or enzymatic destruction of these proteins after release. The association with liver disease was unexpected and is interesting. Inflammation has been described in CF liver disease, although whether this is primary or secondary remains uncertain. The surfactant proteins have recently been identified in many extra-pulmonary sites including the the gastrointestinal tract. As of today, only SP-D has been found in the biliary tree. These data suggest a role for inflammation and host defence proteins in the development of CF liver disease, and if further work is confirmatory, may allow identification of a subgroup at risk of this complication.

**S110** PRELIMINARY IDENTIFICATION OF GENETIC LOCI ASSOCIATED WITH HIGH ALTITUDE PULMONARY HYPERTENSION BY ASSOCIATION MAPPING

L. Long, A.A. Aldashev, A. Henseki, S. Eddahibi, S. Adnot, R.C. Trembath, M.R. Wilkins, N.W. Morrell. University of Cambridge School of Clinical Medicine, Department of Medicine, Addenbrookes’ and Papworth Hospitals, Cambridge CB2 0QQ, UK

Hypoxia-induced pulmonary hypertension is observed in residents at high altitudes and in patients with hypoxic lung diseases, such as chronic obstructive pulmonary disease. Well documented differences between individuals, and between high altitude populations, in susceptibility to pulmonary hypertension in low oxygen environments, suggest that genetic factors may play a role. To identify genes conferring susceptibility to hypoxia-induced pulmonary hypertension in native highlanders, we performed an ECG survey of the inhabitants (age 16 to 30, n=741) of 3 villages in Kyrgyzstan, at an altitude of 2800 to 3100m above sea level. Subjects with and without ECG signs of cor pulmonale underwent echocardiography to define groups of highlanders with and without pulmonary hypertension (defined by mean pulmonary arterial pressure >25mmHg). DNA samples were obtained from 30 cases and 30 controls. We used a DNA pooling technique and performed a whole genome screen using 811 microsatellite markers (Applied Biosystems high density linkage mapping set LMS-HDS), allowing a resolution of 5–10cM across the genome. Association mapping identified alleles that occurred with significantly different frequency between cases and controls. Fifteen markers showed significantly different frequencies (p<0.05) on chromosomes 1,3,5,6,7,8,13,15,17, and 20. An initial search for candidate genes identified the locus for the serotonin transporter (SHTT) lying in close proximity (2Mb) to the marker on chromosome 17. A polymorphism in the promoter of the SHTT gene (L/S) is known to alter the expression of SHTT and is associated with primary pulmonary hypertension. The frequency of the LL genotype, which increases SHTT expression and activity, was 24% in the group with high altitude pulmonary hypertension compared with 12% in the controls. These results require confirmation in a larger cohort of cases and controls, and refinement of the chromosomal loci to aid in the identification of further candidate genes. Nevertheless, this study provides a novel approach to the identification of genes that confer susceptibility to hypoxia-induced pulmonary hypertension.

Funding: Wellcome Trust and British Heart Foundation.

**S111** SMOKING RELATED EMPHYSEMA AND SMALL AIRWAYS DISEASE HAVE INDEPENDENT GENETIC RISK FACTORS IN COPD

B.D. Patel, A. Tasker, N. Screaton, W. Anderson, S. Sharma, E.K. Silverman, D.A. Lomas. Departments of Medicine and Radiology, University of Cambridge, UK; GlaxoSmithKline, North Carolina, USA; Channing Laboratory, Brigham and Women’s Hospital, Boston, USA

We previously have shown that COPD clusters within families suggesting that shared genetic factors predispose some smokers to airflow obstruction. It is unknown whether these genetic factors contribute to the airway disease and/or emphysema components of COPD. This hypothesis was tested in a group with high altitude pulmonary hypertension with 12% in the controls. These results require confirmation in a larger cohort of cases and controls, and refinement of the chromosomal loci to aid in the identification of further candidate genes. Nevertheless, this study provides a novel approach to the identification of genes that confer susceptibility to hypoxia-induced pulmonary hypertension.

We asked to complete a questionnaire enquiring into symptoms, exposure, and job history.

After adjustment for independent risk factors, HLA-DR7 was found to be associated with sensitisation (OR 1.99 CI 1.91–2.07), work-related chest symptoms (OR 2.98 CI 1.66–5.36) and sensitisation with symptoms (OR 4.81 CI 2.29–10.13). HLA-DR3 was protective against sensitisation (OR 0.55 CI 0.31–0.98). Atopy and exposure proved to be more strongly associated with sensitisation and sensitisation with symptoms than HLA.

Amino acid analysis of the associated HLA molecules provides a biologically plausible explanation for these associations.

**S112** IMMUNOGENETICS OF LABORATORY ANIMAL ALLERGY

H. Jeal, A. Draper, M. Jones, J. Harris, K. Welsh, A. Newman Taylor, P. Cullinan. Department of Occupational and Environmental Medicine and ‘Interstitial Lung Disease Unit, Imperial College (NHLI), London, UK

Laboratory animal allergy is a common occupational health problem affecting approximately 30% of the exposed population. Allergic reactions to rats or mice are most common, probably because these animals are most frequently used in experimental studies. HLA class II molecules are involved in the presentation of allergen to the T cell and are therefore likely candidates for controlling the immune response. We hypothesised that HLA class II molecules might be associated with sensitisation to rat urinary protein among individuals exposed to laboratory animals.

We undertook a cross sectional study of 741 employees in contact, at work, with laboratory rats at 6 pharmaceutical sites across the UK. 109 cases (defined as having a skin prick test wheel >=3mm to rat urine and/or a rat urine RAST >2% binding) and 397 non-sensitised referents were HLA typed for DRB1 and DQB1 loci. Participants were asked to complete a questionnaire enquiring into symptoms, exposure, and job history.

Background: Maternal factors including atopy and smoking during pregnancy are associated with the risk of developing asthma in childhood. Suggested mechanisms include transmission of specific maternal alleles to the child and maternal influences on the intrauterine environment. We have previously shown that polymorphism in gluta-thione S-transferase, GSTP1 is associated with asthma, asthma-related airway responsiveness (AHR) and atopy in adults. We now hypothesise that GSTP1 genotypes in the both mother and child, but not the father, mediate asthma phenotypes in the child.

Methods: 145 Caucasian families were recruited via an asthmatic proband aged 7–18 years. Atopy and asthma were assessed using a...
Asbestos and the pleura

**S114 DIFFUSE ASBESTOS-RELATED PLEURAL FIBROSIS; A POOR GUIDE TO HEAVY DUST EXPOSURE?**

C McGavin, K Smith, L Sykes. Derriford Hospital, Plymouth, UK

There has been an assumption that diffuse pleural fibrosis (DPF) is an indicator of heavy dust exposure. This has considerable implications in the diagnostic process as to whether a given lung cancer has been caused by asbestos. The UK Industrial Injuries Advisory Council consider that lung cancer in the presence of DPF is an industrial tumour, but not in the presence of pleural plaque (PP).

**Method:** We have tested the hypothesis that DPF is a marker of heavy exposure by comparing estimated asbestos burden in 192 workers from the Devonport Dockyard, 96 with PP and 96 with DPF (43 bilateral). Dust burden was calculated from previously published data of exposure to asbestos by individual trades within the Yard multiplied by years spent in that trade prior to 1972. Detailed occupational histories were taken by one experienced observer who had also read all the radiographs (C McCg).

**Results:** There were no differences between the groups in terms of age or time since first exposure. There were no differences in estimated dust burden between men with PP and DPF (independent samples t-test, DF adjusted for unequal variances, t=1.045, DF=179, p=0.3), nor between PP and unilateral and bilateral DPF analysed separately, using logs of asbestos burden because of unequal variances (F2, 189=2.56, p=0.08). However there was evidence that men with bilateral DPF had more exposure than those with unilateral (F=2.86, DF=88, p=0.004, t-test adjusted for unequal variances).

**Conclusion:** We found no evidence that men with DPF have had a greater exposure to asbestos than men with PP, and conclude that there is no justification for using the presence of DPF as an indicator of heavy exposure, for example in qualifying a lung cancer for industrial status. Bilateral DPF suggests a heavier dust burden than unilateral.


**S115 TRANSFORMING GROWTH FACTOR BETA (TGFβ) INDUCES MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) SIGNALLING IN MALIGNANT MESOTHELIOMA**

M.K. Wood, K.S. Abayasiriwardana, G.J. Laurent, S.E. Mutsaers, R.J. McAnulty. Centre for Respiratory Research, University College London, London WC1E 6JJ, UK

Malignant Mesotheliomas (MM) are fibrous tumours containing abundant collagen. MM cells produce collagen as well as TGFβ, which is a potent inducer of collagen synthesis. We have shown that antibody neutralisation of TGFβ or inhibition of collagen synthesis using a proline analogue inhibits collagen production in MM cells and reduces tumour growth. TGFβ signals predominantly via the Smad pathway, but also through the MAPKs. Over-expression of Smad7, the natural inhibitor of the Smad pathway, blocks collagen production in fibroblasts. However, in MM cells, we demonstrated enhanced collagen production and tumour growth following transfection with Smad7. From these findings we hypothesised that TGFβ-induced collagen production by MM cells occurs via MAPK signalling. To assess this hypothesis we performed Western blotting to determine if TGFβ stimulated activation of two components of the MAPK pathway, ERK1/2 and p38 kinase, in MM cells. The effect of blocking these pathways using specific inhibitors U0126 (10µM) and SB203580 (10µM) respectively, on collagen production was assessed by measuring hydroxyproline levels using HPLC (nmol hydroxyproline/106 cells).

**Results:** Exogenous TGFβ, activated both ERK1/2 and p38 kinase in MM cells within 5min. Blocking ERK1/2 activity increased procollagen production basally (control 0.26±0.01, U0126 0.49±0.02, p<0.01) and after TGFβ stimulation (control 0.58±0.004, U0126 0.72±0.02, p<0.01). However the fold increase in collagen production in response to TGFβ, was 2.3 and 1.5 times basal levels in control and U0126 treated groups respectively, suggesting a decrease in the response to TGFβ. Blocking p38 kinase activity had a small inhibitory effect on collagen production basally (control 0.48±0.02, SB203580 0.39±0.02, p<0.01) and after TGFβ, (control 0.39±0.01, SB203580 0.47±0.04, p<0.02).

**Conclusions:** (1) the ERK1/2 and p38 kinase MAPK pathways are rapidly activated by TGFβ, in these cells, which may be important in MM tumorigenesis; (2) MAPKs appear to have a role in TGFβ stimulated collagen production by MM cells but do not appear to be the major route of signalling in this response. Further elucidation of the TGFβ signalling pathways involved in the regulation of collagen synthesis and the specific roles of the MAPKs in MM may identify unique pathways in this tumour, which might be exploited as potential therapeutic targets.

This work was funded by Cancer Research UK and British Lung Foundation.

**S116 IMMUNOHISTOCHEMICAL PROGNOSTIC MARKERS IN MALIGNANT MESOTHELIOMA**

N. Chaudhuri, I. Cawkwell, M.E. Cowen, A.P. Campbell, M.J. Lind. Academic Dept. of Oncology and Surgery, Castle Hill Hospital, Cottingham, UK

**Objective:** A nihilistic attitude exists towards malignant mesothelioma of the pleura (MMp) as most people die within a year of diagnosis regardless of treatment or palliation. Some patients do survive longer, multimodality treatment has increased survival in some centres and there are promising novel therapies on the horizon. Immunohistochemical markers have shown promise in predicting survival in other solid tumours and they could be used to select patients for further treatment in MMp.

**Methods:** Archival specimens were identified from a pathological database. Immunostaining was carried out with p53, proliferative markers—MB1 and PCNA and apoptotic markers—Bcl2 and BAX. Up to 90 blocks analysed from 74 patients (M:F—66:8, median age 67 years) diagnosed with malignant mesothelioma between 1997 and January 2001.

**Results:** Median and mean survivals were 218 and 314 (SD331) days respectively. Patients were divided into two groups. See table.

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Mean Survival (days)</th>
<th>SD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>epithelial</td>
<td>425 ± 8</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>biphasic</td>
<td>212 ± 2</td>
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<tr>
<td>sarcomatous</td>
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**Abstract S116**

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<tr>
<th>Survival &gt; 10 mths</th>
<th>Survival &lt; 10 mths</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>p Value</td>
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<tr>
<td>61.4 ± 10.2</td>
<td>68.5 ± 9.8</td>
</tr>
<tr>
<td>MB1 +ve stain</td>
<td>43.8 ± 14.9</td>
</tr>
<tr>
<td>PCNA +ve stain</td>
<td>79.4 ± 14.4</td>
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<tr>
<td>BAX score</td>
<td>4.7 ± 1.6</td>
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<tr>
<td>Bcl2 score</td>
<td>0.9 ± 1.4</td>
</tr>
<tr>
<td>PS1 score</td>
<td>3.8 ± 1.3</td>
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<tr>
<td>PS3 stain</td>
<td>57.0 ± 18.3</td>
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</tbody>
</table>

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Conclusions: Age and histological subtype influence survival in malignant mesothelioma as has been shown in other studies. In our study we found MIB1 could predict long-term survival in patients with MMP.

ST117 SURVIVAL IN SURGICALLY DIAGNOSED PATIENTS WITH MALIGNANT MESOTHELIOMA IN CURRENT PRACTICE
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Objective: There is an epidemic of malignant mesothelioma in Europe that presents a challenge to thoracic surgeons. The median survival is quoted as five months (150 days) but reports are from ten or more years ago. To evaluate results of new treatments we set out to establish survival statistics for current practice.

Methods: We searched back five years in the pathology database of our two hospitals for all pleural biopsies in which mesothelioma was diagnosed.

Results: We found a total of 426 cases and report on 409 where we know vital status (table). Survival was 174 days (82%) longer at one hospital than the other. This difference is not explained by histological type, sex, or age. Epithelioid type and age (younger) were associated with better survival as is consistently shown.

Conclusion: Claims for improved treatments are made with reference to historical data for the natural history of the disease. Not only are survival times often longer than those quoted but the difference between two hospitals is far greater than the likely gain from any novel or more radical therapy. The possible explanations include lead time bias due to earlier referral in Harefield as opposed to Guy’s or differences in histological diagnostic threshold. Whatever the explanation it illustrates the need for a contemporaneous control group and our data emphasise the case for a randomised controlled trial.

ST118 ACTIVATION OF PROTEASE ACTIVATED RECEPTOR-2 IN MESOTHELIAL CELLS: A NOVEL MECHANISM OF PLEURAL INFLAMMATION
Y.C.G. Lee, D.A. Knight, K.B. Lane, D.S. Cheng, M.A. Koay, I.R. Teixeira, P.J. Thompson, R.W. Light. Vanderbilt University and St. Thomas Hospital, Nashville, TN, USA. We have recently shown that PAR-2 are present in abundance on human epithelial cells in vivo. We hypothesised that PAR-2 in mesothelial cells has a functional role in pleural inflammation.

Methods: C57BL/6 mice were given a single intrapleural injection of 10mg/kg of SLIGRL-NH2 (a specific PAR-2 activating peptide), or PBS (88±35pg/mL) or PBS (88±35pg/mL), p<0.001. Similarly, peritoneal injection of 10µg of ovalbumin in 0.1ml saline on two occasions 10 days apart. 21 days after the second sensitisation mice were challenged with 400µg of ovalbumin in 50µl saline by intra-tracheal instillation daily for 6 days. Control mice were sham sensitised/sham challenged. 12 days after the final challenge mice were killed. Lungs were inflated with a 1:3 embedding matrix:saline mixture at a pressure of 25cm water, set in embedding matrix and frozen in liquid nitrogen for histological analysis. 7µm frozen sections were stained overnight using cupromeronic blue and a critical electrolyte concentration of 250mM magnesium chloride. Sub-epithelial proteoglycan staining was quantitated using a computer-assisted image analysis system. Airways were selected using pre-defined criteria and airway lumen was examined using separate colour thresholds for lumen and sub-epithelial proteoglycans. Results were expressed as amount of proteoglycan per unit airway lumen perimeter.

Conclusions: Increased sub-epithelial proteoglycans in the airways of mice following ovalbumin sensitisation and challenge. In this study we have investigated changes in proteoglycan deposition in sections of murine lung using a selective histological stain and computer-assisted image analysis.

ST119 INCREASED SUB-EPITHELIAL PROTEOGLYCANS IN THE AIRWAYS OF MICE FOLLOWING OVALBUMIN SENSITISATION AND CHALLENGE
A.K. Reinhardt, S.E. Bottoms, G.J. Laurent, R.J. McNally. Centre for Respiratory Research, University College London, London WC1E 6JJ, UK

The sub-epithelial thickening of asthmatic airways is manifested by increased fibroblast/myofibroblast proliferation and deposition of extra-cellular matrix components including collagen and proteoglycans. The degree of proteoglycan deposition has been correlated with airway responsiveness. Existing murine models of asthma, including our own, have demonstrated increased amounts of airway sub-epithelial collagen following ovalbumin sensitisation and challenge. However, we are not aware of any studies examining altered airway proteoglycan deposition in an asthma model. In this study we have investigated changes in proteoglycan deposition in sections of murine lung using a selective histological stain and computer-assisted image analysis.

Wild-type SV129/C57BL/6 mice were sensitised by intraperitoneal injection of 10µg of ovalbumin in 0.1ml saline on two occasions 10 days apart. 21 days after the second sensitisation mice were challenged with 400µg of ovalbumin in 50µl saline by intra-tracheal instillation daily for 6 days. Control mice were sham sensitised/sham challenged. 12 days after the final challenge mice were killed. Lungs were inflated with a 1:3 embedding matrix:saline mixture at a pressure of 25cm water, set in embedding matrix and frozen in liquid nitrogen for histological analysis. 7µm frozen sections were stained overnight using cupromeronic blue and a critical electrolyte concentration of 250mM magnesium chloride. Sub-epithelial proteoglycan staining was quantitated using a computer-assisted image analysis system. Airways were selected using pre-defined criteria and airway lumen was examined using separate colour thresholds for lumen and sub-epithelial proteoglycans. Results were expressed as amount of proteoglycan per unit airway lumen perimeter.

Lung sections from a total of 19 animals were examined (10 ovalbumin sensitised/challenged and 9 controls). A total of 52 ovalbumin sensitised/challenged and 32 control airways were analysed. The mean area of proteoglycan/µm airway perimeter was 5.46±0.39µm² in the ovalbumin sensitised and challenged group and 4.13±0.44µm² in the sham sensitised/sham challenged group (p=0.03). This represents a mean increase of 32% in sub-epithelial proteoglycan deposition following ovalbumin sensitisation and challenge. Interestingly, in view of the association between proteoglycans and collagen fibroblast assembly, sub-epithelial collagen is increased by 33% using the same sensitisation/challenge protocol. We conclude that the increase in sub-epithelial proteoglycan and collagen deposition found in the airways of asthmatics can be reproduced in mice following ovalbumin sensitisation and challenge and that this may be a useful model to assess the mechanisms regulating sub-epithelial airway remodelling.

Work funded by the Wellcome Trust.

Abstract ST117

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Number of cases</th>
<th>Median of survival (days)</th>
<th>Days to 25% dead</th>
<th>Days to 75% dead</th>
<th>Age median (IQR)</th>
<th>Males</th>
<th>Epithelioid histology</th>
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<tbody>
<tr>
<td>Guy’s Hospital</td>
<td>175</td>
<td>213</td>
<td>93</td>
<td>478</td>
<td>67 (59–74)</td>
<td>80%</td>
<td>54%</td>
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<td>Harefield Hospital</td>
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<td>387</td>
<td>162</td>
<td>–</td>
<td>68 (62–74)</td>
<td>83.4%</td>
<td>58%</td>
</tr>
</tbody>
</table>

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WNT SIGNAL TRANSDUCTION IN ADULT BRONCHIAL EPITHELIAL CELLS

M.D. Steel, D.E. Davies, S.M. Puddicombe, S.T. Holgate, J.E. Collins. Division of Inflammation, Infection and Repair, School of Medicine, University of Southampton, Southampton, SO16 6YD, UK

Wnts are a highly conserved family of secreted glycoproteins that play a fundamental role in cell fate determination and tissue morphogenesis during embryonic development. Through binding to members of the Frizzled (Fzd) receptor family, class-1 Wnts induce the accumulation of hypophosphorylated β-catenin by inhibiting the GSK-3β/axin/APC destruction complex. Consequent translocation of β-catenin to the nucleus gives rise to activation of TCF/LEF-1 transcription factors, leading to expression of genes involved in cell migration (CD44, MMP7) and proliferation (c-myc, cyclin-D1). In mammalian embryonic lung, activation of this "canonical" pathway in airway epithelial cells has been implicated in the process of branching morphogenesis, and Wnt secretion by underlying mesenchymal cells is thought to play a key role. Despite reports that several WNT and FZD genes are expressed in adult human lung tissue, very little is known about which cells are involved, and their functional significance remains unclear. Using an RNAse protection assay, we have identified expression of FZD-2, -3, -5 and -6 in both H292 and primary bronchial epithelial cells. In addition, these cells also express the gene encoding secreted Frizzled receptor protein-1 (SFRP1), the product of which is capable of modulating Wnt signals in the extracellular compartment. Postulating that human airway epithelial cells retain the ability to transduce a canonical Wnt signal in adult life, we employed RT-PCR and observed expression of TCF-4 mRNA in primary cells, with weaker expression of TCF-3, but no detectable message for TCF-1 or LEF-1. Using a TCF reporter construct (TOPFLASH) in H292 cells, we demonstrate repression of TCF transcription at baseline, with activation induced by stimulation with lithium, an inhibitor of GSK-3β and mimicker of class-1 Wnt activity. Our data supports our hypothesis, and we speculate that reactivation of this morphogenetic pathway in adult human lung may play an important role in airway epithelial regeneration, as well as remodelling in airways disease.

This study is funded by: Medical Research Council (UK) G084/5708.


FACTORS INFLUENCING CROSS SECTIONAL AND LONGITUDINAL ASSOCIATIONS BETWEEN EXHALED NITRIC OXIDE AND INDUCED SPUTUM EOSINOPHIL COUNT IN ADULTS WITH ASTHMA

M.A. Berry, R.H. Green, A.J. Wardlaw, I.D. Pavord. M.A. Berry, R.H. Green, A.J. Wardlaw, I.D. Pavord. Groby Road, Leicester LE3 9QP, UK

There is increasing evidence that a management approach that includes monitoring airway inflammation in asthma leads to an improved outcome. Induced sputum eosinophil count and exhaled nitric oxide (NO) concentration are both potential non-invasive measures of airway inflammation, although exhaled NO is more suited to serial measurements. Little is known about the relationship between these two measurements and the factors which influence it. We have investigated the relationship in 246 non-smoking and 75 smoking adults with stable asthma at variable severity who had both exhaled NO and induced sputum eosinophil counts measured on the same visit. We have also examined the relationship between change in sputum eosinophil count and exhaled NO in 75 patients with moderately severe asthma who were participating in a prospective longitudinal study with paired measurements over the period of one year. We found a significant positive correlation between exhaled NO and sputum eosinophil count in males and females. This could be due to the effect of female sex hormones on NO-synthase. The relationship between the variables is much closer in cross sectional study than between change in the variables, suggesting that they identify a common airway abnormality but are regulated differently by factors that alter airway inflammation.

SIMVASTATIN HAS AN ANTI-INFLAMMATORY EFFECT IN A MURINE MODEL OF ALLERGIC ASTHMA

A. McKay, 1 B. Peule, 1 I.B. McIntyre, 1 S. Culpshaw, 1 N.C. Thomson, 1 F.Y. Liew. 1 Departments of Immunology and 1Respiratory Medicine, Western Infirmary and University of Glasgow, UK

Introduction: Asthma is an eosinophilic inflammatory airways disease. There is increasing evidence that statins, such as simvastatin, have anti-inflammatory properties which are unrelated to their lipid-lowering activity. We therefore wished to study the effect of simvastatin in a murine model of asthma.

Methods: BALB/c mice primed with ovalbumin (OVA) were re-challenged with OVA on three consecutive days. Simvastatin 40mg/kg or 4mg/kg or vehicle control were given intraperitoneally (i.p.) at the time of these challenges. Analysis was done one day after the last challenge.

Results: Simvastatin treatment at a dose of 40mg/kg i.p. resulted in a significant reduction in bronchoalveolar lavage (BAL) total cellularularity (mean ± SD: simvastatin 17.9 ± 5.53 × 10^6/ml vs control 9.4 ± 4.99 × 10^6/ml, p < 0.01) and eosinophils (simvastatin 5.99 ± 3.17 × 10^6/ml vs vehicle control 19.9 ± 9.92 × 10^6/ml, p < 0.01). Both high and low dose i.p. simvastatin treatment were associated with a reduction in BAL interleukin (IL)-4 and IL-5 levels and also in OVA-induced IL-4 and IL-5 production in thoracic lymph node (LN) cultures. See table.

Reduced inflammation was observed in lung histology in the simvastatin-treated mice. Serum OVA-specific IgG1, IgG2a, and total IgE levels were unaltered by simvastatin treatment.

Conclusion: These results demonstrate that simvastatin has anti-inflammatory effects in this murine model of allergic asthma.

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<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Simvastatin 40mg/kg i.p.</th>
<th>Simvastatin 4mg/kg i.p.</th>
<th>Vehicle control</th>
</tr>
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<tbody>
<tr>
<td>BAL IL-4 (pg/ml)</td>
<td>13.2 (21.9)**</td>
<td>26.0 (20.2)*</td>
<td>52.6 (32.2)</td>
</tr>
<tr>
<td>IL-5 (pg/ml)</td>
<td>57.8 (30.2*)</td>
<td>90.2 (34.5*)</td>
<td>219.3 (52.2)</td>
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<tr>
<td>LN IL-4 (pg/ml)</td>
<td>55.1 (15.1)**</td>
<td>99.8 (18.3)*</td>
<td>160.9 (11.8)</td>
</tr>
<tr>
<td>IL-5 (pg/ml)</td>
<td>510 (40)**</td>
<td>1096 (76.5)**</td>
<td>1747 (239)</td>
</tr>
</tbody>
</table>

*p.i. intraperitoneally.

A CASE-CONTROL STUDY OF MEMBRANE FATTY ACIDS IN ASTHMA

E. Broadfield, A. Whitehead, N. Lawson, J. Britton, A. Fogarty. University of Nottingham, UK

Rationale: As substrates for eicosanoid production, it is hypothesised that omega-6 polysaturated fatty acids (PUFA) may increase the prevalence and/or severity of asthma. Furthermore as competitive antagonists of this process, omega-3 fatty acids may have a protective role. This study was designed primarily to explore whether asthmatics have increased levels of eicosanoid membrane omega-6 PUFA compared to non-asthmatics, and secondarily whether there are differences in the levels of the other main fatty acids between asthmatics and controls.

Method: Fasting blood samples were taken from 89 asthmatics on inhaled steroids and 89 community controls, matched for age, sex, and area of residence. Percentage levels of the 8 most abundant eicosanoid membrane fatty acids were measured using gas chromatography, and the levels in cases and controls compared using the paired t test.

Results: The levels of two PUFA (palmitoleic and eicosapentaenoic acids) were too small to be measured and were therefore excluded from the analysis. Cases were found to have significantly lower eicosanoid membrane levels of the omega-6 fatty acid linoleic acid and higher levels of the saturated fatty acid stearic acid. See table.

S123
**Drug therapy in cystic fibrosis**

**S124** SEVERAL AND SPUTUM CONCENTRATIONS FOLLOWING THE ORAL ADMINISTRATION OF LINEZOLID IN ADULT PATIENTS WITH CYSTIC FIBROSIS

D. Saralaya, D. Peckham, B. Hulme, C. Tobin, S. Conway. Regional Adult Cystic Fibrosis Unit, Seacroft Hospital, Leeds LS14 6UH, UK

**Introduction:** Linezolid is a new antibiotic with efficacy against Staphylococcal aureus (MRSA). Although licensed for the treatment of respiratory tract infections, there are, as yet, no published trials of its use in cystic fibrosis (CF).

**Methods:** The objective of the study was to evaluate the absorption and sputum penetration of oral Linezolid in CF patients.

**Results:** Mean (SD) serum Linezolid levels were 2.3 mg/l (1.5) at 12 hours following the 5th dose and 13.5 mg/l (4.3) and 8.1 mg/l (3.3) at 2 and 4 hours following the 6th dose. High sputum concentrations were obtained with mean (SD) levels of 3.6 mg/l (2.1) and 17.3 (6.9) at 2 and 4 hours following drug administration. Good sputum penetration was observed with mean sputum to plasma ratio of 1.4 at 2 hours. There was a significant variation in peak levels within the studied population. However, the lowest peak concentration exceeded the MIC 90 for MRSA (2–4 mg/l). Serum levels in this study are slightly lower than levels obtained in non-CF historical controls.

**Conclusion:** The administration of 12 hours, 600mg oral Linezolid to CF patients results in sputum levels that exceed the MIC90 of MRSA for almost the whole dosing period. Further clinical trials are needed to assess the efficacy of Linezolid against MRSA in this patient group.

**S125** A PROSPECTIVE, DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, CROSSOVER TRIAL OF AZITHROMYCIN IN PEDIATRIC CYSTIC FIBROSIS


**Conclusions:** These findings are consistent with the hypothesis that dietary omega-6 PUFAs may be involved in the aetiology of asthma, but not with a protective role for omega-3 fatty acids. The unexpected finding of increased levels of the erythrocyte membrane saturated fatty acid stearic acid warrants further investigation.

**Conclusion:** Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet 1998;351:420.


Cystic fibrosis (CF) may best be managed by therapy directed at restoring the volume of airway surface liquid (ASL). We tested a strategy to increase ASL, and hence mucociliary clearance, by providing an osmotic stimulus to the lower airways using icodextrin, a high molecular weight glucose polymer used in peritoneal dialysis to produce colloid osmosis but never tested in the human lung. In a four to six month trial of azithromycin, 13/41 children on rhDNase, 11/15 needed intravenous antibiotics whilst on azithromycin compared with 6/15 when on placebo (p<0.005). Of the 12/15 children on rhDNase, 11/15 needed intravenous antibiotics whilst on azithromycin compared with 6/15 when on placebo (p<0.005). There were no significant overall changes in forced vital capacity or mid expiratory flow rates but the effect of rhDNase usage was similar for these measurements. Overall, 17/41 subjects had fewer oral antibiotic courses when on azithromycin compared with placebo and 5 subjects had 6 extra courses (p<0.005). Of the 12/15 children on rhDNase, 11/15 needed intravenous antibiotics whilst on azithromycin compared with 6/15 when on placebo (p<0.005). There were no significant overall changes in forced vital capacity or mid expiratory flow rates but the effect of rhDNase usage was similar for these measurements.

**Conclusion:** A four to six month trial of azithromycin is justified in children with CF not responding to conventional therapy.

**Conclusion:** The relative difference in FEV1 between azithromycin and placebo was +5.4% (95% CI 0.8 to 10.5%). 13/41 subjects improved by >13% and 5/41 (p=0.059). In a median relative difference between azithromycin and placebo was +11.5% (5.3 to 16.5) when not receiving concurrent rhDNase (n=26) and –3.6% (–22 to 4.3) for the 15 receiving rhDNase (Mann Whitney p=0.003). There was no significant overall change in forced vital capacity if rhDNase concentrations were outcome measures. Side effects were assessed by pure tone audiometry and liver function tests.

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interaction between aerosol delivery system altered tissue distribution in adults with the utility of salivary levels for monitoring chest tightness in adult and paediatric patients. These data suggest biotics is recommended practice to prevent inhaled antibiotic induced studies have reported the use of salivary trough levels to monitor once of these drugs make monitoring of levels mandatory. Two previous exacerbations of cystic fibrosis (CF) includes an aminoglycoside (AG)

S127 interaction between aerosol delivery system and bronchodilators in CF patients taking colistin

M.E. Dodd, S. Conway, R.J. Marsden, P.H. Weller. Wythenshawe Hospital, Manchester, UK; St. James’s Hospital, Leeds, UK; Profile Therapeutics, UK; The Birmingham Children’s Hospital, Birmingham, UK

Chest tightness is a recognised side effect of nebulised antibiotics (AB). We describe a sub group of patients who nebulised colistin in a clinical trial. Patients using nebulised AB and DNase for >90 days were randomised to use the HaloLite AAD system (AAD) or a conventional high output nebuliser (NEB) over a 182 day period (study MAL 25-70). All patients used bronchodilators, some of the patients in each nebuliser group used a pMDI or DPI (INHL) others used a solution (SNL) form through the study device. This abstract reports preliminary analysis of % predicted FEV1 mean change from baseline to day 28, and to day 182 for each combination of nebuliser (AAD or NEB) and bronchodilator (SNL or INHL).

Results: 189 of 259 patients used colistin. See table.

Two way analysis of variance demonstrated a significant interaction between device type and bronchodilator type for change in FEV1, (p=0.001).

Conclusions: The use of a bronchodilator prior to nebulising antibiotics is recommended practice to prevent inhaled antibiotic induced chest tightness in adult and paediatric patients. These data suggest that the use of a bronchodilator solution with colistin in patients using AAD has a positive effect on maintaining both short and long-term FEV1. This effect was not seen in the NEB group, nor was it evident in patients using INHL.

This study was sponsored by Profile Therapeutics, UK.

S128 the utility of salivary levels for monitoring once daily intravenous aminoglycosides in children with cystic fibrosis

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First line intravenous antibiotic treatment for children with pulmonary exacerbations of cystic fibrosis (CF) includes an aminoglycoside (AG) such as gentamicin or tobramycin. The nephro and ototoxic side effect of these drugs makes monitoring of levels mandatory. Two previous studies have reported the use of salivary trough levels to monitor once daily AGs in patients without CF. Although a correlation was shown between saliva and serum values, there was no confirmation that the method could reliably detect toxic levels. In view of this, and the fact that CF saliva is known to be abnormal, we have assessed the utility of this approach in children with CF. CF children prescribed once daily AGs (10–12 mg/kg) were eligible for inclusion if they were old enough to produce saliva, and if they and their parent consented to the study. 28 patients (21 gentamicin, 7 tobramycin, median (range) age9.9 years (3.9 to 16.7) had simultaneous serum and saliva samples immediately prior to the 3rd dose of drug. In the majority (n=25), a few crystals of citric acid were placed on the tongue to stimulate saliva production, up to 2 ml of which was collected into a sterile polystyrene container. Blood samples were taken by peripheral venepuncture. Saliva collection was well tolerated in all cases. 27/28 patients had a serum level of <1 (mg/L). In 24 of these (89%), the salivary level was also <1, but in 3 patients higher levels were obtained (8.9, 4.9, 4.3). Only one patient had a toxic serum level of 1.6; this patient also had a high salivary level (7.7).

This study demonstrates that both gentamicin and tobramycin can be detected in saliva. The salivary level measured a safe serum level (<1 mg/L) in 89% of children, but in a minority, salivary levels were spuriously high. With regards to safety of salivary monitoring, only one patient had a serum trough level that was considered toxic at >1 (mg/L). In this child, the saliva sample detected this and was also abnormally high. Although these data are promising, confirmation of safety will require evidence from further children that salivary levels are consistently raised in the presence of toxic serum levels.

S129 altered tissue distribution in adults with cystic fibrosis

C.E. Bolton, A.A. Ionescu, W.D. Evans, R. Petit, D.J. Shale. Sections of Respiratory Medicine and Medical Physics, University of Wales College of Medicine, Llandough Hospital, Penarth, Cardiff CF64 2XX, UK

We studied the distribution of altered body composition in 51 adults with cystic fibrosis (CF) colonised with Pseudomonas aeruginosa and 18 age and sex matched healthy subjects. Using DEXA scanning we derived height indices for total fat mass (FM), fat free mass (FFM) and bone mineral content (BMCI) of the right arm, leg and trunk. Spirometry, height, weight, and physical activity (METS) data were determined.

In patients, FMM of the arm and leg were less (p<0.05). The trunctual FMM difference was not significant (possibly due to group diversity or that visera are classified as FFM). Amongst the patients, there was a greater deficit (compared with the mean control) of FMM in the leg than arm than the trunk (18.9%, 14.86%, <0.09%, p<0.02). For patients, FM% for arm, leg and trunk were less (p<0.05) in the severe (FEV1 <45%) than the mild (FEV1 >65%) disease group. Amongst the severe group, there was (p<0.02) greater deficit of FMM in leg (28.68%) than arm (23.76%) than trunk (3.93%). See table.

Patients with a normal BMI, low total FMM (n=10) had a lower (p<0.01) arm, leg and trunk FMM than those with a normal BMI, normal total FMM (n=13). The BMCI of the arm, leg, and trunk of patients were less (all p<0.001) than the controls. There was a lesser BMCI in the severe than the mild (p<0.03) disease. Patients with a normal BMI, low total FMM had a lower (p=0.03) arm, leg, and trunk BMCI than those with a normal BMI, normal total FMM. In all cases, there was no significant difference in the deficit of BMCI between arm, leg, and trunk. Fat mass in patients was not reduced.

<table>
<thead>
<tr>
<th>Device</th>
<th>Baseline age (median (IQR))</th>
<th>Baseline FEV1 (% predicted mean (CI))</th>
<th>% Change in FEV1, % predicted at 28 days (mean (CI))</th>
<th>% Change in FEV1, % predicted at 182 days (mean (CI))</th>
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<tbody>
<tr>
<td>AAD SLN</td>
<td>51</td>
<td>19 (13 to 26)</td>
<td>50 (44 to 56)</td>
<td>6.6 (1.0 to 12.1)</td>
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<tr>
<td>NEB SLN</td>
<td>43</td>
<td>19 (14 to 28)</td>
<td>53 (47 to 60)</td>
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<td>AAD INHL</td>
<td>43</td>
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<td>65 (59 to 70)</td>
<td>-7.3 (-12.5 to -2.1)</td>
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<tr>
<td>NEB INHL</td>
<td>41</td>
<td>15 (13 to 18)</td>
<td>64 (57 to 72)</td>
<td>-0.8 (-4.7 to 3.2)</td>
</tr>
</tbody>
</table>

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### TFN-α: Its role in respiratory disease

**ST30** GENETIC SUSCEPTIBILITY TO OZONE EXPOSURE

I.A. Yang1, O. Holz2, R.A. Jores1, H. Magnussen1, S.J. Barton1, J.A. Cackett1, J.W. Holloway1, S.T. Holgate1. 1Asthma Genetics Laboratory, Division of Human Genetics & IIK (Respiratory, Cell and Molecular Biology), University of Southampton, UK; 2Hospital Grosshansdorf, Center for Pneumology and Thoracic Surgery, Grosshansdorf, Germany

Ozone is a major air pollutant with adverse health effects, yet there is variability in response between individuals. Genetic determinants that modulate ozone-induced lung inflammation have been found in mice specifically inbred to be prone or resistant to ozone exposure. We hypothesised that polymorphisms in homologous human genes would influence response to ozone.

**Methods:** 37 participants (12 asthmatic, 25 healthy) who had undergone ozone challenge (intermittent exercise during inhalation of ozone > 200 ppb) were genotyped using ARMS-PCR for tumour necrosis factor-α (TNF), glutathione peroxidase (GPX1), manganese superoxide dismutase (SOD2) and toll-like receptor 4 (TLR4) polymorphisms.

**Results:** There was no difference in lung function response between asthmatics and healthy participants. Mean change in FEV₁ with ozone challenge was -9.0% baseline in TNF -308G/G individuals, compared to -0.6% baseline in TNF -308G/A or A/A individuals (95% CI for difference between means -14.5 to -2.3, p=0.008, t test). This difference remained significant even when only including 250 ppb exposures for 3h (p=0.007, Mann-Whitney U test, n=32).

No significant differences were detected with GPX1 or SOD2, whereas the TLR4 polymorphism was too infrequent to analyse. No significant interactions between genotypes were observed (General Linear Model, SSAS V11).

**Conclusions:** This is the first study to extend the genetic linkage findings of ozone exposure in mice to clinical ozone challenges. These results suggest that the TNF locus is a genetic factor for susceptibility to ozone exposure, as it is in the mouse. TNF haplotyping of larger cohorts and functional analysis of cellular models are required to confirm these findings.

Supported by: Allen+Hanburys/Thoracic Society of Australia and New Zealand Respiratory Research Fellowship

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**ST31** POLYMORPHISMS IN THE PROMOTER OF TUMOR NECROSIS FACTOR (TNF) ALPHA GENE IN PATIENTS WITH SICCOSSIS AND THE DEVELOPMENT OF PROGRESSIVE MASSIVE FIBROSIS

Y. Ohtuka, X. Wang, K. Kimura1, T. Ishida, J. Saito, M. Munakata, Department of Pulmonary Medicine, School of Medicine, Fukushima Medical University, Fukushima, Japan; 1Wamizawa Rousai Hospital, Hakkaido, Japan

It is well known that there was pronounced individual variation in the severity of silicosis even in the same exposure environments. To explain this, we made our hypothesis that there might be an association between genetic polymorphisms of TNF-α promoter region and lung responses to silica particles in silicotic patients. To examine our hypothesis, we studied the association of TNF-α promoter polymorphisms (−308, −238 and −376) with the coenotypological severity of silicosis in 124 sex, smoking, and exposure history - matched Japanese silicotic patients. Silicotic patients were divided into three groups, Pr (profusion rate) 1 (1/0–1/1, n=47), Pr3 (2/0–2/2, n=36) and PMF (progressive massive fibrosis) (4c, n=43) according to the ILO classification. We also examined 122 healthy controls within the same regional district. TNF-α promoter polymorphisms were determined using PCR-RFLP method. Results showed that frequency of A-308 (GA/AA) genotype is significantly higher in Pr 1 and Pr3 patients, (17% and 22%) as compared with PMF and controls (0% and 4%) (p=0.005). There were no significant differences at the −238 and −376 loci among the groups and controls. There are no linkage disequilibrium among these regions. From these results, the TNF promoter single nucleotide polymorphism (SNP) −308 might affect the development of silicosis.

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**ST32** TFN PROMOTER REGION SINGLE NUCLEOTIDE POLYMORPHISM IN ARDS

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Critical illness in adults frequently predisposes to, or is accompanied by acute lung injury (ALI), which in its most severe manifestation is termed the acute respiratory distress syndrome (ARDS). Therapy for ARDS is supportive and mortality rates remain high (30-70%). The incidence of ARDS in a given patient population is dependent in part upon the nature of the precipitating insult, and by inference upon individual susceptibility. Genetic variation may therefore contribute to the onset of ARDS in at risk populations. Acute inflammation is a major contributing factor to ARDS and TNF is a major mediator of the inflammatory response. We therefore performed a case control study to test the association of a TNF promoter region polymorphism (−857) with ARDS. Patients were consented and DNA extracted from whole blood and stored until time of analysis in sterile water at −20°C. Archived controls were used for comparison. The genotype of the biallelic single nucleotide polymorphism was determined by polymerase chain reaction in association with sequence-specific primers incorporating mismatches at the 3’ end.

Patients with established ARDS (15 UK patients, 28 USA patients) were typed for the TNF −857 promoter region polymorphism and compared with a normal control population (347 UK controls) and an at risk group of surgical lung resection patients (26 UK patients). A significant increase in the risk group (28/347) vs controls was observed in the ARDS group when compared to controls (31% v 14%, p=0.01) and the at risk group (31% v 4%, p=0.006). These preliminary results indicate that variation in the expression of TNF a major pro-inflammatory cytokine may contribute to the onset of ARDS. However increased patient numbers and functionality studies will be required before firm conclusions can be drawn.

Work in part funded by the Dunhill Medical Trust and The British Lung Foundation.

**ST33** AUGMENTATION OF TNF-α-INDUCED APOPTOSIS OF HUMAN NEUTROPHILS BY THE AMINOPEPTIDASE INHIBITORS BESTATIN AND ACTINONIN

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Neutrophil apoptosis plays an important role in the control of lung inflammation, resulting in cell clearance without a pro-inflammatory response. Therapeutic enhancement of this process therefore represents a valid experimental goal. TNF is unique in its ability to induce both neutrophil apoptosis and priming. Aminoapeptidase enzymes (AP) are involved in both protein maturation and degradation, and their inhibition has been shown to induce apoptosis in leukemic cell lines. The aim of this study was to investigate the effect of aminoapeptidase inhibition on TNF-α-induced apoptosis in human neutrophils. Neutrophils were isolated from human blood using...
Epidemiology and ethnicity in respiratory disease

**ST335** EFFECT OF ETHNICITY ON ASTHMA PREVALENCE AND HEALTH SERVICE UTILISATION IN THE UK: A SYSTEMATIC REVIEW


**Background:** Healthcare providers perceive asthma prevalence to be higher in some ethnic minorities than in the white majority UK population but epidemiological studies to date have reached conflicting conclusions.

**Introduction:** Differences in lung function between people of varying ethnic origins may affect interpretation of individual results if inappropriate predicted values are used. Our aim was to characterise differences in spirometry in Asian, black, and white children and relate these to differences in chest dimensions. We hypothesised that Asian children would have smaller values for lung function and the differences would be explained by variations in chest size.

**Methods:** Children were seen in primary schools for measurements of FVC, FEV1, PEF, MMFR, and FEF25 using a spirometer. Chest circumference, chest height, transverse diameter and AP diameter were measured using anthropometric tape measure and anthropometer. Relationships between standing height, lung function, and chest dimensions, gender, and ethnicity were assessed using multiple linear regression analysis.

**Results:** Ninety-three white and 201 Asian children were included in the study. The final models explained 78% of the variability in FVC, 72% in FEV1, and 45% in PEF (adjusted R2). Standing height was the single most important predictor, however height squared, chest height, gender, and chest volume were also useful predictors for some outcomes. Ethnicity also remained an important predictor for all three measures, particularly FVC and FEV1, having adjusted for all other variables. FVC and FEV1 were smaller in the Asian children by 0.23L (95% CI 0.17 to 0.28) and 0.18L (95% CI 0.13 to 0.23) respectively. The average decrement in PEF in Asian children was 10L/min (95% CI -0.2 to 20.6). The influence of chest dimensions (both singly and in combinations to represent the chest volume) was a cylinder or a box on the prediction was examined to see if they explained the ethnic differences in lung function. Only small differences in the regression coefficients for ethnicity were observed when variables related to chest volume were included in the model.

**Conclusions:** Equations taking account of ethnicity have been generated and can be used for the accurate prediction of spirometry. The influence of ethnicity on lung volumes is not explained by differences in chest dimensions. Further research in genetic and socio-economic factors is required in order to determine what factors are responsible for the ethnic differences in lung function reported here.

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**ST334** TREATMENT OF CHRONIC SEVERE ASTHMA WITH A SOLUBLE TNF ALPHA RECEPTOR (ETANERCEPT)

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Tumor Necrosis Factor Alpha (TNF-α) is a pro-inflammatory cytokine implicated in the pathogenesis of asthma. TNF-α is increased in the airways of asthmatics and is involved in the production of IL-8, RANTES and GM-CSF by airway epithelial cells. Therefore, TNF-α is a good case for blocking TNF-α as a therapeutic strategy in asthma. This open labelled study evaluated the efficacy of etanercept— a soluble TNF-α receptor (p75) linked to the Fc portion of human IgG1, in the treatment of chronic severe asthma.

**Methods:** 10 patients (18–65 years) with chronic severe asthma on regular oral corticosteroids (13 ± 10 mg/day), high dose inhaled steroids, long acting inhaled β2 agonists and/or oral theophyllines were enrolled. They had an FEV1 of at least 50% of predicted and demonstrated a reversibility of at least 15% with inhaled salbutamol. The study involved administration of 25mg of etanercept twice weekly for 12 weeks. Lung function measurements, methacholine response, and asthma control questionnaire were completed before and after the study.

**Results:** Treatment with etanercept resulted in clinically significant improvements in the lung function. FEV1 improved from 2.21L/sec (1.81–2.52), median (IQR) to 2.68 L/sec (1.77–2.75, p = 0.037) and the FEV1/FVC ratio improved from 73.63% (68.03–81.27) to 82.39% (69.6–88.72, p = 0.028). The mean asthma control symptom score improved from 26 (18.25–28.5) to 11.5 (4–16, p<0.005). Airway hyper-responsiveness as measured by methacholine dose response improved from 234.44 mg/ml to 9.21 mg/ml (p=0.021). All patients successfully withdrew their nebulised β2 agonist medication from a mean dose of salbutamol 8.25 mg/day.

**Conclusions:** Etanercept improves FEV1, FEV1/FVC ratio, asthma control symptom scores, airway hyperresponsiveness and the use of rescue nebulised bronchodilator medication in patients with chronic severe asthma. Blocking the effects of TNF-α could prove to be an effective and novel therapeutic strategy for the treatment of patients with chronic severe corticosteroid dependent asthma. This abstract was supported by Wyeth Laboratories, Berks, UK.

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**ST34** DETERMINANTS OF VARIATION IN CHEST WALL DIMENSIONS AND HEALTH SERVICE UTILISATION IN THE UK: A SYSTEMATIC REVIEW

G. Netuveli1, A. Sheikh1, B. Hurwitz1, M. Barnes1, M. Fletcher1, M. Levy1, S.R. Durham1. 1.Dept of Primary Health Care, Nottingham, UK

**Background:** Healthcare providers perceive asthma prevalence to be higher in some ethnic minorities than in the white majority UK population but epidemiological studies to date have reached conflicting conclusions.

**Introduction:** Differences in lung function between people of varying ethnic origins may affect interpretation of individual results if inappropriate predicted values are used. Our aim was to characterise differences in spirometry in Asian, black, and white children and relate these to differences in chest dimensions. We hypothesised that Asian children would have smaller values for lung function and the differences would be explained by variations in chest size.

**Methods:** Children were seen in primary schools for measurements of FVC, FEV1, PEF, MMFR, and FEF25, using a spirometer. Chest circumference, chest height, transverse diameter and AP diameter were measured using anthropometric tape measure and anthropometer. Relationships between standing height, lung function, and chest dimensions, gender, and ethnicity were assessed using multiple linear regression analysis.

**Results:** Ninety-three white and 201 Asian children were included in the study. The final models explained 78% of the variability in FVC, 72% in FEV1, and 45% in PEF (adjusted R2). Standing height was the single most important predictor, however height squared, chest height, gender, and chest volume were also useful predictors for some outcomes. Ethnicity also remained an important predictor for all three measures, particularly FVC and FEV1, having adjusted for all other variables. FVC and FEV1 were smaller in the Asian children by 0.23L (95% CI 0.17 to 0.28) and 0.18L (95% CI 0.13 to 0.23) respectively. The average decrement in PEF in Asian children was 10L/min (95% CI -0.2 to 20.6). The influence of chest dimensions (both singly and in combinations to represent the chest volume) was a cylinder or a box on the prediction was examined to see if they explained the ethnic differences in lung function. Only small differences in the regression coefficients for ethnicity were observed when variables related to chest volume were included in the model.

**Conclusions:** Equations taking account of ethnicity have been generated and can be used for the accurate prediction of spirometry. The influence of ethnicity on lung volumes is not explained by differences in chest dimensions. Further research in genetic and socio-economic factors is required in order to determine what factors are responsible for the ethnic differences in lung function reported here.

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**ST336** NORMATIVE DATA FOR TOTAL SERUM IMMUNOGLOBULIN E MEASUREMENTS IN CHILDREN OF 3 ETHNICITIES

E.Y. Chan, S.A. McKenzie. Department of Paediatric Respiratory Medicine, Barts and the London NHS Trust, UK

**Background:** It is about 20 years since total immunoglobulin E (IgE) measurements were published for children without atopic disease. It is possible that the recent increase in atopic disease is reflected in altered measurement in subjects who have no clinical expression of atopy. If the measurement of IgE is to be used as a clinical test of atopy, then contemporary normative data must be available.

**Aim:** To measure total serum IgE in healthy children of three ethnicities born and living in an inner city environment.

**Method:** Subjects were aged 1–12 years of Afro-Caribbean, Bangladeshi, and white British ethnicities with no personal history of allergic disease (asthma, eczema, hayfever, or food allergy). Extra blood (1ml) for the measurement of total IgE was collected when blood was taken for other purposes or when a surgical procedure was being undertaken.

**Results:** Measurements from 151 boys (median age 5.4 years) and 106 girls (median age 6.0 years) included 127 Bangladeshi, 58 Afro-Caribbeans, and 72 white British children. Log10 total IgE increased with age (Log10 IgE = 1.291+0.077*age; p<0.001) but was not related to gender or ethnicity. The data were significantly (6-fold) higher than previously published measurements.

**Conclusion:** These contemporary normative data can be used to determine how useful IgE measurements are in separating healthy children from children with atopic illnesses.


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Spoken sessions

iii41

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Objective: To review systematically the effect of minority ethnic status on asthma prevalence and service utilisation in Britain.

Methods: A systematic review of studies reporting prevalence of and/or hospitalisation for asthma were identified using the standard search strategies. Outcome variables were self reported asthma or wheeze. Only studies on populations living in the UK, reporting data on at least one minority ethnic group and the white majority and on children (below 16 years) were included. Differences in proportions and odds ratios, if reported, were pooled using both fixed and random effects models.

Results: Of the 36 studies identified, five studies reporting data on prevalence and two studies on hospital admission met the inclusion criteria. Meta-analysis of prevalence data was performed on the outcome measures and ethnicity separately using a random effects model. We found no significant difference in asthma or wheeze prevalence between whites and minority ethnic groups in the UK. The two studies reporting hospital admission rates could not be synthesized. Nevertheless, one group (3 to 14 years old) in one of the studies showed a greater odds ratio for Asians for hospitalisation for asthma (OR 2.03, 1.32 to 3.12).

Conclusions: There is no difference in the prevalence of asthma or wheeze between minority ethnic groups and the white majority in the UK. The dearth of data currently available does not allow conclusions to be reliably drawn regarding hospital admission rates for asthma.

Acknowledgments: A NHS R&D National Primary Care Fellowship supports AS. This work has been supported by a grant from the National Asthma Campaign, UK.

Background: Asthma prevalence is higher in males during childhood reversing to a female predominance during adolescence. The timing of this "gender switch" and its relation to other atopic diseases in whole populations is less clear.

Methods: Prevalences of currently active asthma, eczema, and hayfever were extracted from individuals who consulted their GP at least once for one or more of the above in the year April 1998–99. Records were extracted from 47 Scottish Morbidity Recording General Practices (population 252 538).

Results: Changes in the sex distribution were apparent during the adolescent period such that hayfever and asthma became more prominent in females. Females also had a higher prevalence of eczema in childhood that become more prominent in early adulthood. The gender switch for eczema precedes hayfever which in turn precedes that for asthma. See figure.

Conclusion: The similar, although differently phased, patterns in the adolescent gender switch suggests a shared underlying mechanism. Further studies on the relative contributions of sex hormones and socio-cultural influences seem justified.

S139 DO HOUSING IMPROVEMENTS IMPROVE RESPIRATORY HEALTH?

M Somerville1, M Basham2, C Foy2, A Barton3 for the Torbay Healthy Housing Group. 1Plymouth and South Devon Research and Development Support Unit, University of Plymouth, Tamar Science Park, Plymouth, UK; 2Gloucestershire Research and Development Support Unit, UK

Cold, damp housing has been associated with poor respiratory health, but few studies have tried to evaluate the effect of improving housing on the occupants’ health. During a community development project in a deprived area of Torquay, local residents surveyed their council-owned homes and reported high levels of damp, mould, and respiratory illness. Torbay Council agreed to improve the houses over a 12-month period and funding was obtained for evaluation. Of the 142 houses on the estate, 119 agreed to randomisation, which was carried out at a public meeting: 50 houses were selected for improvement in the first year. Measurements of the indoor environment, general and respiratory health were taken at baseline and annually for the next two years in all houses and for all occupants.

At baseline, there were 480 people living in 119 houses. The population profile was young, with 58% aged 20 and under and 10% aged 50 and over. Bedroom and living room temperatures improved after renovation (central heating and insulation), but only bedroom temperatures showed a significant difference (p=0.002) between improved and unimproved houses at the end of the first year.

Self-reported asthma prevalence in those aged under 18 years declined from 24% at baseline to 14% at the end of the study. Frequency of asthma symptoms reported in the month before each survey also reduced. The difference between those living in improved and unimproved houses at the end of the first year was not significant. Severity, as estimated by BTS asthma steps, remained unchanged in those continuing to report asthma. The study demonstrates the feasibility of evaluating the health effects of housing improvements. Further work is in progress to evaluate the social and economic impact of the renovations.


S140 FACTORS ASSOCIATED WITH QUALITY OF LIFE IN A COMMUNITY BASED SAMPLE OF YOUNG ADULTS WITH ASTHMA

W Chaudhri1, J Knox1, D Jarvis1, B D W Harrison1, R Hall1, D Seaton1, P Burney1, S Chinn1, C Luczynska1. 1Dept of Public Health Sciences, Kings College, London, UK; 2Norfolk and Norwich Hospital, Norwich, UK; 3IPsich Health, Health Road, Ipswich, UK

Quality of life (QOL) in asthma patients provides a measure of the effect of the disease on an individual’s everyday life but there is little information on factors associated with QOL in asthmatics in the UK. In 1997/1998 a short questionnaire was sent to 1140 subjects who took part in the East Anglia Respiratory Health Survey (EARHS I) in 1991. Responders with symptoms suggestive of asthma (waking with shortness of breath OR having an asthma attack in last twelve months OR current use of asthma medication) completed the Marks’ QOL Questionnaire (4 domains—breathlessness, mood, social, and concerns). Regression analyses were conducted on the square root transformed QOL score to determine the difference in mean adjusted QOL score (MEAN DIFF) by gender, age group, (<35, 35–44.9, ≥45), social class group, smoking status, and whether symptoms were present in EARHS I. To examine associations within each domain Mann Whitney tests were performed. Of the 983 who responded, 242 subjects aged between 27 and 53 years had symptoms of asthma and information on QOL. Worse QOL was reported by women (MEAN DIFF: 0.19; 95% CI 0.04,0.33) and those who had asthma in EARHS I (MEAN DIFF: 0.27, 95% CI 0.11,0.43). Worse QOL was observed in social class V and those with undetermined social class (housewives/students). Women had higher scores than men in the mood (p<0.01), social (p=0.02) and concern domains (p=0.04) but not in the breathlessness domain (p=0.14). Compared to those with “new onset asthma” those with asthma at EARHS I had higher scores in the breathlessness (p<0.01), social (p<0.01) and concern (p<0.01) domains but not in the mood domain (p=0.24). These findings show that amongst asthmatics, women and those who have had disease for a longer period of time report worse quality of life.

Funded by the National Asthma Campaign.

Abstract S138 “Active” asthma and eczema.

S138 MIND THE GAP! AGE AND SEX RELATED CHANGES IN THE EXPRESSION OF ASTHMA, ECZEMA, AND HAYFEVER

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DO HOUSING IMPROVEMENTS IMPROVE RESPIRATORY HEALTH?

M Somerville1, M Basham2, C Foy2, A Barton3 for the Torbay Healthy Housing Group. 1Plymouth and South Devon Research and Development Support Unit, University of Plymouth, Tamar Science Park, Plymouth, UK; 2Gloucestershire Research and Development Support Unit, UK

Cold, damp housing has been associated with poor respiratory health, but few studies have tried to evaluate the effect of improving housing on the occupants’ health. During a community development project in a deprived area of Torquay, local residents surveyed their council-owned homes and reported high levels of damp, mould, and respiratory illness. Torbay Council agreed to improve the houses over a 12-month period and funding was obtained for evaluation. Of the 142 houses on the estate, 119 agreed to randomisation, which was carried out at a public meeting: 50 houses were selected for improvement in the first year. Measurements of the indoor environment, general and respiratory health were taken at baseline and annually for the next two years in all houses and for all occupants.

At baseline, there were 480 people living in 119 houses. The population profile was young, with 58% aged 20 and under and 10% aged 50 and over. Bedroom and living room temperatures improved after renovation (central heating and insulation), but only bedroom temperatures showed a significant difference (p=0.002) between improved and unimproved houses at the end of the first year. Self-reported asthma prevalence in those aged under 18 years declined from 24% at baseline to 14% at the end of the study. Frequency of asthma symptoms reported in the month before each survey also reduced. The difference between those living in improved and unimproved houses at the end of the first year was not significant. Severity, as estimated by BTS asthma steps, remained unchanged in those continuing to report asthma. The study demonstrates the feasibility of evaluating the health effects of housing improvements. Further work is in progress to evaluate the social and economic impact of the renovations.


Funded by the National Asthma Campaign.

Abstract S138 “Active” asthma and eczema.
Drug therapy in COPD

**S141** BUDESONIDE/FORMOTEROL IN A SINGLE INHALER (SYMBICORT®) REDUCES SEVERE EXACERBATIONS IN PATIENTS WITH MODERATE TO SEVERE COPD

L.M. Campbell, W. Szafrański on behalf of the study group. 1Department of Medicine, University of Glasgow, UK; 2Department of Lung Diseases, Voivodeship Specialist Hospital, Radom, Poland

The efficacy of budesonide/formoterol in a single inhaler (B/F, Symbicort®) on COPD exacerbations was evaluated in a placebo-controlled, parallel-group, multicentre study. 812 adult patients with established COPD (median 5 years since diagnosis, mean age 64 years, mean baseline FEV1 0.99 L (36% predicted)) received two inhalations of either B/F 160/4.5 µg (total delivered dose 320/9 µg), budesonide (B) 200 µg metered dose, formoterol (F) 4.5 µg delivered dose, or placebo (Pl) bid for 12 months.

Numbers of severe exacerbations (requiring oral steroid course (OSC) and/or antibiotics and/or hospitalisation) were recorded. Mean severe exacerbation rates were 1.4, 1.6, 1.8, and 1.9 exacerbations per patient in the B/F, B, F, and Pl groups, respectively. Severe exacerbations were reduced by 24% (p=0.035), 15% (p=0.224) and 2% (p=0.895) in Pl with B/F, B and F; B/F also reduced mean exacerbation rates by 23% (p=0.043). The lowest rates of OSC associated with exacerbations were in the B/F and B groups (0.74 and 0.76 OSC/patient/y v 1.04 and 1.07 with F and Pl). B/F and B reduced the number of OSC by 31% and 29% v Pl (both p<0.05), and B/F v F by 28% (p<0.05).

Thus, budesonide/formoterol in a single inhaler (Symbicort®) produced statistically and clinically significant reductions in severe exacerbations in patients with moderate to severe COPD and was more effective than either budesonide or formoterol alone.

**S142** BUDESONIDE/FORMOTEROL IN A SINGLE INHALER (SYMBICORT®) PROVIDES EARLY AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION IN MODERATE TO SEVERE COPD

P. Anderson on behalf of the study group. Dept. Respiratory Medicine, Sheffield Chest Clinic, Sheffield, UK

COPD patients (n=812, median 5 y since diagnosis, mean age 64 years, mean baseline FEV1 0.99 L [36% predicted]) received 2 inhalations of budesonide/formoterol (B/F, Symbicort®) 160/4.5 µg (total delivered dose 320/9 µg), budesonide (B) 200 µg metered dose, formoterol (F) 4.5 µg delivered dose or placebo (Pl) bid for 12 months.

Lung function was assessed by FEV1 and PEF. All treatments significantly improved FEV1 v Pl, B/F increased FEV1 by 15% v placebo, 9% v B (both p<0.001) and 1% v F [ns]. These improvements were maintained throughout the 12-month study. In the first day, B/F increased morning PEF (mean change from run-in) by 10.9 L/min (Pl by 0.3 L/min, B−0.3 L/min; F 6.4 L/min; B/F v Pl and B, p<0.001, B/F v F, p=0.081). After the first week, B/F increased morning PEF by 15.6 L/min (Pl by 1.1 L/min, B 3.4 L/min, F 8.8 L/min; B/F v Pl and B, p<0.001, B/F v F, p=0.002). At 12 months, B/F improved morning PEF by 26.4 L/min (Pl by 2.4 L/min, B 10.6 L/min, F 14.7 L/min; B/F v Pl and B, and F all p<0.001) and improved evening PEF by 23.1 L/min (Pl by 3.0 L/min, B 8.6 L/min, F 11.8 L/min; B/F v Pl and B and F all p<0.001). Budesonide/formoterol (Symbicort®) provides rapid and sustained, clinically relevant improvements in lung function in patients with moderate to severe COPD, with greater improvements in PEF than placebo or either monocomponent.

**S143** BUDESONIDE/FORMOTEROL IN A SINGLE INHALER (SYMBICORT®) PROVIDES SUSTAINED RELIEF FROM SYMPTOMS IN MODERATE TO SEVERE COPD

L.M. Campbell, W. Szafrański on behalf of the study group. 1Department of Medicine, University of Glasgow, UK; 2Department of Lung Diseases, Voivodeship Specialist Hospital, Radom, Poland

Symptom relief with budesonide/formoterol (B/F, Symbicort®), budesonide (B), formoterol (F) or placebo (Pl) was compared in patients with moderate to severe COPD. 812 patients (mean age 64 years) received 2 inhalations of either B/F 160/4.5 µg [total delivered dose 320/9 µg], B 200 µg metered dose, F 4.5 µg delivered dose or Pl bid for 12 months. Daytime symptom scores of shortness of breath, cough and chest tightness, night-time awakenings due to symptoms (all 0–4 [none to severe], total symptom score (0–16) and reliever medication use were recorded. B/F decreased individual and total scores after 1 week v Pl, B, and F (all p<0.001). At 12 months, B/F reduced the total scores v Pl, B and F by 1.12 (both p<0.001) and 0.41 (p=0.043). B/F reduced shortness of breath scores by 0.36 v Pl and 0.26 v B (both p<0.001), decreased chest tightness scores by 0.21 v Pl (p=0.001) and 0.13 v B (p=0.043), decreased cough scores by 0.19 v Pl (p=0.002) and 0.22 v B (p<0.001) and decreased awakening scores by 0.34 v Pl (p<0.001), 0.20 v B (p=0.003) and 0.16 v F (p=0.019). B/F increased symptom-controlled days by 7% v Pl (p<0.001), increased awakening-free nights by 14% v Pl (p<0.001) and 10% v B (p<0.001), increased days free from shortness of breath by 12% v Pl (p<0.001) and increased days free from chest tightness by 7.5% v Pl (p=0.015). B/F reduced use of reliever medication by 1.3 and 0.7 inhalations/24h v Pl and B (both p<0.001), and increased reliever-free days by 8.6% v Pl (p=0.003). Budesonide/formoterol (Symbicort®) provides early and sustained relief from symptoms in patients with moderate to severe COPD.

**Abstract S144**

<table>
<thead>
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<th>Study</th>
<th>Clariatrmycin</th>
<th>Placebo</th>
<th>p Value</th>
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</tbody>
</table>
Effect of budesonide/formoterol on severe exacerbations and lung function in moderate to severe COPD

P.M.A. Calverley on behalf of the Symbicort® study group. University Hospital Aintree, Liverpool, UK

Inhaled corticosteroids (ICS) are recommended in the prevention of COPD exacerbations in patients with an FEV₁ < 50% predicted. Whether long-acting β-agonist therapy is equally effective as ICS, or the combination superior to the components, is not known. We studied 1022 adults (mean age 64 yrs; mean FEV₁ 0.99 L [36% predicted]) with a history of at least one exacerbation in the previous year. To ensure baseline stability, all received formoterol (F) 9 µg bid and oral prednisolone 30 mg od for two weeks. Patients were then randomised to receive either F 9 µg, budesonide (B) 400 µg, budesonide/formoterol in a single inhaler (B/F, 320/9 µg respectively) or an identical placebo (PL), all given bid for 12 months. Severe exacerbations (as episodes requiring oral corticosteroid and/or antibiotics and/or hospitalisation) and lung function on 6 occasions post-randomisation were measured. B/F prolonged time to the first exacerbation v F (p<0.01), B and PL (both p<0.05); B/F reduced the relative risk of exacerbating by 30% v F, 29% v PL (both p<0.01) and 23% v B (p<0.05). The mean number of exacerbations/patient/year was 1.38, 1.60, 1.85 and 1.80 for B/F, B, PL, and F, respectively. The time to first severe exacerbation increased as the number of oral steroid courses was reduced by B/F compared with all other treatments: reductions of 45% v PL (p<0.001), 28% v B (p<0.05) and 30% v F (p<0.05). In addition, significantly fewer patients withdrew while taking B/F (p=0.001) v PL and F (p=0.05 v B). Post-dose FEV₁ increased significantly with B/F: 14% v PL (p<0.001), 11% v B (p=0.001) and 5% v F (p=0.01).

These data show that combining budesonide and formoterol produces a greater reduction in the severe exacerbation rate than either drug alone, even in moderate to severe COPD, and that this can be achieved with relatively modest doses of the inhaled corticosteroid.

A double blind double cross over comparison of high dose combined β₂ agonist and anticholinergic bronchodilators delivered by nebuliser or by inhaler and spacer in moderate to severe stable COPD patients

S.C. Johnson¹, E. Gardener¹, S.P. Hanley¹. Physiotherapy department, ¹Department of Research and Development ³Medical Directorate, North Manchester General Hospital, M8 6RL, UK

Introduction: This abstract reports a comparison of high dose salbutamol + ipratropium bromide delivered by inhalerspacer or by nebuliser in a group of moderate to severe COPD patients. The effects on breathlessness and peak flow are reported.

Methods: Study design: baseline assessment followed by two crossover treatment cycles of 28 days. The two treatment periods in each cycle, given in random order, comprised: (a) 14 days of nebulised 2.5mg salbutamol and 500mcg ipratropium bromide or (b) 14 days of ‘Combivent’ (100mcg salbutamol +20mcg ipratropium bromide) 6 puffs via VolumaticJ spacer. A double dummy technique was used to blind patient and operator. The San Diego Shortness of Breath Questionnaire (SOBQ) was measured at the end of each treatment period. Peak flow (PEF) was recorded twice daily. Visual analogue score (VAS) of breathlessness was recorded each evening. Analogue score differences.

Results: Fifty patients entered the study, mean age 68 years (SD7.5) FEV₁ 0.8 litres (SD 0.31) FEV₁% 34% (SD 11.7). Analysis depending on the order of treatment) was assessed using a graphical test was used to detect any between treatment differences.

Conclusions: Although patients often request nebuliser treatment, this study does not support its prescription in stable COPD patients.

Survey of attitude of 100 patients with COPD to artificial ventilation and cardiopulmonary resuscitation

K.A. Gaber, M. Barnett, Y. Blanchant, C.R. McGavin. Chest Clinic, Derri- ford Hospital, Plymouth, UK

Doctors are being encouraged to discuss and document end of life decisions with vulnerable patients admitted to hospital as part of involving patients in their own management. We wanted to ascertain the views of COPD patients.

Method: Patients with COPD under follow up by Respiratory Nurse Specialists (RNS) and the Chest clinic (of Derriford Hospital) were surveyed. Patients were approached by letter and personally by RNS. Written information about COPD and its clinical management including Non Invasive Ventilation (NIV), Invasive Ventilation (IV), and Cardiopulmonary Resuscitation (CPR) were given and discussed with each patient. Consent was obtained. Patients were asked to fill in Quality Of Life Questionnaire (locally developed at Plymouth University). The following information were obtained: age, sex, spirometry, hospital admissions, or antidepressant usage in the last 12 months and oxygen usage. Patients were asked to consider scenario in which they were admitted to hospital and after standard treatment, failed to improve, continued to deteriorate or developed cardiopulmonary arrest.

Reaching that stage, would you wish to have NIV, IV or CPR?

Results: 100 patients were surveyed (41 were males and 59 females), mean age of 74 (48–92) years. The mean FEV₁ was 0.78 (0.41–1.3) l and FEV₁% 42.7% (11–96%). 50% of patients had FEV₁ < 40% predicted and 35% had FEV₁ between 40 and 59 predicted. 24 patients (24%) were on LTOT, 8 (8%) used antidepressant and 56 (56%) had been admitted to hospital over the last 12 months. 48 patients (48%) wanted all treatments (CPR, NIV and IV) and 12 (12%) wanted none. 19 patients (19%) said No for CPR but “Yes” to NIV and IV. 10 patients (10%) said “No” for CPR and IV but “Yes” for NIV. The remaining 11 patients (11%) gave mixed answers. Using ANOVA analysis and Chi Square test there were no significant statistical differences between the groups. Conclusion; The commonly available measurable parameters of COPD could not predict patients views on CPR, NIV, or IV. These issues should be discussed with vulnerable patients preferably before hospital admission.
These data demonstrate that breathlessness, cough and sputum production are frequent and important symptoms in patients with COPD, and that physicians may underestimate the severity and restrictive impact of these symptoms, and others, on COPD patients quality of life.

<table>
<thead>
<tr>
<th>Abstract S149</th>
<th>WHAT DOES THE GENERAL PUBLIC KNOW ABOUT COPD?</th>
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<tbody>
<tr>
<td>D.M.G. Halpin(^1), C. Ferenbach(^2), D. Bellamy(^3), M. Rudolf(^4) on behalf of the BTS COPD consortium. (^1)Royal Devon &amp; Exeter Hospital, (^2)St Mary’s Hospital, Portsmouth, UK, (^3)James Fisher Medical Centre, Bournemouth and (^4)Ealing Hospital</td>
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As part of continuing activities to promote the implementation of key messages contained in the BTS COPD guidelines the BTS COPD consortium undertook market research among the general population to help understand public knowledge about COPD and their attitude to chronic respiratory symptoms. MORI were commissioned to add a number of questions drafted by members of the Consortium to their weekly omnibus survey. A representative sample of 866 adults (age 15 and over) were interviewed in their own homes in 188 locations around the UK. 49% were lifelong non-smokers, 20% ex-smokers and 31% current smokers. Over 90% of respondents said that they had heard of asthma. Parkinson’s disease, cervical cancer, MS and chronic bronchitis. 79% had heard of emphysema but only 35% had heard of COPD. A larger proportion of smokers had heard of COPD (45%) compared with non-smokers (24%). Knowledge about smoking as a causative factor for various conditions was mixed. A majority of respondents (53%) thought that cervical cancer was the most common of these conditions. Only just over half of the respondents suggested that breathlessness on exertion or coughing could be the first signs of a serious lung disease. Many respondents had experienced persistent respiratory symptoms, but only just over half had consulted their GP about them. In 2 out of 3 cases this was because they were unconcerned or unaware that the symptoms may be important, and in nearly 1 in 4 cases this was because they thought they would simply be told to stop smoking. See table.

One in three members of the public state that they had heard of COPD, but many more recognise the terms chronic bronchitis and emphysema. Few were aware that COPD is common and is caused by smoking. Many individuals experience persistent respiratory symptoms but nearly half had not reported these to their GP often because they were unaware of their importance.

<table>
<thead>
<tr>
<th>Abstract S150</th>
<th>MORTALITY PROJECTIONS FOR OBSTRUCTIVE LUNG DISEASE IN ENGLAND &amp; WALES</th>
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<tbody>
<tr>
<td>COPD: 56.9 61.3 62.3 69.9 75.1 78.9 79.4 &lt;0.001</td>
<td>All: 60.76 63.04 65.21 69.05 71.98 75.52 78.63 &lt;0.001</td>
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</table>

COPD dying in hospital. Examination of all-cause mortality figures showed a similar trend. See table.

The figures for asthma showed a less striking trend to increase but this increase was not evident in the younger age group (under 40), perhaps reflecting the problems with mis-certification of asthma deaths.

**Conclusion:** An ever increasing proportion of patients with COPD die in hospital, reflecting a trend in the population in general. The reason for this trend needs further investigation and the observation should inform discussions on resource allocation and end of life care for patients with COPD.

<table>
<thead>
<tr>
<th>Abstract S151</th>
<th>WHERE DO COPD PATIENTS DIE?</th>
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<tbody>
<tr>
<td>M. Sridhar(^1), I. Grace(^1), M.R. Partridge(^1) (^1)Imperial College of Science, Technology and Medicine, NHS HU Division; (^2)Department of Statistics at Charing Cross Hospital, London</td>
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</table>

**Background:** We analysed mortality statistics for England and Wales from the Office of National statistics to determine the place of death of patients certified as having died primarily due to COPD (COAD, chronic bronchitis or emphysema) between the years 1970 to 2000 (at 5 year intervals). Deaths were classified as having occurred in a hospital or other health care institution (nursing home, NHS Mental health Units) or at home (the usual residence of the deceased or other, including residential homes). As a comparison the place of death of patients certified as having died with asthma and all causes were also analysed.

**Results:** Over the years between 1970 and 2000 there was gradual and significant increase in the proportion of patients dying at home, which could be interpreted as a reflection of the fact that patients are living longer, and that physicians may underestimate the severity and restrictive impact of these symptoms, and others, on COPD patients quality of life.

**Abstract S152 | THE EFFECT OF MITE ALLERGEN CONTROL BY THE USE OF ALLERGEN-IMPERMEABLE COVERS IN ADULT ASTHMA: THE SMAC TRIAL**

A. Custovic, L. Forster, E. Matthews, J. Martin, L. Lelley, M. Vickers, J. Britton, D. Strachan, P. Howarth, D. Altman, C. Frost, A. Woodcock and MRC GP research framework. MRC General Practice Research Framework at the MRC Clinical Trials Unit, Stephenson House, 158–160 North Gower Road, London NW1 2ND

There is a considerable controversy about the effectiveness of dust mite allergen avoidance in asthma. We carried out a randomised, parallel...
group, double-blind, placebo controlled trial of dust mite avoidance (allergen-impermeable covers for mattress, pillow, and quilt) in adult asthmatics. At entry, mite-specific IgE was determined, and patients were randomised with minimisation on smoking, pet ownership and mite-specific IgE. Patients and assessors were blind to the patients’ dust mite sensitivity status. From 2479 patients who were screened for eligibility, 1150 from 135 general practices were randomised to receive active (n=574) or placebo (n=576) bed covers. PEFR was recorded twice daily during a 4 week run-in period and during months 6 and 12 of the study. In the first 6 months of the trial patients took their usual inhaled steroid therapy. Following this, a controlled reduction of inhaled steroids was attempted until either all inhaled steroid was discontinued, or until asthma control deteriorated (Months 7–12). Homes were visited at the start in all patients, and revisited at 6 and 12 months in a 10% random sample to collect mattress dust for measurement of Der p.1. Der p 1 was significantly lower in the active group at 6 months (p=0.023), but there was no difference between the groups at 12 months. 65.4% and 65.1% of patients were mite sensitive in the active and placebo group respectively. A total of 457 active and 459 placebo patients had PEFR data at both baseline and 6 months. PEFR improved significantly in both groups (active 409.7 to 417.7 l/min, p<0.0001; placebo 419.3 to 428.9 l/min, p<0.0001). After adjusting for baseline differences using analysis of covariance, there was no significant difference between the two groups (difference 4.11 [−6.55, 2.32], p=0.35; mite sensitive subjects −1.71 [−7.28, 3.85] p=0.55). There was no difference between the groups in complete cessation of inhaled steroids or the proportionate change in steroid dose during reduction at 12 months, either in all subjects or in mite sensitive subjects only. In conclusion, allergen-impermeable bed covers seem clinically ineffective for routine management of adult asthma in primary care in the UK.

**S153 EXPOSURE TO INDOOR AEROALLERGENS AND SUBSEQUENT SENSITISATION AND WHEEZE IN AN ENGLISH BIRTH COHORT**

J.M. Harris, P. Cullinan, P. Mills, S. Moffat, C. White, A.J. Newman Taylor. Occupational & Environmental Medicine, Faculty of Medicine, Imperial College of Science, Technology and Medicine, London, UK

A prospective cohort study of childhood asthma and allergic disease based in Ashford, Kent has been underway since 1993. A consecutive series of newborns were recruited (93% of those eligible) and 642 babies were born. Eight weeks after birth samples of dust from the living room floor and infant’s beds were collected. Levels of indoor allergens (Der p 1, house dust mite, and Fel d1, cat fur) were measured. Each child was visited annually, and at ages 5–6 sensitivity to Der p 1, Fel d1 and mixed grass pollens was measured in 552 (86%) children using skin prick tests. The prevalence of sensitisation (mean weal diameter 2mm+ greater than the negative control) to these allergens were 10%, 9% and 9% respectively; 92 (17%) of the children were atopic. Thirty nine atopic children (7% of cohort) were wheezing at the highest exposure levels may be explained by an immunotolerant or by confounding determinants of sensitisation. Further investigations into these are underway.

**S154 ATOPI, ASTHMA, HAYFEVER AND THE RESPONSE TO INTRADERMAL TESTING WITH ENVIRONMENTAL MYCOBACTERIA AMONG CHILDREN IN RURAL CRETE**

C. Zekveld, P. Cullinan, I. Dimitroulis, A. Pedioti, V. Bibaki-Liakou, I. Bibakis, J. Stanford, A. Newman Taylor. Department of Occupational and Environmental Medicine, Imperial College (NHL), London; Anti-Tuberculosis Unit, Venetoallergen, Heraklion, Crete; Department of Medical Microbiology, University College Hospital, London

Subclinical infection with environmental mycobacteria (eMB) may exert a strong immunoregulatory effect. Among 805 children aged between 8 and 18 years, and living in rural Crete, we examined skin responses to intradermal inoculation with four locally prevalent eMB species (M. gordonae, M. fortuitum, M. intracellulare, and M. chelonae) identified by pilot testing with 20 species in three villages. We compared the skin responses between children with or without atopy (as judged by skin prick testing), asthma or hayfever. Virtually all children had received BCG vaccination. 643 (80%) children had a positive response (3mm or more) to at least one eMB species; 147 (18%) reacted to all four. 182 (23%) children had a positive skin prick test to one or more local allergen; the prevalences of current wheeze (4%) and seasonal rhinitis (5%) were much lower. Intradermal responses to eMB were unrelated to any of the outcomes in this population. This was true for each or all of the eMB species, and also for stronger (10mm or more) responses. Moreover there was no evidence, among atopic children, of a relationship between eMB skin responses and the presence of absence of allergic symptoms. These findings do not support the suggestion that early infection with environmental mycobacteria is protective in the development of childhood allergic diseases.

**S155 DOES VACCINATION INCREASE THE RISK OF DEVELOPING ALLERGIC DISEASE?: A BIRTH COHORT STUDY**

T.M. McKeever, S.A. Lewis, C. Smith, R. Hubbard. Division of Respiratory Medicine, University of Nottingham, UK

**Objectives:** There has been a rise in allergic disease prevalence in the last couple of decades, and one hypothesis for this increase is the introduction of widespread immunisation against infectious diseases.

**Methods:** Using the West Midlands General Practice Research Database, we have used a previously established birth cohort to examine the effect of vaccination to diphtheria, polio, pertussis and tetanus (DPT) or measles, mumps and rubella (MMR) on the incidence of doctor diagnosed asthma and eczema.

**Results:** In univariate analysis there was an association between vaccination and the development of allergic disease such that vaccination to DPT increased risk of asthma (HR 14.0 95% CI 7.3–26.9) and eczema (HR 9.4 95% CI 5.9–14.9) and similar strong effects were seen for vaccination to MMR. However there were significant interactions between vaccination and consulting behaviour, such that the effect of vaccination was limited to those in the lowest level of consulting behaviour, and was no longer significant in subsequent levels of consulting behaviour, suggesting that the initial observed effects were due to ascertainment bias.

**Conclusions:** Our data suggest that it is unlikely that currently recommended routine vaccinations are a risk factor for asthma or eczema.

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### Abstract S153

<table>
<thead>
<tr>
<th>Der p1</th>
<th>n (%) sensitised</th>
<th>n (%) atopic wheezing</th>
<th>Fel d1</th>
<th>levels (µg/g)</th>
<th>n (%) sensitised</th>
<th>n (%) atopic wheezing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02–0.39</td>
<td>10 (7%)</td>
<td>7 (5%)</td>
<td>0.01–0.53</td>
<td>8 (6%)</td>
<td>7 (5%)</td>
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<tr>
<td>0.39–1.28</td>
<td>18 (14%)</td>
<td>13 (10%)</td>
<td>0.33–1.76</td>
<td>11 (8%)</td>
<td>11 (8%)</td>
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<tr>
<td>2.58–6.6</td>
<td>17 (12%)</td>
<td>11 (8%)</td>
<td>1.76–18</td>
<td>17 (12%)</td>
<td>11 (8%)</td>
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<tr>
<td>6.6–385</td>
<td>7 (5%)</td>
<td>7 (5%)</td>
<td>18–1415</td>
<td>11 (8%)</td>
<td>10 (7%)</td>
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</table>
REGULAR OILY FISH CONSUMPTION IS PROTECTIVE AGAINST SYMPTOMATIC ASTHMA

B. Patel, R. Luben, D. Lomas, N. Wareham. Departments of Public Health and Primary Care, and Department of Medicine, University of Cambridge, Hills Road, Cambridge

Oily fish is rich in n-3 polyunsaturated fatty acids (PUFAs). While n-6 PUFAs are the main substrate for the production of arachidonic acid (AA), n-3 PUFAs are competitive inhibitors of AA metabolism, and may reduce the production of 4-series leukotrienes and bronchoconstricting prostaglandins such as PGD2 from AA.

To assess the association between oily fish consumption and symptomatic asthma, we conducted a nested case control study within the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort. Between 1993 and 1998 all participants completed a baseline health and lifestyle questionnaire (HLQ). Cases were selected by a positive response and controls by a negative response to the question “has your doctor ever told you have asthma?” in the HLQ. Frequency of oily fish consumption was also recorded in the HLQ. In 1998 potential cases and matched controls were asked to complete the East Anglia Respiratory Questionnaire about respiratory symptoms experienced in the previous 12 months.

Complete data were available on 333 cases who reported wheeze in the previous 12 months, and 437 asymptomatic controls. Significantly more controls than cases reported eating oily fish at least twice a week (12.4 % v 7.5 %, p=0.03). In logistic regression analysis, after adjusting for age, sex, BMI, social class and smoking, regular oily fish consumption (= twice a week) relative to rare (< than once a week) was associated with a reduced odds ratio (OR) for wheeze with regular oily fish consumption in this group was 0.54 (p=0.28).

In conclusion we have shown an association between oily fish consumption and symptomatic wheeze in people with diagnosed asthma and without diagnosed asthma. These data support the hypothesis that regular consumption of oily fish may be protective against symptomatic asthma.

Abstract S157

<table>
<thead>
<tr>
<th>Maternal vitamin E intake</th>
<th>Wheeze in the 2nd year† (n=98)</th>
<th>Eczema in the 2nd year† (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet + supplements</td>
<td>Diet only</td>
<td>Diet + supplements</td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.65 (0.30–1.34)</td>
<td>0.57 (0.27–1.17)</td>
</tr>
<tr>
<td>3</td>
<td>0.56 (0.27–1.15)</td>
<td>0.61 (0.31–1.23)</td>
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<tr>
<td>4</td>
<td>0.55 (0.26–1.16)</td>
<td>0.50 (0.24–1.07)</td>
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<tr>
<td>5</td>
<td>0.58 (0.26–1.19)</td>
<td>0.50 (0.23–1.07)</td>
</tr>
<tr>
<td>p (trend)</td>
<td>0.107</td>
<td>0.065</td>
</tr>
</tbody>
</table>

*p< 0.05; †logistic regression: odds ratio (95% CI) adjusted for gender, maternal age, maternal atopy, social class, maternal smoking & antibiotics; *Quintiles of intake.

THE EFFECTS OF MATERNAL DIET AND EARLY ANTIBIOTIC USE ON ALLERGIC DISEASE IN THE SECOND YEAR OF LIFE

S. Fleming, G. McNeill, G. Devereux, A. Seaton. Department of Environmental and Occupational Medicine, University of Aberdeen, UK

The suggestion that maternal and early life influences may be important in the onset of allergic disease is being investigated. A cohort of 2000 pregnant women was identified and their diet assessed by food frequency questionnaire during pregnancy. Allergic disease was assessed in their children at 6, 12 & 24 months of age. Questionnaire data were available from 1371 children for the 2nd year of life. Wheeze and eczema were associated with male gender, maternal atopy, social class and maternal smoking but not with maternal dietary antioxidant vitamins. However when the analysis was restricted to atopic mothers only (n=714), an inverse association between maternal vitamin E intake and eczema was found as shown in the table.

There were positive associations between eczema and early antibiotic administration, which remained when the analysis was restricted to antibiotics given for non-skin conditions in the first 6 months and the development of eczema from 7–24 months (OR 1.33, p=0.038). A similar association with wheeze disappeared when restricted to antibiotics given for non-chest conditions. This may be an indication of the effect of early antibiotics on the development of atopy. Vitamin E intake during pregnancy and early introduction of antibiotics may be related to the onset of allergic disease in childhood.

Abstract S157

<table>
<thead>
<tr>
<th>Wheeze in the 2nd year† (n=98)</th>
<th>Eczema in the 2nd year† (n=160)</th>
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<tbody>
<tr>
<td>Maternal vitamin E intake</td>
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<tr>
<td>Diet + supplements</td>
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<td>1</td>
<td>1.00</td>
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<td>4</td>
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<td>5</td>
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</tr>
<tr>
<td>p (trend)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

*p< 0.05; †logistic regression: odds ratio (95% CI) adjusted for gender, maternal age, maternal atopy, social class, maternal smoking & antibiotics; *Quintiles of intake.
P1 MULTIDISCIPLINARY MOTOR NEURONE DISEASE CLINICS: DO THEY IMPROVE PATIENT CARE?
B.V. Prathibha, C. Wylie, N. Pease, F.J. Thomas. Nevill Hall Hospital, Brecon Road, Abergavenny, South Wales, UK

Motor neurone disease is a progressive neurological disorder which results in respiratory failure eventually. Currently the respiratory input into the management of these patients occurs at the terminal stages of their life. In addition, these patients need input from other specialties including palliative care and gastroenterology. We describe here a multidisciplinary approach with a new type of clinic set up so that the patients are seen by these specialists early on in the illness in the hope of improving the quality of care.

Aim: The aim was to set up a one stop clinic providing combined respiratory, neurological, and palliative care advice with input from voluntary organisations (MND association) and social workers and to assess any perceived benefits from the patients and carers point of view.

Design: The clinic is scheduled once a month and the three physicians (respiratory, neurology, and palliative care) sit in the same room with the other organisation representatives in the next room. The patients are offered an appointment in the specialist MND clinic following confirmation of the diagnosis by the neurologist. A special proforma has been designed to include the neurological, respiratory, gastroenterological, and social aspects of care. At each visit, the different variables including spirometry and blood gases are recorded. All patients undergo baseline overnight sleep study. The subject of NIPPV and intubation is introduced during these visits depending on the symptoms. The patients then make informed choices about their treatment. A patient feedback questionnaire has been designed and is given to each new patient.

Results: The clinic was established in November 2001 and to date 11 patients (7 males and 4 females) have been seen. The median age is 63 for men and 62 for women. The median FVC at presentation is 89% predicted and median PO2 and PCO2 are 11.5 and 4.8 respectively. The decline in the FVC over 9 months is associated with increasing PCO2 and symptoms. Three have been opted for NIPPV for symptom palliation. All patients rated the clinic highly, preferred to come to a single clinic than to three different ones and felt that they had adequate time to discuss all their concerns and have them allayed.

Conclusion: MND patients need specialised input from many professionals and too often this is patchy and unsatisfactory. The organisation of a combined clinic of the type described above has improved patient care and communication between the different specialists and has resulted in the efficient use of time and other limited resources.

P2 OUTCOMES OF ASSISTED VENTILATION IN MOTOR NEURONE DISEASE
S. Sundaram, I.E. Smith, J.M. Shneerson. Respiratory Support And Sleep Centre, Papworth Hospital, Cambridge, UK

Assisted Ventilation may prolong survival in patients with respiratory failure in motor neurone disease (MND), but there are few published reports.

We performed a retrospective study of all patients referred to our tertiary care centre between 1993 and 2002. We identified 109 patients, mean age 60 (SD 9.0) years, 74% of whom were male. Fifty-one per cent had bulbar symptoms. Sixteen patients were transferred from intensive care units elsewhere with tracheostomy ventilation (TV). Fifty-five patients were offered non-invasive ventilation (NIV) of whom 43 accepted and 12 declined treatment. Thirty seven patients were assessed at our unit and were thought not to require any assisted ventilation. One patient required only a tracheostomy with no assisted ventilation. Nine of the TV patients were weaned to NIV. Patients who still required TV at the time of discharge managed to self ventilate by day, but within three months were once again continuously dependent on it. Among patients offered NIV de novo, 36 had hypercapnia (mean PaCO2, 8.0 kPa) and 19 had orthopnoea causing sleep disturbance. The arterial blood gases while self ventilating on air improved in patients treated with NIV. At first follow up, the mean fall in PaCO2 (95% CI) was 2.3 kPa (1.2 to 3.4; p<0.001) and the mean rise in PaCO2 was 1.1 kPa (0.30 to 2.0; p<0.01). Bulbar weakness was as frequent in patients given NIV as those that declined (p=0.66).

There have been 86 deaths. Using the Kaplan-Meier method, the median survival was four months in patients who declined treatment and 11 months in those thought not to need NIV. There was no difference in survival between patients transferred intubated from ICU (12 months) and other subjects who started assisted ventilation (14 months; p=0.89).

Many MND patients treated with tracheostomy ventilation can be weaned to NIV. In our cohort bulbar weakness did not preclude NIV. Survival was best for patients using assisted ventilation and worst for those who declined treatment.

P3 OUTCOME OF NON-INVASIVE DOMICILIARY VENTILATION FOR PREVIOUS POLIOMYELITIS: IMPACT OF SCOLIOSIS
Y. Tai, D. McKeon, I.E. Smith, J.M. Shneerson. Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, UK

Survivors of poliomyelitis can develop new respiratory disability many years after the acute illness. Scoliosis, muscle weakness, and decreased respiratory drive may all contribute. We examined the effect of scoliosis on survival in 51 patients (20 women) with previous poliomyelitis established on home mechanical ventilation (HMV) in our centre.

Poliomyelitis was contracted at a median age of 6.5 years; 82% of the patients had a thoracic scoliosis. The mean interval from contracting poliomyelitis to HMV was 46 (SD 8.8) years. Arterial blood gases on room air prior to HMV showed PaO2, 7.2 kPa and PaCO2, 8.6 kPa, which significantly improved (p<0.05) after one month of treatment to PaO2, 9.5 kPa and PaCO2, 6.6 kPa. The improvement was maintained at a mean follow up of 58 months. The Kaplan-Meir plot for life expectancy from initiation of ventilation is shown in the figure: survival was 7.35 years for subjects without scoliosis (solid line) v 12.1 years for subjects with scoliosis (dashed line) (p=0.048).

Comparing subjects with and without scoliosis there were no differences in blood gases or overnight monitoring at presentation or during follow up on HMV; those with scoliosis had a smaller vital capacity 1.18 L v 1.49 L (p=0.013) and were younger when they had contracted poliomyelitis (median age 5 v 20 years; p=0.003); the time interval from poliomyelitis to HMV was similar for the two groups and so those with scoliosis started ventilation at an earlier age. Recalculating life expectancy from birth there was no difference between the two groups (p=0.989).

This study confirms that HMV can normalise arterial blood gas tensions in patients with previous poliomyelitis and the improvement is maintained. Overall survival is good. Compared to subjects with a scoliosis survival from the initiation of HMV is worse for subjects without a scoliosis largely because they are older when they develop ventilatory failure.
COMPARISON OF PRESSURE AND VOLUME TARGETED NON-INVASIVE VENTILATION IN CHEST WALL DEFORMITY

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Introduction: The use of domiciliary non-invasive ventilation (NIV) in chest wall deformity is established and of proven benefit in terms of arterial blood gas tensions, sleep quality and daytime function. Previous studies have compared in the short term, volume, and pressure targeted ventilation. As part of a larger study, we investigated the effect of ventilation mode on minute ventilation and mask leak.

Method: 10 patients (mean age 64; mean FVC 0.55 l) with chest wall deformity, established on home NIV randomised a crossover study comparing pressure support and volume ventilation using the Breas PV403 ventilator. Ventilator parameters were set following a daytime titration period according to patient comfort and so that MVe was identical for both PSV and VCV. Patients used the machine at home for four weeks for each modality. At the end of each period, patients were admitted for a sleep study, including measurement of ventilation using a pneumotachometer connected to the ventilator circuit, adjacent to the nasal mask. Delivered tidal volume (Vti), expired tidal volume (Vte), expired minute volume (MVe) and respiratory rate (fR) were measured throughout the night. Minute leak was calculated by (Vti-Vte) × fR.

Results: See figure. Ventilation was slightly greater in the volume group. There was significantly more leak during PSV than compared to VCV (16 ± 6 l/min).

Conclusion: Volume cycled ventilation results in less leak without compromising ventilation compared to PSV. Excessive amounts of leak during PSV may result in greater arousals and sleep fragmentation.

JT is funded by the NHG Northern & Yorkshire Executive

COMPARISON OF PRESSURE AND VOLUME CYCLED VENTILATION IN KYPHOSCOLIOSIS (A RANDOMISED, SINGLE BLIND, CROSSOVER, PILOT STUDY)

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Introduction: This study compared pressure controlled (PCV) and volume controlled ventilation (VCV) in patients with kyphoscoliosis (KS). Two previous studies have been published with conflicting results. One study compared pressure controlled (PCV) and volume controlled ventilation (VCV) in patients with kyphoscoliosis (KS). The second study found no differences between the modes but suggested that patient fatigue was reduced using PCV.

Patients & methods: Twelve patients with KS (nine males, mean age 59 ± 8.9 years) who were receiving domiciliary nocturnal pressure ventilation. We measured the following at baseline: ABGs, overnight Pulse Oximetry and transcutaneous CO2, FVC, FEV1, SNIP, Psychomotor Vigilance (PVT), OSIER Sleep latency, Epworth Sleepiness Scale, and Actigraphy & Sleep Diary for 10 days. Each patient was then randomised to one month of PCV or VCV using the BREAS PV403 ventilator. The subjects were blinded to the mode of ventilation. At the end of the one month all of the above parameters were re-measured, the mode changed and the parameters re-measured after a further month. At the end of the study the subjects were asked to express a preference for month one or month two.

Results: Five subjects were excluded (three due to underlying OSA, one due to an unrelated illness, and one was unable to tolerate VCV). In the remaining seven no significant differences were found between PCV and VCV in most of the physiological variables. The hours of ventilation use was greater during PCV compared with VCV (8.22 ± 7.49), but this did not reach statistical significance (p=0.07). Actigraphy revealed a significantly lower sleep fragmentation index in the PCV limb of the study (32.6 ± 38.5; p<0.04). This was supported by the subjects reported sleep quality during PCV (2.17 ± 2.45; p=0.01). In addition, subjects preferred PCV to VCV (p<0.0002).

Conclusions: Patients with KS and CRF are adequately ventilated with both PCV and VCV modes. However patients prefer PCV, and subjective and objective sleep quality is improved with PCV.

COMPARISON OF PRESSURE VOLUME CYCLED VENTILATION IN KYPHOSCOLIOSIS A RANDOMISED SINGLE BLIND CROSSOVER STUDY: QUALITY OF LIFE OUTCOME DATA

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Introduction: Patients with kyphoscoliosis (KS) may require long term ventilatory support as disease progression occurs. The ventilator used may be either volume (VC) or pressure controlled (PC). It is unclear which strategy is most beneficial for patients with KS.

Patients and methods: Twelve subjects with KS (nine males, mean age 59 ± 8) who were receiving long term ventilatory support were enrolled in a single blind randomised crossover pilot study. Ventilators were provided by the manufacturer (Breas PV403) and were set to provide the same minute volume in either volume or pressure control mode.

Results: Pulmonary function and QoL data are shown in table 1. There were no significant differences between pre treatment values and those obtained after four weeks on the two ventilator settings. However these subjects scored on all values much greater than healthy normals, indicating significant impairment of QoL. Beck depression score was not treatment and after four weeks on the trial ventilator at each setting.

Conclusions: Patients with KS on long term ventilation have significantly impaired QoL and the ventilator strategy used (VC or PC) does not affect this.

ADDUCTOR POLLICIS AND QUADRICEPS STRENGTH IN COPD

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Background: Peripheral muscle weakness is common in COPD, but the cause remains controversial. Better understanding of the distribution of muscle weakness may reveal the underlying...
The Relationship Between Respiratory Muscle COPD alters the Diaphragm Motor Area Response to Transcranial Magnetic Stimulation

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Background and Methods: The threshold and stimulus response curve to transcranial magnetic stimulation (TMS) of the diaphragm motor area can provide information about cortical excitability in health and disease. We studied five patients with severe COPD (mean FEV1 20% predicted) and eight healthy controls. Stimulation series were delivered over the vertex using a 110mm double cone coil (Magstim 200 mono-pulse) at a variety of intensities in random order and the surface diaphragm motor evoked potential (MEP) recorded. Series were performed at rest, end expiration and then, facilitated, during inspiratory manoeuvres at 20% and 40% of maximum inspiratory pressure (MIP) and then again at rest. Healthy subjects also performed a run at 60% MIP. The stimulus response curves for COPD patients are shown in the figure. This group showed a significant increase from rest to 20% facilitation but no further increase at 40%. By contrast controls showed a stepwise increase in MEP to 40% with no further increase at 60%.

Conclusion: COPD patients have a reduced cortical reserve perhaps because they are already facilitated at rest by an increased work of breathing. This study was funded by the Wellcome Trust.

Effect of Long Term Domiciliary Non-Invasive Positive Pressure Ventilation (NIPPV) on Respiratory Muscle Function in Chronic Type 2 Respiratory Failure

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In subjects with acute and chronic type 2 respiratory failure (due to kyphoscoliosis, sleep hypoventilation, and chronic obstructive pulmonary disease) application of nasal intermittent positive pressure ventilation (NIPPV) helps to restore arterial blood gases to normal levels, and aid breathing by unloading inspiratory muscles. The effect of NIPPV on inspiratory muscle strength (IMs) and endurance (IME) was tested.

Methods: Two patient groups were studied, group one (n=6, age 63 (7) years; mean (SD)) who had just started with NIPPV and group two (n=6, 66 (14) years) who had undergone domiciliary ventilation (dNIPPV) for longer than six months. Group one patients were tested twice, once soon after the initiation of NIPPV and again after three months of dNIPPV. Inspiratory muscle strength and endurance were tested by asking the patient to perform three maximal inspiratory manoeuvres (a measure of IMs) followed by repeated submaximal (80%) manoeuvres with ever decreasing intermittent rest periods until task failure (a measure of IMe). All patients were naive to the IM testing procedure.

Results: Group one patients (dNIPPV < 1 month) had significantly (p<0.05) lower PaCO2 than group two (dNIPPV >6 month) of 6.7 (2.5) vs 8.6 (1.9) kPa respectively. The PaCO2 was not significantly different at 7.5 (1.3) vs 6.4 (0.9) kPa respectively. The maximal inspiratory pressure (MIP) a measure of IMs was highest in group two (Group 1 32 (4) v Group 2 47 (9) cmH2O) as was sustainable MIP, a measure of IMe (Group 1 102 (50) v Group 2 158 (50) cmH2O). In group 1, three months of dNIPPV improved MIP from 32 (4) to 48 (14) cmH2O but had no effect on sustainable MIP.

Conclusions: These data show that using dNIPPV for three months and longer improves inspiratory muscle strength. Improving inspiratory muscle endurance takes longer to achieve and can only be seen in the patients receiving dNIPPV for over six months (Group two). There are no long term benefits of using dNIPPV in terms of increasing inspiratory muscle strength but there are for endurance. How these improvements in endurance relate to general health status have yet to be evaluated.

**P11 DEVELOPMENT OF A RESPIRATORY HIGH DEPENDENCY UNIT: EXPERIENCE FROM THE FIRST 20 MONTHS**

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Non-invasive ventilation (NIV) has been used at the Royal Devon & Exeter Hospital since the early 1990s. Patients receiving NIV were treated by specialist respiratory physicians, the main aims of the therapy being to prevent hospital admission and enhance the service we are able to offer patients. The opening of the respiratory high dependency unit (rHDU) in November 2000 has allowed significant numbers of patients requiring NIV to be treated without transfer. The rHDU has significantly enhanced the service we are able to offer patients.

**Results:** Out of 120 clinicians, 98 (82%) took part. Patient one: 84% of doctors admitted patient one, with admitters giving a mean predicted hospital survival of 46.1%, and non-admitters a significantly lower mean predicted hospital survival of 12.7% (p<0.00005). Patient one’s SUPPORT probability of 30 day survival was 98%. Patient two: 64.3% of clinicians admitted patient two, with admitters giving a mean predicted hospital survival of 37.9% vs 11.8% for non-admitters (p<0.00005). Patient two’s SUPPORT probability of 30 day survival was 94%. Patient three: 39.8% admitted patient three, with admitters giving a mean predicted hospital survival of 28.2% vs 13.0% for non-admitters (p<0.00005). Patient three’s SUPPORT probability of 30 day survival was 98%.

**Conclusion:** Predicted hospital survival for identical patients following ICU admission differed significantly between clinicians who would admit compared to those who would not. This study suggests that an important source of variability in ICU admission may arise from marked variation in predictions of survival and that objective models of patient outcome might reduce variability and support equity.


**P12 VARIATION IN CONSULTANT’S PROGNOSTIC ESTIMATES FOR IDENTICAL PATIENTS MAY EXPLAIN VARIATION IN COPD INTENSIVE CARE UNIT (ICU) ADMISSION: SIMULATION STUDY FROM ONE CRITICAL CARE NETWORK**

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**Introduction:** Anecdotal evidence suggests variation in gatekeeping decisions for COPD patients with respiratory failure considered for ICU admission. However little is known about the approach of different doctors to the management of identical patients and the causes for the suggested variability. This study exploits the fact that consultants on call will occasionally make ICU admission decisions on the basis of information conveyed over the phone. Simulation of such phone calls allows many clinicians to make decisions about identical patients in a way that mimics real life.

**Methods:** One hundred and twenty consultants caring for acute admissions in the Heart of England Critical Care Network were invited to take part. An investigator in the role of a registrar who had just been transferred to ITU because of failure to respond to CPAP. The number of patients requiring NIV grew steadily and a business case was prepared for an appropriately staffed and equipped respiratory high dependency unit (rHDU). Eventually funding was secured from money allocated to critical care services and the unit opened in November 2000. Here we present an analysis of our experience over the first 20 months.

The unit has four beds and is staffed with a nurse-patient ratio of 1:2. It is located in one bay of the respiratory ward. Two hundred and twenty three patients have been admitted, with 33 admitted more than once. The mean age was 64.5 years (range 18 to 91) and 51% of patients were male. Most admissions (71%) occurred between 8am and 8pm and were mainly transfers of patients admitted acutely to the Emergency Medical Unit. Fifty one admissions (20%) were patients transferred out of the rHDU and as a result of tracheostomy. The median length of stay was 4.04 days (range 1 to 37).

One hundred and nine patients received NIV, with 19 ventilated more than once. The mean age was 69.3 years (range 18 to 91) and 50% were male. The median duration of NIV therapy was 25.0 hours (range 0.5 to 505). There were 29 deaths in patients treated with NIV. In most of these it had been agreed in advance that more invasive treatment would not be undertaken. Ten patients were transferred to ITU because of failure to respond to NIV.

Twenty six patients received CPAP therapy, with one being treated more than once. The mean age was 70.2 years (range 32 to 88) and 64% were male. The median duration of CPAP therapy was 9.5 hours (range 0.5 to 134). There were 9 deaths and four patients were transferred to ITU because of failure to respond to CPAP.

The opening of the rHDU has allowed significant numbers of patients with respiratory failure to be managed effectively. Many of these patients would previously have been admitted to ITU. Appropriately staffing the unit has allowed admissions to be accepted throughout the day and night and nearly one in three admissions occurred outside the normal working day. The rHDU has significantly enhanced the service we are able to offer patients.

The patients was subsequently calculated using the SUPPORT model. Doctors considered three patients all of whom had single organ failure, but who varied in characteristics shown in multivariate analysis to be predictive of outcome. Two results: Out of 120 clinicians, 98 (82%) took part. Patient one: 84% of doctors admitted patient one, with admitters giving a mean predicted hospital survival of 46.1%, and non-admitters a significantly lower mean predicted hospital survival of 12.7% (p<0.00005). Patient one’s SUPPORT probability of 30 day survival was 98%. Patient two: 64.3% of clinicians admitted patient two, with admitters giving a mean predicted hospital survival of 37.9% vs 11.8% for non-admitters (p<0.00005). Patient two’s SUPPORT probability of 30 day survival was 94%. Patient three: 39.8% admitted patient three, with admitters giving a mean predicted hospital survival of 28.2% vs 13.0% for non-admitters (p<0.00005). Patient three’s SUPPORT probability of 30 day survival was 98%.

**Conclusion:** Predicted hospital survival for identical patients following ICU admission differed significantly between clinicians who would admit compared to those who would not. This study suggests that an important source of variability in ICU admission may arise from marked variation in predictions of survival and that objective models of patient outcome might reduce variability and support equity.


**P14 CARDIOVASCULAR COMORBIDITY IS ASSOCIATED WITH HIGHER MORTALITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS ADMITTED TO AN INTENSIVE CARE UNIT**

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**Background:** 30–50% of patients admitted to an Intensive Care Unit (ICU) with respiratory failure due to COPD die in hospital. Studies...
have highlighted the difficulty of predicting mortality in this patient group from standard clinical and other scoring systems. We present results of a retrospective analysis of data examining mortality in an unselected group of COPD patients admitted to the ICU in a district general hospital in England.

Patients and methods: Fifty-nine patients (31 male, 28 female; mean age 66.2 years [50 to 86]) with COPD, who had been admitted with respiratory failure to the ICU at Stafford General Hospital in the last five years were studied. Of these patients, 17 (8 male, 9 female; mean age 72 years [52 to 86]) died while on ICU and 12 (5 male, 7 female) died within a year of their discharge. Age, smoking history (past or present), usage of oxygen or nebulisers at home, and associated cardiovascular diseases (ischaemic heart disease, heart failure, or hypertension), were studied as predictors of mortality. We do not know the severity of COPD before admission (FEV1) in these patients, with associated cardiovascular conditions were found to have the highest mortality. Of the 59 patients, 24 had heart disease (40%) and the death rate in this group was 53% (13 of 24). Of these nine died during their stay in ICU.

Conclusion: COPD patients with cardiovascular comorbidity suffer a higher mortality following admission to ICU with respiratory failure. This information may have a bearing on prognostication and decision making in COPD patients being considered for invasive ventilation and admissions to ICU.


P15 REFERRAL AND OUTCOME OF PATIENTS WITH AN EXACERBATION OF COPD REQUIRING ADMISSION TO INTENSIVE CARE

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Exacerbations of COPD complicated by acidotic respiratory failure which fail to respond to medical management, including non-invasive ventilation, are associated with a high mortality rate. When a reversible aetiological factor is not present the decision to refer to ICU is difficult with reservations on outcome and pressure on ICU resources (Thorax 1997;52 (Suppl 5):S1–S28). To examine our own practice, we performed a retrospective audit of admissions to the Intensive Care Units in our Trust. We identified 56 consecutive patients between April 1999 to April 2001 in whom a primary diagnosis of COPD was recorded. Of these, 37 were excluded as having a reversible cause of respiratory failure or an alternative diagnosis. The median age was 64.5 years (range 49 to 78). Nine patients were previously unknown to respiratory physicians. It was the first admission with respiratory failure requiring ventilatory support in five of the nine previously admitted patients. Previous lung function was only available on five patients: median FEV1, 0.7l (range 0.35 to 1.7). PaO2 was below normal median [H1] 63 ± 22mmHg [IQR 61 ± 33–77]. PaCO2=12.8kPa [IQR 8.93–15.6] and PaCO2=8.2kPa [IQR 6.2–9.0]. The median duration of assessment prior to ICU admission was 5.5 hours (IQR 2–10.1). Seventeen patients required invasive ventilation, one non-invasive ventilatory support. Two patients died in ICU (one of respiratory failure, one of refractory hypotension). The median duration of ICU stay for study patients was three days (IQR 2–6.23) compared to 2.7 days for all ICU patients at the Royal Infirmary and Western General. Sixteen were successfully discharged to respiratory unit. One patient died in respiratory failure but 15 patients were discharged and 14 were alive at one year. The median hospital stay was 13 days (IQR 9–19.3) (mean stay acute exacerbations of COPD in Lothian Trust=8.3 days).

Our data suggest that severe respiratory failure may be the first presentation of COPD to hospital. Limited time and information may be available to make an informed decision on referral to ITU, but length of stay and outcome are comparable to other ICU admissions.

P16 AN AUDIT OF THE USE OF NON INVASIVE VENTILATION IN ACUTE EXACERBATIONS OF COPD

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Introduction: The benefits of non-invasive ventilation (NIV) in the treatment of acute type 2 respiratory failure secondary to chronic obstructive pulmonary disease (COPD) are well documented (Thorax 2000;55:550–4). Guidelines for the use of NIV have been published by the British Thoracic Society (BTS) (Thorax 2002;57:192–21). We investigated whether all patients with an acute exacerbation of COPD who fulfil the BTS’s criteria for NIV are being referred for this treatment.

Methods: We identified 203 patients who were admitted to St Thomas’s Hospital, London, with an acute exacerbation of COPD between 1/11/2001 and 10/7/2002 by the Accident and Emergency (A&E) register, High Dependency Unit (HDU), and Patient At Risk Team databases. The results of arterial blood gas (ABG) analysis on presentation to A&E were obtained from the patients’ A&E notes. We noted whether the patient was admitted to a general ward, received NIV on the HDU, or was intubated in A&E.

Results: Fifty-four patients were excluded because their admission ABGs were not available from their A&E notes, leaving 147 patients’ data for analysis. Of 147 patients, 110 were admitted to a general ward, 33/147 received non-invasive ventilation and 4/147 patients were intubated in A&E. The mean [SD] pH of patients admitted to a general ward was 7.38 (0.06). The mean [SD] pH on admission of patients referred for NIV was 7.27 (0.09). Of 147 patients admitted via A&E, 18 did not receive NIV despite meeting the BTS criteria on the basis of their arterial blood gas analysis on initial presentation. Their mean [SD] pH was 7.28 (0.05).

Conclusion: A significant proportion of patients with acute type 2 respiratory failure secondary to COPD who meet the criteria for NIV do not receive it. Strategies are required to improve the pick up rate of patients who would benefit from NIV at the time of their presentation to A&E.
### P18 RELATIONSHIP BETWEEN AQ20, SGRQ, AND EXACERBATION FREQUENCY IN PEOPLE WITH COPD IN PRIMARY CARE

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Health-related quality of life (HRQoL) is closely related to exacerbation frequency in patients with chronic obstructive pulmonary disease (COPD). The main obstacle to measuring HRQoL in primary care is their size and complex nature. The Airways Questionnaire 20 (AQ20) (Barley EA, et al. Respir Med 1998;92:1207–14) is a short, simple, disease-specific questionnaire. Dimensions range from 0 to 20 (worst health).

Patients were recruited from general practices in East London. Patients were aged 40 and above, current or ex-smokers and were prescribed regular inhaled steroids. We asked patients to complete the AQ20 and the St George’s Respiratory Questionnaire (SGRQ) simultaneously at interview.

One hundred and thirty one patients (68 male) of median age 66 years (range 48 to 87) with COPD were recruited from 12 general practices. Mean (SD) FEV$_1$ was 1.28 (0.55) I, FEV$_1$/FVC predicted 50.0 (18.0)%, mean FEV$_1$/FVC ratio was 57.0 (16.0)%. Patients had a yearly exacerbation rate of 2.4 (2.5). The median AQ20 score was 11 with a range of one to 19. The median SGRQ total score was 51.0 (18.0)%, mean FEV$_1$/FVC ratio was 57.0 (16.0)%. Patients had a yearly exacerbation rate of 2.4 (2.5). The median AQ20 score was 11 with a range of one to 19. The median SGRQ total score was 51.0 (18.0)%, mean FEV$_1$/FVC ratio was 57.0 (16.0)%. Patients had a yearly exacerbation rate of 2.4 (2.5).

The AQ20 shows a strong relationship to yearly exacerbation rate. The AQ20 is simple to implement and can be used to assess health and disease in COPD.

### P20 A REGULAR VISIT TO PATIENTS ADMITTED WITH COPD REDUCES FURTHER HOSPITAL ADMISSIONS

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The Torbay Hospital Outreach Respiratory Team (THORT) has been supporting the early discharge of patients with exacerbations of COPD since 1999. It was noted that certain patients were having frequent admissions often with minor exacerbations that were then managed at home by THORT. It was proposed that regular maintenance visits by the team of patients identified as having frequent admissions or significant problems with anxiety would reduce these.

The first of these visits was in July 2001. In total 12 patients have been placed on the maintenance list and data has been collected on admissions pre and post the start of visits. For the purpose of this study 10 patients were selected who had complete sets of admission data for 12 months prior to the visits, and had been receiving maintenance visits for at least two months.

The results show that in the year prior to the start of visits the average number of bed days and facilitated discharge days under THORT per month for the 10 patients studied was 40.1. After the introduction of maintenance visits the average number of days was 8.7 per month.

Although this study has comparable data on a small number of patients, preliminary results suggest that regular maintenance visits to patients with COPD identified as having frequent exacerbations do have a positive impact on their ability to cope at home and avoid admission to hospital. In conclusion, directing resources towards providing regular support to appropriate patients with COPD would be seen to be a cost-effective way of reducing the use of healthcare resources by COPD patients over the winter months.
and only 12.5% out of hours (no data on three patients). Only 8 patients were seen twice with the same exacerbation prior to admission.

When asked why they had bypassed primary care most patients said either that they or a relative thought the situation too urgent for a GP to manage, or that previous experience was that the GP would send them to hospital anyway. The three patients with no change in symptoms had all bypassed primary care and were admitted because of anxious relatives. In contrast to the time of primary care contact, attendance at hospital was mostly out of hours (51%) or afternoon (36%). About half of the admissions were arranged by GPs, a quarter saw the GP but self presented to A&E anyway, and a quarter bypassed primary care altogether.

We conclude that many patients and relatives admitted with COPD have little confidence in primary care’s ability to deal with exacerbations, especially out of hours. A 24 hour service with specialist trainee cover would perhaps have bypassed primary care altogether.

### Bronchoscopic and other lung investigations

**P22 BRONCHOSCOPY PRACTICE IN ENGLAND AND WALES, 2002**

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**Aims:** To assess current practice in bronchoscopy preparation in England and Wales.

**Methods:** Questionnaires were faxed to respiratory consultants listed in The BTS Directory. We looked at the population, number of consultants and bronchoscopies undertaken, topical anaesthetic use, sedative use and how adequate sedation is judged.

**Results:** There was a response rate of 76% (344 responses to 452 questionnaires). Median consultant numbers per hospital was three (IQR 4–6), median population served per consultant was 116 000 (IQR 90–150 000). The majority of bronchoscopists use lignocaine spray to the throat (70%), sometimes with spray to the nose (43%), together with gel to the nose (65%). The majority use 4% lignocaine to the vocal cords (54%) and 2% to the bronchi (71%). Atropine is used routinely by 13%. Sedation with midazolam (78%) or other combinations (22%) is routine. The option of sedation is only discussed with the patients by 8.4% of consultants. Only three operators use formal sedation scores to assess patient level of sedation. Oxygen saturation was the commonest measurement used (n=98) to judge sedation. Otherwise, response to sedation was judged by clinical experience (n=60), patient response (n=57), and conscious level (n=50).

**Conclusion:** Despite the recent BTS guidelines there is considerable variation in bronchoscopy practice, particularly in sedation practice. Patient level of sedation is not formally assessed and combinations of sedatives and analgesics are used contrary to the recent guidelines on safe sedation practice. Sedation options are not routinely discussed. The wide variations in practice may reflect the lack of consistent evidence based guidance on sedation techniques for bronchoscopy. Further study to determine optimal technique is required.


**P23 FLUORESCENCE BRONCHOSCOPY IN PATIENTS WITH ABNORMAL SPUMT CYTOLOGY**

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**Introduction:** Patients at risk of lung cancer with abnormal sputum cytology or bronchial washings but no other evidence of lung cancer present a management dilemma. Autofluorescence bronchoscopy detects preinvasive endobronchial lesions and carcinomas with greater sensitivity than conventional bronchoscopy. We present a series of patients with abnormal sputum cytology or bronchial wash cytology investigated further with autofluorescence bronchoscopy.

**Methods:** Patients selected had no clinical or radiological evidence of invasive carcinoma and no bronchoscopic abnormality within the preceding two months. The visible bronchial tree was inspected with white light and autofluorescence using the Storz bronchoscope. Biopsies were taken of all areas appearing abnormal bronchoscopically.

**Results:** Ten patients were studied, eight males with a mean age of 66.5 yrs (range 51 to 79 yrs). All were smokers, mean exposure 47 pack years (range 18.5 to 79). The table shows the bronchoscopy results and outcomes for the study patients.

**Conclusions:** In this group of patients, no abnormality detectable at fluorescence bronchoscopy suggests a good outcome, with no evidence of carcinoma at up to 42 months. Abnormal fluorescence may reveal the presence of radiologically occult carcinoma, or high grade preinvasive lesion, but may also be a false positive finding. High grade preinvasive lesions may exfoliate cells that resemble squamous carcinoma cells. Fluorescence bronchoscopy may provide useful information in this difficult group of patients. This study is limited by the small numbers and relatively short duration of follow up, but suggests that a larger study should be undertaken.

**P24 ENDOBRONCHIAL MIMICS OF LUNG CANCER: A CASE REPORT AND REVIEW OF BRONCHOSCOPY DATA BASE**

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**Case report:** A 72 year old ex-smoker and retired fireman with previous asbestos exposure, presented with a six week history of cough, breathlessness, and wheeze. Clinical examination revealed a small basal basal effusion. CXR revealed a loculated effusion and loss of volume in right lower lobe (RLL) with associated distal consolidation. CT scanning revealed a loculated effusion with an area of consolidation which became focal and then progressed to right lower lobe consolidation.

**Background:** The diagnosis of lung cancer is often made by bronchoscopy. The identification of endobronchial tumour and the presence of a normal bronchial wash are useful guidelines and bronchoscopy results are often used to determine management. The study was to review bronchoscopy findings in patients with endobronchial mimics of lung cancer over a 10 year period (1991–2001) at one hospital.

**Methods:** Bronchoscopy results were reviewed over a 10 year period. An electronic data base was used and only those cases with endobronchial mimics of lung cancer were included. The frequency of cases and outcomes were determined.

**Results:** Bronchial washes and biopsies were taken of all areas appearing abnormal bronchoscopically.

**Conclusion:** Over the past 10 years, our team has performed 4199 bronchoscopies of which 1122 (27%) were found to have lesions suspicious of lung cancer. Of these 1004 (89.5%) have had cancer confirmed by histology or cytology and 101 (9.0%) have been treated as cancer although the biopsies were negative. Of patients with suspicious bronchoscopies, 17 (1.5%) had a specific non-malignant diagnosis (see table). Endobronchial mimics of lung cancer account for >1% of suspicious bronchial lesions. We recommend caution in informing patients of cancer until either histological confirmation is obtained or other causes are excluded.
Poster presentations

Abstract P24

BRONCHOALVEOLAR LAVAGE, NON-INVASIVE INVESTIGATIONS AND RADIOLOGY: IMPACT ON TREATMENT IN PATIENTS WITH HAEmatological MALIGNANCIES AND PULMONARY INFILTRATES

A.R. Benjamin, E.F. Bowen. Respiratory Medicine Unit, Hammersmith Hospital, London W12 ONN, UK

Pulmonary infiltrates are a frequent complication in immuno-suppressed patients with haematological malignancies requiring early diagnosis with prompt appropriate treatment. We investigated the diagnostic yield of bronchoalveolar lavage (BAL) and non-invasive sampling (NIS) in this population over a 12 month period and evaluated their impact on treatment modification. We compared high resolution computed tomography (HRCT) findings with these results. Twenty five bronchoscopies (FOB) [21 patients] were performed during this period. Seventeen out of 21 patients were post bone marrow transplant and 4/21, on high dose chemotherapy. Pre FOB, 16/25 cases were neutropenic and/or lymphopenic, 15/25 were thrombocytopenic, 22/25 were pyrexial, and 22/25 were on empirical antibiotics. All were hypoxic and required supplemental oxygen periprocEDURE. Post FOB, 1/21 patient required admission to the intensive care unit.

Blood cultures, sputum cultures, and nasopharyngeal aspirations were negative in 3/41, 4/21, and 1/3 samples respectively and treatment was modified in 2/25, 2/25, and 1/25 cases respectively. Overall, NIS was positive in 8/25 [32%] cases with subsequent treatment modification in 5/25 [20%] cases. BAL was positive in 10/25 [40%] cases. (7/25 bacterial, 2/25 viral, 1/25 PCP) and treatment was modified in 8/25 [32%] cases. Where NIS was positive, BAL confirmed the diagnosis only once and in one case revealed another organism that changed management further.

In 2/25 cases, chest radiograph (CXR) was not done prior to HRCT. CXR was abnormal in 16/25 cases, 13 of which proceeded to HRCT and treatment modification in 5/15 cases. In 7/25 cases, CXR was normal which of all had abnormal HRCTs with treatment modification in 1/7 case. Overall, HRCT led to treatment modification in 6/22 cases, in which BAL confirmed the suspected aetiology in 2/22 cases.

This data indicates that the sequential use of NIS and BAL gives the highest diagnostic yield of pulmonary infiltrates. At our institution, HRCT was not sensitive enough to allow for its confident use as a diagnostic tool in place of BAL. Although FOB is a high risk procedure in this population, this data supports BAL as a safe and useful investigation.

CT GUIDED LUNG BIOPSIES: DO THEY PROVIDE THE DIAGNOSIS?

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When requesting CT guided lung biopsies we are frequently asked “Will the patient tolerate a pneumothorax?”. With this in mind we performed an audit of this technique to assess the success rate of the procedure, frequency of complications, and the sensitivity and specificity for diagnosing lung cancer.

Using the CT record book to identify cases we recorded details of all (n=68) patients recorded as having had “lung biopsy” over the previous four year period. We used patient case notes, the lung cancer database, and the computer based histology records and CT reports to record, where possible, the indication, histology obtained, whether or not further investigative procedures had been required, any documented complications, and the final diagnosis.

Of the 68 patients recorded as “lung biopsy”, 1% actually had pleural biopsy and 4% lung aspirate. Of these there were no complications and the procedure provided the diagnosis. Sixty four patients were scheduled for the procedure: percutaneous core needle biopsy under CT guidance, following infiltration with subcutaneous lignocaine. 1-“multiple” passes were made as required/tolerated. Each patient had a postprocedural CT check for pneumothorax. Of the 64, 6% were cancelled due to radiological improvement and 6% abandoned due to technical difficulties, leaving 56.

The indication for biopsy was suspected lung cancer in 91%. We wanted to know whether the procedure provided the final diagnosis or if further measures needed. Of the 46 patients in whom adequate information was available, the histological sample from biopsy was successful in providing the final diagnosis in 71%. Histology was obtained but further investigations were needed in 26%. No histology was obtained in 4%. Of the 56 patients who underwent any procedure pneumothorax preventing biopsy occurred in just 2%. Smaller pneumothoraces occurred in 13%, and the remaining 85% experienced no complications.

The sensitivity of the procedure for diagnosing lung cancer was 90%, specificity 100%, and false negative rate 8%. These and the complication rate compared favourably with other published studies of lung biopsy. In a DGH this procedure is still useful and we have demonstrated a relatively low complication rate.

SERIAL PEAK FLOW MEASUREMENTS FOR THE DIAGNOSIS OF OCCUPATIONAL ASTHMA: IMPROVING THE QUALITY

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Serial measurements of peak expiratory flow (PEF) are usually the most appropriate first step in the investigation of occupational asthma. Different centres have reported widely different success in obtaining records of sufficient data quality for diagnosis. We have investigated different methods of instruction and determined the return rate and quality of the resulting record for the diagnosis of occupational asthma using predefined criteria.

www.thoraxjnl.com
Methods: Three instruction methods have been investigated: 159 were instructed by post (postal group), 86 were personally instructed by a PEF specialist (personal group), and 40 were instructed by others—for example, GPs, occupational health physicians, or nurses.

Results: The postal return rate was 56% and the personal return rate 85%, adequate data quantity was similar in the postal and personal groups (54.8% and 58.8% respectively). Pre-existing records plotted from graph charts were only adequate in 23%, compared with pre-existing records plotted from occupational forms (61% adequate). Failure of the record to contain consecutive periods of >3 workdays was the most common reason for inadequate data quantity.

Conclusion: The quality and return rate of PEFs for diagnosing occupational asthma is better when patients have been given specific instructions from a PEF specialist and recording is on a dedicated form.

P29 DIFFERENCES IN INDICES OF PEAK EXPIRATORY FLOW VARIABILITY BETWEEN WORKERS WITH OCCUPATIONAL ASTHMA AND IRRITANT (GRAIN DUST) EXPOSED HEALTHY SUBJECTS

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Introduction and Aims: Serial peak expiratory flow (PEF) records have been recommended as a first line investigation in workers suspected as having occupational asthma. It is unclear, however, to what extent they can differentiate between workers with occupational asthma from those with non-occupational asthma or irritant exposed subjects.

Methods: Indices of PEF variability were compared in three groups of subjects. (1) Forty healthy grain exposed farmers and dockers. (2) Forty two consecutive subjects with independently confirmed occupational asthma suspected as having occupational asthma. It is unclear, however, to what extent they can differentiate between workers with occupational asthma from those with non-occupational asthma or irritant exposed subjects. (3) Forty eight non-occupational asthmatics.

Results: The index of PEF variability that best separated the occupational asthmatic workers from the others was the difference in mean PEF between rest and work periods. The upper 95% confidence limit of this index for the grain workers was 2.8% of predicted PEF (16 L/min), for non-occupational asthmatics 3.3% predicted PEF (15 L/min). Sensitivity for diagnosing occupational asthma using this index was 70%. Only 40% of workers with confirmed occupational asthma had a PEF diurnal variability >17% of predicted, the upper limit for grain workers. An increase in diurnal variation on work days of >7% (the upper 95% limit for non-occupational asthmatics) had a sensitivity of only 27% for the diagnosis of occupational asthma. The difference between maximum PEF on work days and minimum PEF on rest days was poor at separating occupational asthmatic workers from those with non-occupational asthma.

Conclusion: Difference in mean PEF between work and rest days is the best simple index for differentiating subjects with occupational asthma from those with non-occupational asthma or irritant exposed healthy subjects.

P30 REPEATABILITY OF CHLORIDE LEVELS IN EXHALED BREATH CONDENSATE (EBC)

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Background: Reproducibility of measurements of EBC is controversial (Effros, et al. Am J Respir Crit Care Med 2002;165:663–9). It has been suggested that there is a wide variation in dilution of the collected sample, which would make interpretation of measurements difficult.

Aim: to assess the repeatability of Sodium [Na] and Chloride [Cl] measurements in EBC in healthy adults and in asthmatic and cystic fibrosis (CF) children.

Methods: EBC were collected for 10 minutes using a Condenser (Ecoscreen (Jaeger) and wearing a nose clip. [Na] and [Cl] were measured with a CIBA Corning M 644 NaCl Analyser. Samples of five healthy adults were collected five times within one day with a 20 minute interval each. To measure period repeatability, the collection was repeated on another day within eight weeks. Technical repeatability was measured by aliquoting each sample into two tubes. Within day repeatability was also assessed in seven asthmatic and eight CF children from two collections within two hours. Repeatability was calculated according to Chinn (Chinn S. Thorax 1991;46:454–6).

Results: Na could not be detected in >30% EBC, so was not analysed further. For normals, the mean (SD) [Cl] was 4.0 (0.95) mmol/L; the technical repeatability by the day within one sample, calculated by the single determination range was ±1.96 mmol/L and the within subject day repeatability assessed as the 95% range for change within a day was ±1.16 mmol/L, the within period (eight weeks) range of change was ±2.18 mmol/L. For asthmatics, the mean [Cl] was 4.4 (0.9) mmol/L with a range of change of ±3.98, in CF patients the mean [Cl] was 5.1 mmol/L and 95% range for change was ±3.38 mmol/L.

Conclusion: The variability of measured levels is similar for within test (paired estimates of the same sample), within day and between visit, for both normals and children with asthma and CF. This suggests that the major source of variability of [Cl] can be explained by limitation of the measurement assay method used, rather than as an effect of intrinsic variability in EBC collection per se. The wide use of EBC is most likely dependant on the development of highly sensitive and reproducible assays, rather than further refinements of the collection technique.

P31 DOES AIRFLOW OBSTRUCTION OR INHALATION OF SALBUTAMOL INCREASE THE VOLUME OF EXHALED BREATH CONDENSATE COLLECTED IN STABLE COPD AND ASTHMA?

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Introduction: Exhaled breath condensate (EBC) collection, although widely accepted as a method for measuring molecules in exhaled breath, is not well characterised methodologically. Factors such as airflow obstruction, bronchodilator therapy, or respiratory rate may affect the volume of EBC volume achieved. The main aims of this study were to examine whether EBC volume collected could be increased post salbutamol inhalation, and whether EBC volume collected was directly linked to airflow obstruction as assessed by FEV1.

Methods: Eighteen volunteers were studied (10 COPD, eight asthmatics). Each completed six collections over three days. On each occasion, subjects were asked to refrain from taking short acting bronchodilators for six hours before the study. Two collections were made on each day (breathing via mouthpiece and two way valve into two Teflon tubes in ice for 15 minutes), pre and post inhalation of 200 µg salbutamol. Spirometry was completed on all volunteers at the end of each of the three collections. On each of the three occasions, volunteers completed the same protocol for reproducibility of volumes.

Results: There was no correlation between airflow obstruction and EBC volume collected. There was no significant difference in EBC volume pre and post bronchodilator when considering all 18 patients (2.26 ml (SD)(0.39) ml pre; 2.31 ml (0.35) post) (p=0.46). For patients with COPD the respective volumes were 2.21 ml (0.30) and 2.35 ml (0.32) (NS) while for asthma they were 2.33 ml (0.42) and 2.22 ml (0.37) (p<0.04).

Conclusion: EBC volume was not related to the degree of airflow obstruction and bronchodilator inhalation did not increase EBC volume.

P32 A NOVEL DEVICE FOR THE PRECISE MEASUREMENT OF RESPIRATORY HEAT AND MOISTURE LOSS

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Background: It is proposed that respiratory heat and moisture loss (RHML) are altered by airway inflammation and that measurements of
COPD: Assessment and treatment

P34 MECHANISMS OF BRONCHIAL HYPER-RESPONSIVENESS IN COPD

P.P. Walker, P.M.A. Calverley. Department of Medicine, University Hospital Aintree, Liverpool, UK

Bronchial hyper-reactivity (BHR) is a hallmark feature of asthma and a common, though not necessarily fundamental, feature of COPD. In asthma the response represents narrowing of the airway lumen due to contraction of airway smooth muscle (ASM). In COPD there is a relationship between BHR and airflow obstruction and we hypothesise that responsiveness is related less to changes in ASM and resistance and more to increase in hyperinflation. Hence an increase in residual volume (RV) will reduce the ability of the airway-parenchymal interface to overcome narrowing of the airway lumen.

We studied 10 subjects with mild to moderate COPD—baseline FEV1 1.59 l (SD 0.45 l), FEV1/FVC ratio 0.49 (0.1) —who underwent standard methacholine challenge testing. At baseline subjects had moderate increases in airway resistance measured by body plethysmography (Raw 3.04 — predicted 1.86), moderate increases in resistance (R5Hz 0.67 — predicted 0.32) and reactance (Z5Hz 0.77 — predicted 0.56). The device is a compact trolley mounted air conditioning module delivering air at up to 1500 ml/s with a controllable temperature (3°C to 40°C) and moisture content (5 to 40 g/kg dry air). Air is delivered to the inspiratory side of a 2 way valve by means of a flow past configuration. Temperature and humidity sensors located on inspiratory and expiratory sides of the breathing valve allow accurate, continuous recording of the thermodynamic state of air entering and leaving the respiratory tract. A computer linked to an ultrasonic flow-meter in the expiratory limb is used to generate auditory and visual feedback cues to help subjects control respiratory rate and flow rate respectively, allowing standardisation of ventilatory pattern between subjects. RHML at steady state is calculated as the product of mass flow rate and “enthalpy” difference between inspired and expired air. Six normal volunteers breathed inspirate at 7°C at a target minute ventilation of 15 l/min with either a slow deep pattern (rate 10/min, tidal volume 1455 (101) ml (SD)) or rapid shallow pattern (30/min, tidal volume 525 (36) ml).

Results: Mean respiratory heat loss was 15.7 (1.4) Watts during rapid shallow breathing and increased to 18.3 (1.3) Watts during the slow deep pattern (p=0.009). At the same tidal volumes respiratory water loss was measured as 334 (30) µl/min and 408 (46) µl/min respectively (p=0.008).

Conclusions: This new measurement device was sufficiently sensitive to detect a significant increase in RHML with increasing tidal volume at fixed minute ventilation in normal subjects. When normal ranges are defined it will be used to measure RHML under matching conditions in patients with COPD, asthma, and cystic fibrosis.

P33 EFFECT OF VARYING RESPIRATORY PATTERN ON EXHALED BREATH CONDENSATE COLLECTION

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Background: Exhaled breath condensate (EBC) has been proposed as a non-invasive means of measuring pulmonary inflammation. At present little is known about how the respiratory pattern during collection influences the properties of the EBC sample. We hypothesised that variations in respiratory pattern would have significant effects on volume and concentration of EBC.

Methods: Ten control subjects had EBC collected three times for six minute periods each on the same day. For the three collections (90 l) but constant total respired volume (Vt), (1500, 750, and 500 mls) but constant total respiratory rate and flow rate respectively, allowing standardisation of ventilatory pattern between subjects. RHML at steady state is calculated as the product of mass flow rate and “enthalpy” difference between inspired and expired air. Six normal volunteers breathed inspirate at 7°C at a target minute ventilation of 15 l/min with either a slow deep pattern (rate 10/min, tidal volume 1455 (101) ml (SD)) or rapid shallow pattern (30/min, tidal volume 525 (36) ml).

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P33 CHRONIC BRONCHITIS, SMOKING AND SOCIOECONOMIC STATUS IN THE NHANES III DATASET

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Background: While some studies have suggested that differences in the prevalence of chronic bronchitis in the various socioeconomic groups is due to differences in smoking habits, others suggest an explanation unrelated to smoking.

Methods: We have examined the relation between the prevalence of chronic bronchitis (M. Sridhar, G. Netuveli, A. Sheikh) and smoking. Of these, being male, ethnicity, and higher SES were protective. In SIB, within each stratum of SES, the only consistently significant risk variable was current smoking status was significantly associated with increased chronic bronchitis. In DDB, within each stratum of SES, the only consistently significant risk variable was current smoking status. No significant interaction was observed. In DDB, within each stratum of SES, the only consistently significant risk variable was current smoking status. No significant interaction was observed. In DDB, within each stratum of SES, the only consistently significant risk variable was current smoking status. No significant interaction was observed.
Conclusions: Socioeconomic status had a significant influence on the prevalence of SIB that was independent of cigarette smoking. The protective effect of higher socioeconomic status was most significant for current smokers. This effect seemed to be independent of smoking behaviour in the different SES strata and merits further scrutiny.

Acknowledgements: An NHS R&D National Primary Care Fellowship supports AS. GN is supported by a grant from the National Asthma Campaign, UK.

P36 MEDICAL RESEARCH COUNCIL DYSPNOEA SCALE IS A MEASURE OF FUNCTIONAL CAPACITY AND GLOBAL PERCEIVED HEALTH STATUS

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Introduction: The Medical Research Council Dyspnoea scale (MRCD) has been used to categorise disability in patients with COPD, though it remains unclear what the scale measures.

Participants: All 218 participants had stable COPD. Sixty per cent reported MRCD scale grade 3, 29% grade 4, and 11% grade 5. Forty four per cent were male and mean (95% CI) age was 68.8 (67.8 to 69.7) years.

Methods: Participants were graded on the MRCD scale on the basis of self report information. Incremental shuttle walking test (ISWT) distance, spirometric, and anthropometric measurements were recorded. Self report data were recorded to assess: perceived health status (Chronic Respiratory Disease Questionnaire (CRDQ)); personal cognitions of illness (Illness Perceptions Questionnaire); affect (Hospital Anxiety and Depression Scale); and self efficacy (COPD Self Efficacy Scale). χ² And One way and Kruskal Wallis ANOVA analysis were carried out to assess differences in respondent characteristics across MRCD grade.

Results: Mean percent predicted FEV1 was 9.93% higher people with grade 3 than those with grade 5 (F = 4.33, p=0.01). Resting oxygen saturation was significantly higher in people with grade 3 compared with those with grade 4 and 5 (F = 9.11, p<0.001). People with grade 3 had a mean ISWT of 235.0 m compared with 153.0 and 117.7 m for grades 4 and 5 respectively (F = 20.05, p<0.001). On the CRDQ, mastery, and emotional functioning were significantly higher, and fatigue and dyspnoea were significantly lower, in people with grade 3 compared with those with grade 4 and 5 (p<0.02). Anxiety was significantly higher in people with grade 3 compared with those with grade 4 (χ² = 6.13, p=0.04) and people with grade 5 had a higher perception of treatment control compared with those with grade 4 (χ² = 8.24, p=0.016). Of people with grade 3 31.8% regarded themselves as being in good health, compared with 16.7% with grade 4, and only 4.5% with grade 5 (χ² = 10.38, p=0.006). There were no significant differences across MRCD grade in body mass index, age, depression, self efficacy, or gender.

Conclusion: Only the ISWT and patients’ Global Perceived Health showed significant differences across all three grades of MRCD scale. The MRCD scale reflects patients’ functional capacity but also their global perceived health status.

P37 THE INFLUENCE OF BMI ON LUNG CT DENSITOMETRY IN EMPHYSEMA

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Lung CT densitometry correlates well with pathological and physiological measures of emphysema and is the most sensitive measure for detecting disease progression in alpha-1 antitrypsin deficiency (AATD) (Dowson, et al. Am J Respir Crit Care Med 2001;164: 1805–9). Long term reproducibility is subject to errors arising from limitations in the reconstruction algorithm, with changes in denser tissues affecting lung density measurements by altering beam hardening effects. Emphysematous lung is of similar density to air, and therefore changes in air density reflect influences on lung densitometry. We looked at the effect of body mass index (BMI) on measured values for air density within the patient. Using a lung phantom, we then measured the effects on lung densitometry of an increase in chest wall thickness as would occur with increasing BMI.

Methods: We performed voxel densitometry of tracheal air on single slice inspiratory high resolution CT images at the level of the aortic arch in 41 patients with AATD (PiZ) and related the results to BMI. In addition, a thoracic phantom containing fixed, whole dog lung (KCARE, KCH, London) was imaged before and after attaching to the outer surface two flexible water filled containers of total volume 3.5L (Durex,UK) simulating increasing chest wall mass. Lung densitometry was performed on two images taken from each series using the PULMO-CMS software (B Stoel, Leiden University). Three techniques were used; relative area at a threshold of –910 HU, the 15th percentile point and the mean lung density.

Results and conclusions: Tracheal air density measurements correlated well with BMI (Spearman’s rho = 0.55, p<0.001). Lung phantom densitometry was influenced by chest wall thickness as shown in the table. A change in BMI over time will alter measured lung density. The effect of an increase in BMI could therefore be to reduce apparent emphysema severity

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<th>Abstract P37</th>
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<tbody>
<tr>
<td>Densitometry method</td>
</tr>
<tr>
<td>Relative area (-910HU)</td>
</tr>
<tr>
<td>15th Percentile point</td>
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<tr>
<td>[HU]</td>
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P38 CT SCANNING IN SUBJECTS WITH COPD AND THEIR RELATIVES

P.P. Walker1, J. Griffiths1, J. Curtis2, E. Thrwaite2, P.M.A. Calverley1. 1Department of Respiratory Medicine, 2Department of Radiology, University Hospital Aintree, Liverpool, UK

Participants in a prospective COPD genetics study underwent thoracic HRCI scanning. Ninety two scans were performed in 71 subjects with COPD and 21 smoking siblings. We documented the frequency of lung nodules and other abnormalities and assessed their follow up to identify possible tumours. We also correlated spirometry and presence of visually scored emphysema on CT and compared the presence of bronchiectasis with clinical symptoms. Mean FEV1 was 1.46L, % predicted FEV1, 50%, COPD severity by GOLD criteria: grade 1= 9(10%), grade 2A= 20(22%), grade 2B= 30(33%), grade 3= 12(13%), no COPD= 21(23%).

Twenty one (23%) subjects had lung nodules—4/21 in siblings without COPD. No malignancies have to date been confirmed. Ten (11%) subjects required investigation for other abnormalities including lobar collapse and asbestosis. Thirty nine additional radiology investigations have been completed so far (29 CT). Twenty one (23%) subjects had bronchiectasis on CT scan. In this population 42/92 subjects had chronic bronchitis clinically but only 6/21 subjects with bronchiectasis had symptoms of chronic bronchitis—no positive correlation.

The worse the spirometry the more likely emphysema was to be present but 33% of smokers with normal spirometry had CT evidence of emphysema. Pulmonary nodules were common and hence resource implications high. Spirometry was imprecise in identifying mild to moderate emphysema but severe obstruction correlated well with CT findings. In subjects without a recent infection bronchiectasis is frequently present without symptoms.

<table>
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<tbody>
<tr>
<td>GOLD criteria</td>
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<tr>
<td>Normal</td>
</tr>
<tr>
<td>GOLD 1</td>
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<tr>
<td>GOLD 2A</td>
</tr>
<tr>
<td>GOLD 2B</td>
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<tr>
<td>GOLD 3</td>
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P39 MULTIDIMENSIONAL (IDS) ASSESSMENT OF COPD IN THE COMMUNITY: CLINICAL IMPACT IS UNDERESTIMATED BY CURRENT GUIDELINES

A.D. Lawrence, N.P. Keaney. Chest Clinic, Sunderland Royal Hospital, Sunderland, Tyne & Wear, UK

The staging of the severity of COPD is based on the degree of airflow limitation. Specific FEV1 cut points are used by the BTS, ATS, and ERS Guidelines. GOLD mentions the impact of COPD, and the imperfect relationship between impaired spirometric values and symptomatology, COPD also has systemic consequences. The IDS system of classifying COPD incorporates airflow limitation (impairment), dyspnoea (disability) and nutritional depletion (BMI-systemic involvement).

Our community database provided information on 401 patients (203 female) attending COPD clinics in eight general practices in Sunderland. Airflow limitation was classified according to standard BTS, ATS, ERS, and GOLD criteria using pre and post bronchodilator FEV1, and compared with IDS.

Use of post bronchodilator FEV1, does not perturb the IDS classification. All guidelines significantly underestimate the impact of COPD with their methods of classifying severity from spirometric impairment alone.

Abstract P39 Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV1 % PREDICTED</th>
<th>IDS criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>&gt;50%</td>
<td>mild/mod dyspnoea, no nutritional depletion</td>
</tr>
<tr>
<td>Stage II</td>
<td>35-49%</td>
<td>mild/mod dyspnoea, no nutritional depletion</td>
</tr>
<tr>
<td>Stage III</td>
<td>&lt;35%</td>
<td>severe dyspnoea, nutritional depletion</td>
</tr>
</tbody>
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P40 A COMPARISON OF INTENSIVE, MDI-DELIVERED AND NEBULISED BRONCHODILATOR THERAPY IN SEVERE COPD

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Background: We have investigated whether nebulised therapy provides superior bronchodilation to a combination of high-dose anticholinergic and long acting β2 agonist therapy, delivered via MDI and large volume spacer, in a well characterised group of stable patients with severe COPD (FEV1 <40% predicted).

Methods: We undertook a comparison of three regimes of four times daily nebulised therapy (salbutamol 5 mg/ipratropium bromide 160 µg four times daily via MDI and large volume spacer, in an open label, sequential, cross over study. The outcome measure was self recorded peak flow rates, measured in the morning, pretreatment (am), afternoon (pm) and night time (nocte).

Results: Seventy three patients were enrolled, until the required number of 42 subjects with adequate data was obtained. Each of the three nebulised regimens was highly significantly, and probably clinically, superior to the MDI therapy, but there was no significant difference between them (ANOVA and paired t tests), see table.

Conclusions: Overall in this group of patients with severe COPD, nebulised therapy produced greater improvement in peak expiratory flow rate than could be achieved with intensive MDI-based therapy.

Abstract P40

<table>
<thead>
<tr>
<th>Time of day</th>
<th>MDI Ipra/ Salbutamol</th>
<th>Nebulised Salbutamol</th>
<th>Nebulised Ipratropium</th>
<th>Nebulised Combivent</th>
</tr>
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<tbody>
<tr>
<td>am</td>
<td>189 (10)</td>
<td>223 (12)</td>
<td>224 (12)</td>
<td>227 (12)</td>
</tr>
<tr>
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<td>204 (11)</td>
<td>229 (13)</td>
<td>226 (12)</td>
<td>231 (13)</td>
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</table>

P41 ECONOMIC IMPLICATIONS OF REDUCTIONS IN COPD REHOSPITALISATION DUE TO TREATMENT WITH INHALED CORTICOSTEROIDS (ICS)

M.D. Spencer. GlaxoSmithKline, Greenford, UK

Background: A study in an Ontario observational database has demonstrated reductions in the rate of COPD rehospitalisation and death of 24% and 29% respectively using ICS (Sin, et al. Am J Respir Crit Care Med 2001;164:580-4). Based on Hospital Episode Statistics there were 78 908 admissions for COPD in the year 2000/1 in England & Wales, with an average length of stay of 9.1 days, Sin and Tu’s data suggest over 15 000 of these would have been rehospitalisations (assumes current ICS usage 50%). This equates to a hospitalisation cost of over £155.8 m with over £31 m for rehospitalisations. The economic implications of reductions in exacerbations have been assessed by modelling these risk reductions on a hypothetical population of 1000 patients, accounting for uncertainty in parameters by second order “Monte Carlo” simulation techniques. The implications of a hypothetical increase in the use of ICS by patients with an initial hospitalisation from 50% to 100% in England & Wales are then considered.

Results: For the hypothetical cohort of 1000 patients a comparison with and without ICS produces a reduction in hospital days of 622 (95% CI 494 to 760) equivalent to a cost saving of £135.6K (95% CI 95K to 189K). Applying this to an increase in ICS use from 50% to 100% for all patients with an initial hospitalisation, would result in a reduction in hospital days of 19.751 (95% CI 15.799 to 24.256) equivalent to a cost saving of £4.29m (95% CI £3.08m to 5.74m), thus offsetting a considerable portion of the drug purchase cost.

Conclusion: These results suggest that, additional to the obvious clinical benefits of avoiding COPD hospitalisation and mortality, valuable NHS resources may also be freed. In addition the financial cost (over £4m) of these hospital days may undervalue these resources during periods of high hospital bed occupancy.

P42 THE ASSOCIATION OF SURVIVAL WITH THE USE OF INHALED CORTICOSTEROIDS (ICS) SEEN IN OBSERVATIONAL STUDIES OF COPD CANNOT BE Explained BY UNOBSERVED MARKERS OF DISEASE SEVERITY (FEV1% PREDICTED, HEALTH STATUS, BODY MASS INDEX)

M.D. Spencer. GlaxoSmithKline, Greenford, UK

Background: Recent COPD studies performed in observational databases have shown benefits of ICS and ICS + LABA in terms of reductions in mortality and of hospitalisation (Sin, et al. 2001; Soriano, et al. 2002). A criticism of such studies, is the lack of randomisation and hence potential bias caused by the confounding of unobserved factors. This study investigates the relationship of a number of potential markers of disease severity in COPD to ICS prescription, and hence the potential for confounding.

Methods: The Health Survey for England 95, 96, and 97 (96 only for health status) forms the population for this study. Respondents with

Abstract P39 Table 2

<table>
<thead>
<tr>
<th>IDS</th>
<th>GOLD</th>
<th>ATS</th>
<th>BTS</th>
<th>ERS</th>
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<tr>
<td>Pre %</td>
<td>Pst %</td>
<td>Pre %</td>
<td>Pst %</td>
<td>Pre %</td>
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<tr>
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<td>37</td>
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<td>37</td>
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<td>Moderate stage II</td>
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<td>37</td>
<td>37</td>
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</tr>
</tbody>
</table>

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Abstract P42

Mean (Median) by ICS prescription group

<table>
<thead>
<tr>
<th>FEV1, % predBMI</th>
<th>EQ-SD</th>
<th>SF-6D</th>
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<tbody>
<tr>
<td>ICS</td>
<td>47 (47)</td>
<td>0.66 (0.69)</td>
</tr>
<tr>
<td>No ICS</td>
<td>55 (57)</td>
<td>0.78 (0.79)</td>
</tr>
</tbody>
</table>

Abstract P43

AudiT of LTOT Prescriptions in Blaenau Gwent

B. Perreira, S. Venn, B. V. Prathibha. Nevill Hall Hospital, Brecon Road, Abergavenny, South Wales, UK

Introduction: The ex-mining area of Blaenau Gwent has a high incidence of occupational and smoking related lung diseases. Provision of high quality clinical care to those individuals with severe disease includes the appropriate prescription of LTOT along with education to facilitate compliance. This audit was conducted with the aim of establishing whether the prescription and use of long term oxygen therapy in Blaenau Gwent complies with established guidelines.

Method: Audit criteria and standards were set using guidelines given in the Royal College of Physicians report Domiciliary Oxygen therapy services. Patients in Blaenau Gwent using oxygen concentrations in June 2000 were identified from Health Authority records. Criteria were measured from a review of hospital notes and by using a short postal questionnaire.

Results: Fifty patients were identified as using oxygen concentrations in Blaenau Gwent in June 2000. Notes were obtained for 48 of these patients (96%) and questionnaires were returned from 44 patients (88%). Thirty five (73%) of the patients were under the care of a respiratory physician. Only 15 (31.2%) had documented evidence of complete adherence to the guidelines prior to LTOT prescription (all under the care of a respiratory physician), although 39 (81.3%) of the patients had blood gases recorded. Thirty three (69%) had documented evidence of prescription for 15 hours a day, although the information given to patients was not recorded in the majority of cases. Of the respondents to the questionnaire, 38 (86.4%) reported using their oxygen for long periods of time rather than intermittently and 34 (77.3%) reported daily use of 15 hours or more. Thirty six (81.8%) understood to use the oxygen correctly and 22 (50%) were able to give a written explanation for their need of oxygen therapy.

Conclusion: The majority of patients who are prescribed LTOT report using it appropriately, although fewer understood the reason for treatment. However, it is of concern that appropriate assessment prior to LTOT prescription can only be confirmed in 31% cases and a chest physician had not seen 27% of the patients receiving LTOT. Following this audit a specially designed nurse led LTOT clinic has been started with referral to the chest physician. A patient information booklet has been introduced along with a blood gases record. A further audit will be conducted in one year to assess the impact of the clinic on the quality of care that patients using LTOT receive.

Abstract P44

Weight Change in Chronic Obstructive Pulmonary Disease (COPD): Not Just a Problem of Undernutrition

C.E. Weekes, N.T. Bateman. Departments of Nutrition & Dietetics, Respiratory Medicine, Guy’s and St Thomas’ Hospital NHS Trust, London, UK

Weight loss is frequently reported in patients with COPD and is associated with increased morbidity and mortality. In contrast, for the past 30 years the general population has become more overweight and therefore at increased risk for heart disease and diabetes. While reviewing patients for a nutrition intervention study it was noted that many patients presenting to chest clinic were overweight. The aims of this study were to establish the number of outpatients with COPD who were overweight, obese, or at risk as a result of weight loss.

Two hundred and seventy six consecutive patients with COPD (143 male; 133 female) were reviewed by the dietitian during a routine visit to the chest clinics at Guy’s and St Thomas’ Hospitals. Weight, height, and history of weight change were recorded, together with smoking status, presence of oedema, and steroid use. Medical records were reviewed to establish the length of chest related hospital stays and mortality. Mean age was 67.3 (10.3) years and body mass index (BMI) 26.2 (6.7) kg/m². Patients were categorised as overweight, acceptable, overweight, or obese (BMI <20.0, 20.0 – 24.9, 25.0 – 29.9 or >30.0 kg/m²). Weight change was considered significant if it exceeded 5% in either direction.

Approximately half the patients were overweight (n = 80 (29%)) or obese (n = 61 (22%)) while one in six (n = 43 (16%)) were underweight. Sixty one (22%) patients reported significant weight loss and 53 (19%) reported weight gain. Oedema was noted in 26 (9%) patients.

Recent weight loss was associated with chest infection in 25 (9%) patients, gastrointestinal symptoms in nine (3%), and social reasons in five (2%), while 22 (8%) patients reported gradual weight loss over one to two years. Twenty two (8%) patients with significant weight loss had BMI >20.0 kg/m², and 15 (5%) had BMI >25.0 kg/m².

Recent weight gain was associated with smoking cessation in 17 (6%) patients, oedema in six (2%) and recent oral steroid use in two (<1%). The remaining 28 (10%) reported a gradual increase over several years.

There was a non-significant trend for increasing BMI to be associated with shorter length of hospital stay (5.9 (12.7) days for underweight to 5.9 (8.4) for obese) but neither BMI nor weight change were associated with mortality.

The majority of publications on COPD are on the undernourished, yet it would appear from this study that about half the outpatients with COPD seen in this Trust were overweight or obese. The effect of being overweight on patients with COPD deserves further study.

Abstract P45

Bronchoscopic Lung Volume Reduction (BLVR) with Endobronchial Valve Implants


Background: Surgical lung volume reduction (LVR) can palliate symptoms in selected patients with advanced emphysema. We hypothesised that a similar effect could be achieved by blocking segmental bronchi leading to areas of bullous emphysema.

Aim: In this study we investigated the safety and efficacy of BLVR using the Emphasis® valve implant and delivery system, in patients unsuitable for surgical LVR.

Methods: Three male patients have undergone so far unilateral BLVR under general anaesthesia. Three valves were placed in each patient in the most affected lobe as evaluated on ventilation/perfusion scans and CT scans.

Results: See table. BLVR was effective in shrinking emphysema lung and expanding a collapsed lobe in one patient. The effect was
sustained at one month follow up. Post procedure complications included: one pneumothorax at day 36 which resolved without drain- age, and one COPD exacerbation at day 40 treated with antibiotics and steroids. None of the implants became dislodged.

**Conclusion:** This pilot study suggests that lung volume reduction can be achieved in humans with flexible bronchoscopy and specific valve implants. The implants are safe and easy to place and have the potential for extending indications and reducing morbidity, mortality and costs in patients with severe emphysema.

**Sleep assessment and treatment**

**P46** AN ATTEMPT TO ASSESS THE DURATION OF PROBABLE MORBIDITY PRIOR TO THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNOEA SYNDROME (OSAS)

R. Ghiasi, M.R. Partridge. The Sleep Laboratory, Imperial College of Science, Technology and Medicine, NHU Division at Charing Cross Hospital, London, UK

Recent work from Canada has suggested that hospital admissions and physician costs in the two years prior to diagnosis of OSAS was significantly higher in those with OSAS than in a control group. In the year prior to diagnosis it has also been shown that prescribed medi- cation costs were significantly higher; medication being needed for hypertension, ischaemic heart disease, and congestive heart failure. The rate of road traffic crashes and occupational accidents is also higher amongst those with untreated OSAS.

To gain an insight into the duration of possible prediagnosis morbidity, we administered a questionnaire to 117 consecutive OSAS patients being treated with CPAP who attended this laboratory for review. Of these 107/117 (91.5%) reported that prior to diagnosis someone had complained about loud snoring and responders recorded that first mention of this had been a median of 12 years prior to diagnosis (range 2 to 47). Also 91/117 (77.8%) reported witnessed apnoea prior to diagnosis and this had been observed a median eight years prior to diagnosis (range 1 to 49). Ninety seven out of 117 (82.9%) reported sleepiness in the day time now or in the past and this had been present for a median of seven years (range 0.5 to 62 years). Seventy eight respondents were in employment and 37.2% of these reported having had two or more jobs in the last five years. Of the respondents, 85 were drivers and 21 of these (24.7%) reported having had a road traffic accident in the previous five years with five respondents having had two and one having had four such crashes. Overall these results suggest the likelihood of significant prediagnosis morbidity and greater public and primary care awareness of OSAS is needed.


**P47** URINARY SYMPTOMS DO NOT CORRELATE WITH SEVERITY OF OBSTRUCTIVE SLEEP APNOEA OR COMPLIANCE WITH CPAP

K.E. Lewis1, A.J. Watkin1, L. Seale1, I.E. Bartle1, P. Ebden1. 1Prince Philip Hospital, Dafen, Llanelli, Wales, SA14 8QF, UK

**Introduction:** Studies have found increased urinary disturbance in patients with obstructive sleep apnoea (OSA). The reason remains unclear and may be due to in part to prostatic symptoms in middle aged men. We examined whether higher urinary symptom scores prior to treatment are correlated with more respiratory disturbance in OSA, and if more symptoms reduce compliance by interfering with machine use.

**Methods:** Seventy four consecutive males with OSA, mean (SD) age of 55.2 (9.0) years, mean BMI 34.5 (5.9), mean Epworth Sleepiness Score 15.4 (5.2), mean AHI 28.1 (22.8) per hour and mean 5% desaturation rate of 31 (21.7) per hour were prospectively studied. They completed the International Prostate Symptom Score and American Urological Questionnaire prior to CPAP therapy. Machine clock timers were hidden and machine on time was checked at one month. Corre- lations between the various subscores for urinary symptoms and measures of respiratory disturbance and machine on time were assessed using Spearman’s rho.

**Results:** Our patients had a mean Total Urinary Score of 5.72 (4.27), range 0 to 19. The correlation between Urinary Obstructive Scores and AHI was rho = 0.229 (p=0.121). The correlation between Urinary Irritative Scores and AHI was rho = 0.100 (p=0.506). The correlation between Urinary Total Scores and AHI was rho = 0.197 (p=0.185).

**Conclusion:** Patients with OSA have Urinary Symptoms similar to the normal population as measured by standard urology tools, and any increased urinary disturbance, prior to CPAP is not significantly corre- lated with either the respiratory disturbance or reduced compliance with CPAP.

**P48** APOLIPOPROTEIN E: A ROLE IN SLEEP DISORDERED BREATHING?

R.L. Riha, P. Brander, M. Vennelle, N.J. Douglas. Dept of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh

Apolipoprotein E e4 (Apo E e4) is an important risk factor for the development of early onset Alzheimer’s disease, as well as being an independent risk factor for cardiovascular disease. A recent study by Kadotani et al demonstrated a correlation of Apo E e4 with a higher apnoea/hypopnoea index in a population with sleep disordered breathing (SDB). The aim of our study was to examine the distribution of Apo E alleles and genotype in patients in the UK with SDB compared to controls.

**Method:** A case control study was undertaken from 1997–2002. One hundred and thirty five consecutive patients with SDB were recruited randomly from the clinic register. Each case was matched to a sibling. All cases and controls were asked to complete a self administered questionnaire and underwent clinical examination. All subjects underwent routine PSG or home monitoring. Studies were scored manually. All subjects had 20 ml of blood taken. Genotyping was performed on DNA extracted from peripheral blood lymphocytes using PCR-RFLP with polymorphisms for the three Apo E alleles determined according to published techniques.

**Results:** Results for 38 matched pairs are presented. Male:female ratio was 46:30. Mean age did not differ significantly between index patients and siblings (50.5 (SD)(8) years). Seventy four consecutive males with OSA, mean (SD) age of 55.2 (9.0) years, mean BMI 34.5 (5.9), mean Epworth Sleepiness score 15.4 (5.2), mean AHI 28.1 (22.8) per hour and mean 5% desaturation rate of 31 (21.7) per hour were prospectively studied. They completed the International Prostate Symptom Score and American Urological Questionnaire prior to CPAP therapy. Machine clock timers were hidden and machine on time was checked at one month. Correlations between the various subscores for urinary symptoms and measures of respiratory disturbance and machine on time were assessed using Spearman’s rho.

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**Conclusion:** Patients with OSA have Urinary Symptoms similar to the normal population as measured by standard urology tools, and any increased urinary disturbance, prior to CPAP is not significantly corre- lated with either the respiratory disturbance or reduced compliance with CPAP.
P49 REACTION TIME (RT) TESTS IN OBSTRUCTIVE SLEEP APNOEA (OSA) AND NARCOLEPSY PATIENTS: THE PSYCHOMOTOR VIGILANCE TASK (PVT) IS A BETTER DISCRIMINATOR THAN THE SIMPLE UNPREPARED REACTION TIME (SURT)  


RT tests are commonly used to assess performance of patients with sleep disorders and healthy subjects who undergo sleep deprivation but it is unclear which is most suitable for use in the clinical setting as an additional tool for assessing the effectiveness of treatment. The aim of this study was to compare the performance of four groups: healthy volunteers, treated narcolepsy patients, OSA patients treated with nCPAP, and untreated OSA patients (desaturation index = 15). Ephysoc Sleepiness Score scale = 10) on two different tests of sustained attention used in our lab: the PVT and the SURT.  

Methods: Subjects completed the 10 min tasks in the afternoon, in random order. Subject demographics are presented in the table.  

Results: One way ANOVA showed that there was a significant difference between the four groups on PVT slope (time on task increment) (F₃,₄₅₆ = 3.6, p<0.005). Bonferroni post hoc tests revealed that both narcolepsy and untreated OSA patients showed more reaction time fluctuation than healthy volunteers on this test and the untreated OSA group were more susceptible than the other groups to this effect.  

Discussion: Despite treatment, narcolepsy patients showed impairments on both tasks of sustained attention. Unlike the PVT, the SURT did not distinguish between untreated patients with OSA and healthy volunteers or those on nCPAP and may not be appropriate to follow treatment effects.  

P50 ANALYSIS OF SLEEP STAGE USING A NEURAL NETWORK: COMPARISON TO MANUAL SCORING IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA (OSA)  

F. Buchanan, N. Wilshire, J.R. Catterall A.H. Kendrick. Dept Respiratory Medicine, Bristol Royal Infirmary, Bristol, UK  

Sleep is a continuum, often with short 2–3s events. Traditional scoring using Rechtschaffen & Kales (R&K) uses multiple channels and assigns one of seven sleep stages to each 30s epoch with further analysis for arousals. Neural net analysis uses 1s epochs and analyses sleep using one EEG channel, assigning a probability of a sleep stage to each epoch.  

Aim: To compare R&K scoring to neural net in patients with OSA.  

Methods: Patients underwent one night’s full polysomnography (SleepLab 1000e, Jaeger). A single scorer manually scored the study using R&K and American Sleep Disorders Association arousals criteria. Data files were converted into European Data Format (EDF) and analysed using a neural network (BioSleep v4.0, Oxford BioSignals) using a single EEG channel. Median filter was set to 15s and a threshold of 0.25 was used to score arousals, which had a minimum duration of 3s. Data are median (range).  

Results: Twenty two patients (two female) were compared. Median AHI = 24.1 (0.10–231) and Apnoea+hypopnoea index = 16.6 (7.0–93.2). The conversion to EDF took 40 mins and analysis 15 mins, as against a median of 120 mins using R&K. The EEG analysis is summarised below (see table).  

Conclusion: The differences observed between R&K and Neural Net reflect the shorter epoch analysis time of 30s against 1s.
Sound was recorded continuously from a throat microphone and an external microphone 1 m above the patient’s head. We analysed all snores, defined as sound level peaks during sleep, lasting 0.1 to 3 seconds, and at least 45 dBA in amplitude measured 1 m above the patient’s head, and calculated three acoustic parameters for each snore: centre frequency, SD frequency (a measure of spread about the centre frequency) (Clin Otolaryngol 1996;21:119–23), and peak factor ratio (the ratio of peak to RMS sound energy) (Clin Otolaryngol 1999;240:130–3). For each subject we calculated the mean value for each of the three parameters, for the external and throat microphones separately.

Results: We analysed an average of 1018 snores per subject. The mean values for each acoustic parameter are given in the table.

<table>
<thead>
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<th>Parameter</th>
<th>External mic</th>
<th>Throat mic</th>
<th>Difference</th>
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<tr>
<td>Centre frequency</td>
<td>562 Hz</td>
<td>351 Hz</td>
<td>−211 Hz (p=0.0005)</td>
</tr>
<tr>
<td>SD frequency</td>
<td>875 Hz</td>
<td>304 Hz</td>
<td>−571 Hz (p=2×10⁻⁴)</td>
</tr>
<tr>
<td>Peak factor ratio</td>
<td>2.36</td>
<td>2.37</td>
<td>−0.01 [ns]</td>
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</table>

Discussion: Clearly, the recording site has a profound influence on the acoustic qualities of snoring sounds. In particular, frequency-domain indices (centre and SD frequency) are affected, implying the throat microphone preferentially attenuates the higher frequencies.

Conclusion: When performing acoustic analysis of snoring sounds, it is essential that the recording site is selected with care.

Acknowledgements: We wish to thank the British Lung Foundation for their financial support of this work.

**P53**

**EFFECTS OF SIMULATED OBSTRUCTIVE APNOEA ON THE CAROTID BARORECEPTOR: VASCULAR RESISTANCE REFLEX**

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Obstructive sleep apnoea may lead to hypertension. This study was designed to determine whether the changes in inspiratory pressure and the asphyxia that occurs in this condition can change the gain and/or setting of the carotid baroreflex to maintain arterial pressure at a higher level.

In eight healthy subjects (aged 21–62) we changed the stimulus to carotid baroreceptors using a neck chamber and graded pressures of 40 to +60 mmHg and assessed vascular resistance responses in the forearm from changes in the blood pressure (Finapres) divided by brachial flow velocity (Doppler ultrasound). Stimulus response curves were defined during (a) sham (no additional stimulus), (b) inspiratory resistance (–10 mmHg), (c) breathing asphyxic gas (12% O₂, 5% CO₂), and (d) resistance and asphyxia. Sigmoid functions were applied to the curves and the maximal differential (equivalent to peak gain) and the corresponding carotid pressure (equivalent to “set point”) were determined.

The sham test had no effect on either the gain or the “set point”. Inspiratory resistance alone had no effect on blood pressure. However it reduced the gain from −3.0 (0.6) to −2.1 (0.4) units (p<0.5) but the curve was not displaced. Asphyxia alone increased blood pressure (+7.0 (1.1) mmHg, p<0.0005) and displaced the curve to higher pressures by +16.8 (2.1) mmHg (p<0.0005) but had no effect on gain. The combination of resistance and asphyxia both reduced gain and displaced the curve to higher pressures.

These results show that inspiratory resistance decreases the gain of the carotid baroreflex and in combination with asphyxia also shifts the curve to higher blood pressure levels. If these changes were sustained, they would provide a mechanism to link hypertension with obstructive sleep apnoea.

**P54**

**PREVALENCE OF SLEEP DISORDERED BREATHING IN PATIENTS WITH CONGESTIVE HEART FAILURE**

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Introduction: Despite recent advances in medical and surgical therapy, congestive heart failure (CHF) remains a common and serious condition. CHF has been associated with sleep disordered breathing (SDB) in 51% patients (Javaheri, et al. Circulation 1998;97:2154–9), including Cheyne-Stokes respiration (CSR) in 40%, and obstructive sleep apnoea (OSA) in 11%. SDB is associated with frequent arousals, leading to a persistent activation of the sympathetic nervous system and elevation of catecholamines with deleterious effects on left ventricular function. Heart rate variability (HRV) is considered to be a surrogate for arousals and serves as an independent prognostic indicator for cardiovascular events (Narkiewicz et al. Auton Neurosci 2001, 90:89–94).

Methods: Patients suffering from CHF were selected on the basis of echocardiographic findings of ejection fraction (EF) less than 35%. We contacted 72 patients by letter, out of whom 36 patients (32 male and four female) agreed to participate in the study. Patients were sent portable pulse oximeters with a digital probe to wear overnight. The patients returned were studied for episodes of desaturations, and an oxygen desaturation index (ODI) was calculated. Desaturations were defined as dips in oxygen saturation greater than 3% and SDB was defined as an ODI greater than five.

Results: The overall prevalence of SDB in CHF patients was found to be 47.2% (17/36) and the mean ODI amongst these patients was 22.2/hr. The prevalence in patients with an EF less than or equal to 25% was 53.8% (7/13) with a mean ODI of 26.2/hr, whereas in patients with an EF between 25% and 35%, it was 43.5% (10/23) with an ODI of 19.5/hr. Increased heart rate variability was noted but was not found to correlate with SDB in our study. Twenty four out of 36 patients had increased HRV associated with concomitant dips in oxygen saturation in only 13. The remaining 11 patients having no SDB as defined here and raising the question as to additional burden of “subclinical” respiratory disturbance.

Conclusion: Our study confirms that nearly half the patients affected by CHF, even in stable condition, have severe nocturnal respiratory disturbances, which increase with increasing severity of CHF.

**P55**

**IS MORE CPAP BETTER IN CLINICAL PRACTICE IN THE MEDIUM/LONG TERM?**

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Background: In a trial setting, hours of continuous positive airway pressure (CPAP) use by obstructive sleep apnoea (OSA) patients is correlated with the fall in subjective sleepiness at one month. Our aim was to examine this relationship in a clinical setting after a longer follow up.

Methods: A retrospective review of patients who (a) were diagnosed with OSA according to the criteria as in (1) (oxygen desaturation index (ODI) >10/hr and Epworth Sleepiness Scale (ESS) score >10); and (b) were started on CPAP in the year 2000 and continued to use it for an average of >1 hour each night after >100 days. Correlation was assessed using Kendall’s tau_b coefficient.

Results: One hundred and three subjects (82 male) met the study criteria (table). Hours of CPAP use per night and change in ESS continued to use it for an average of >1 hour each night after >100 days. Correlation was assessed using Kendall’s tau_b coefficient.

Discussion: In a month long trial setting only 4% of subjects withdrew from using CPAP. In our experience approximately 15–20% discontinue CPAP in the long term. Those who use CPAP very little and gain no benefit will increase the correlation between hours of CPAP use and change in ESS early on. After a longer period of time these people have stopped using CPAP. The hours of use of long term compliers with CPAP may be more dependent on intrinsic sleep requirement, the benefits gained from decreased snoring and the level of belief in a decreased risk from cardiovascular events rather than a simple relationship with perceived change in daytime sleepiness.


**Methods:** Seventy consecutive SAHS patients were randomised to receive standard care (SC, n=35) or standard care plus a specialist nurse home visit at seven days (HV, n=35). Patients completed a symptom score, Epworth score, Hospital Anxiety and Depression Score (HADS), and SF-36 at baseline and three months after initial review. CPAP hours of use were recorded.

**Results:** CPAP therapy resulted in significant improvements in symptoms, Epworth, HADS (table), and in the energy/vitality and mental component summary scores of the SF-36 in both groups. There was no difference between groups in any outcome measure or in hours of use of CPAP.


**P60** **COMPULSORY REFERRAL FOLLOWING ABNORMAL CHEST X-RAY VERSUS CHOICE**


The British Thoracic Society recommends that General Practitioners should immediately refer patients to a respiratory physician if a radiology report suggests the possible diagnosis of lung cancer (Thorax 1998; 53 Suppl 1):S1–8). Some Units see such patients directly from the x-ray department while others (including ours) rely on the patients GP to refer patients to the rapid access clinic. An audit of 2369 reports from GP requested chest x-ray, dating from 1st January to 28th February 2002 was conducted. In total, 63 reports were suspicious of malignancy. Of these, 40 advised referral to a chest physician, 16 advised computerised tomography (CT) scan, and seven did not give any advice. Of the 63 positive reports 48 were referred to a chest clinic (31 to the rapid access lung clinic and 16 to another chest clinic). Four patients were already under regular chest follow up and six were under the care of other physicians. Three patients had CT scan undertaken by the Consultant Radiologist and no further action deemed necessary. One patient was admitted via the Casualty Department because of symptoms and one elderly lady in a nursing home subsequently died without being seen. The time patients seen in a clinic ranged from zero to 49 days with a median of eight days. We have found that only five patients were not referred to outpatient of whom three were investigated with CT directly by the x-ray department. One of the remaining two patients presented with symptoms within two days to casualty and only one was missed (this was an elderly lady in a nursing home). Thus we have found that most patients with abnormal x-rays are referred in a timely fashion but suggest that the x-ray report should specifically suggest rapid access clinic referral. This system preserves both primary care and patient choice and prevents inappropriate referrals.

**P61** **EXPERIENCE FROM THE FIRST 24 MONTHS OF A FAST TRACK LUNG CANCER CLINIC**

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In May 2000 a dedicated Fast Track Lung Cancer Clinic was introduced at the Royal Devon & Exeter Hospital to facilitate referrals via the newly established two week wait (TWW) for suspected tumours. The clinic commenced as a weekly, Consultant provided service with the capability to see up to five urgent referrals weekly. General Practitioners were informed about the new clinic by means of a letter, which also included local guidelines for referral via the "two week wait criteria". Here we present an analysis of our experience over the first 24 months of this initiative. A total of 378 new referrals were seen, with 180 (47.6%) of these being referred by the two week wait. Other referrals were via urgent GP letter (95), non-urgent GP letter (73), and Consultant referral (30). Of the TWW referrals seen, 169 (93.9%) were appropriate according to local guidelines and 100% of these referrals were seen within two weeks. Over the 24 month period the number of referrals via the TWW route has increased from 36 (1 st six months of audit) to 64 (final six months).

Eighty-three patients seen in the FTLC, 148 (39.1%) have been diagnosed with primary lung cancer or mesothelioma. A further 11 have been diagnosed with secondary cancer. Eighty eight (48.8%) of the TWW referrals had a diagnosis of primary lung cancer. Since the introduction of the TWW and the FTLC there has been a sizeable decrease in the number of patients diagnosed as lung cancer following an emergency admission.

The establishment of a FTLC has enabled us to fully achieve the TWW target. Referrals via the TWW are increasing and, in the main, are appropriate. The FTLC may have reduced the number of patients admitted acutely with newly diagnosed lung cancer, but further follow up data will be required before this hypothesis can be confirmed.

**P62** **APPROPRIATENESS OF REFERRAL PATTERNS UNDER THE TWO WEEK RULE FOR LUNG CANCER**

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The Calman-Hine proposals for the management of lung cancer have forged the “two week rule” as the expected standard practice. Although many Trusts are able to meet these targets, less is known about the appropriateness of the actual General Practitioner (GP) referral patterns. This is particularly relevant against a background of direct or partial booking schemes for hospital appointments increasingly being made available to GPs. At this Trust, over a 12 month period to April 2001, there were 126 requests as possible lung cancer categorised under the two week rule; under the TWW target, referrals had been received centrally by the next working day and 121 (96%) had been offered outpatient appointments within the two weeks. At least 13 (90%) of these patients met at least one of the preset published criteria for referral. Four of the 13 inappropriate referrals were from one GP practice. Of the 126 referrals, for 92 the criteria were based on radiological abnormalities alone with similar numbers (both n=46) specifically prompted by the radiologists or on the GPs own initiative. Chest film changes accompanied 15 patients with haemoptysis and one had stridor. Haemoptysis alone was reported in six. Collectively, these two week rule referrals made up 48 (36%) of the 132 patients with diagnosed malignant disease presenting to the chest. A further 35 were diagnosed having been admitted acutely, 22 were detected at follow up clinics (including post admission), 15 were referred as routine whether by their GPs (n=9) or via other consultants (n=6), similarly nine others urgently outside two week rules by GPs (n=6) or via other consultants (n=3), and one patient remained with a non-respiratory physician throughout. Two others are undefined. Although we cannot presently comment on the patterns of referral of those outside the two week rule, this audit provides an insight into the appropriateness of two week referrals encountered here. It recognises the heterogeneous modes of presentation and referral but as expected singles out abnormal radiology as the main determinant. Importantly it also defines a large number (n=24) still electively referred outside the two week rule by both GPs and hospital teams. It concludes (1) that the majority (90%) referred under the scheme met the appropriate criteria for referral, (2) that only 48 (38 %) of these were then found to have malignant disease, and (3) that there are areas for improvement advising referral guidelines and timescales both within primary and secondary care.

**P63** **HAEMOPTYSIS IN PATIENTS WITH A NORMAL CHEST X-RAY: CURRENT PRACTICE OF UK CHEST PHYSICIANS BASED ON A POSTAL SURVEY**

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Do patients who present with an isolated episode of haemoptysis and a normal chest x-ray (CXR) need further investigation? If so, should this be done by bronchoscopy (Br), computerised tomographic scan of the thorax (CT) or both? We sent a postal questionnaire to 610 UK chest
The effectiveness of a lung cancer multi-disciplinary team (MDT): A DISTRICT GENERAL HOSPITAL (DGH) experience


Introduction: A number of strategies have been developed to combat lung cancer in the United Kingdom starting with the Calman Hine Report in 1995. The MDT approach incorporating various medical and paramedical specialties has been uniformly advocated to provide efficient and effective delivery of care. The effectiveness of the MDT approach has not been evaluated.

Aim: To assess the effectiveness of a lung cancer MDT in the management of lung cancer.

Methods: We audited the management of patients with lung cancer from Glan Clwyd DGH over a one year period before and after MDT was instituted at the North Wales Cancer Centre.

Results: See table.

Conclusions: In our audit, there were no significant differences in the diagnosis or treatment of patients after the formal MDT approach was adopted. More non-invasive investigations were performed and data collection was more extensive and structured. Further larger audits on the effectiveness of the MDT approach in lung cancer are required to determine if it indeed provides more effective delivery of care than previously practised.

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<th>Repeat CXR(s) alone</th>
<th>CT alone</th>
<th>Br alone</th>
<th>CT &amp; Br</th>
<th>Repeat CXR(s) &amp; Br</th>
<th>CT &amp; Br</th>
</tr>
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<td>8%</td>
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<td>30%</td>
<td>7%</td>
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CXR, chest x-ray; CT, computed tomography; Br, bronchoscopy.
LUNG CANCER IN WOMEN THROUGH THE 1990s
A. Bastin, D. Erout, A. Davison, A.S. Haque, A. Hutchings, A. Lamont, C. Trask. Southend Associate University Teaching Hospital, Southend on Sea, Essex SSO ORY, UK

Lung cancer incidence is rising in females (F) and falling in males (M) in the UK. Smoking in young females increased in the early 90s. We have analysed the pattern of lung cancer in 2127 new cases [1421 M (67%) + 706 F (33%)] presenting over a 10 year period from 1990 to 1999 from the Southend Lung Cancer Study. This includes every case in a well defined population of 325 000. The mean age of F was 70.8 yrs (SD 10.3) and M 71.7 yrs (SD 9.7) (p=0.04). There was a higher percentage of F never smokers [8.5%] compared with M [1.9%] (p<0.001). The proportion of never smokers was greater in elderly F compared to younger F (p=0.019). There was a higher percentage of M ex-smokers [60.2%] compared with F [51.1%] (p<0.001). There were 39.6% of M current smokers compared to 37.9% M (p=0.47). The proportion of current smokers falls with increasing age at diagnosis in both M and F (test for trend p<0.001).

We found a lack of evidence that the proportion of F to M had increased from 1990 to 1999 overall (test for trend p=0.3) nor in under 65s alone (p=0.151). In patients with confirmed squamous, adenocarcinoma, or small cell histology (total 1342), there was an overall difference (p=0.001) in the proportion of histological types between M and F: squamous cell carcinoma 54% M & 41% F; adenocarcinoma 23% M v 28% F; small cell carcinoma 23% M v 31% F (χ² p=0.001). Never smoking F were more likely to have adenocarcinoma than F who smoked (χ² p<0.001). We found no evidence that the proportion of adenocarcinoma in smokers and never smokers changed over time in M and F (test for trend p>0.67). The proportion for M (10.5%) and F (8.9%) having either radical radiotherapy or surgery differed by 1.6% (95% CI –1.1% to 4.2%) (χ² p=0.26).

Conclusion: In comparing M and F with lung cancer through the 90s we have found: (i) F to be slightly younger than M; (ii) differences in histological types, with adenocarcinoma and small cell being more common in F and squamous cell carcinoma in M; (iii) more F never smokers; (iv) older F were more likely to be never smokers than younger F; (v) F never smokers were more likely to have adenocarcinoma than F smokers; (vi) no difference in the proportion of men and women presenting over time, and (vii) no evidence of a gender bias in those receiving “curative” treatment.

LUNG CANCER IN OCTOGENARIANS, THE ROLE OF THE SURGEON
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Objective: To analyse the pattern of management of patients in their eighties referred to the surgeon with clinical evidence of lung cancer.

Methods: A retrospective series of 62 80 year old patients (42 males) with a clinical diagnosis of lung cancer referred to the surgeon over a 13 year period. The surgical management of these patients was reviewed.

Results: Pathological confirmation of tumour type was in 54 patients (87%) with 39 lung cancers (28 squamous cell, eight adenocarcinoma, one large cell, and one small cell carcinoma), seven diffuse malignant mesotheliomas, three metastases, and five other tumour types. Of the lung cancer patients, 10 had tumours that were unreatsectable (mean survival 8.4 months) and 29 had resectable lesions. Of the latter group, eleven patients had comorbid disease making them inoperable (mean survival 6.4 months). Eighteen patients had lung tumour resection. There were four pneumonectomies, 13 lobectomies, and one bilobectomy. Ten patients had stage 1, five had stage two, and three had stage 3a lung pathology. Operative mortality was 11% (two patients). One, two, and three year survivals were 72%, 64%, and 23% respectively. Four of the nine late deaths were from tumour spread and there are seven disease free survivors.

Conclusion: Age should not be a discriminating factor in determining operability in lung cancer patients. The surgeon plays an important role in the management of octogenarians with lung cancer, offering a wide range of services from minor diagnostic procedures to definitive surgery.

COPYING CORRESPONDENCE TO CHEST CLINIC PATIENTS: A SURVEY OF PATIENT VIEWS
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Introduction: As part of the NHS plan to improve communication between health professionals and patients by 2004, it is expected that all future patients will receive copies of correspondence. It is likely that this directive will have important effects on the way in which providers deliver their service in addition to changing the way they relate to their patients.

Methods: From mid April to mid June 2002, we surveyed all patients attending our general respiratory clinics in addition to those visiting our dedicated Lung Cancer Clinic. Patients were asked to complete a self administered questionnaire with tick box format, designed to identify which patients wished to receive all or some copies of their correspondence and which patients preferred to receive no copies. The patient's wishes were then recorded on their correspondence and letters were forwarded to the patients if required. Patients were requested to discuss any errors in their medications at their next clinic visit. Our medical secretaries recorded any incidents arising out of the introduction of this system. Patient preferences for receiving copies of correspondence at general respiratory and specialist lung cancer clinics (table)

A significantly greater proportion of patients attending our dedicated Lung Cancer Clinic preferred to receive no copies of correspondence than their general respiratory counterparts (27% v 14%, p=0.013 using Fisher's exact test). Overall, 84% of our patients expressed a preference to receive copies of correspondence. Throughout the study period, no incidents were recorded bar one patient who wished to point out a medication error.

Conclusions: Based on our two month experience, we recommend caution for those planning to introduce copies of correspondence to all patients attending clinics as a small proportion would not wish to receive this. This proportion rises to almost a third for those patients attending Lung Cancer Clinics.

<table>
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<th>General respiratory</th>
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<td>All or some copies</td>
<td>273 (86%)</td>
<td>45 (73%)</td>
<td>318 (84%)</td>
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<td>No copies</td>
<td>44 (14%)</td>
<td>17 (27%)</td>
<td>61 (16%)</td>
</tr>
<tr>
<td>Total</td>
<td>317</td>
<td>62</td>
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</table>
Lung injury, inflammation, and infection

P70 EPIDEMIOLOGY OF LUNG FUNCTION AND IMMUNOLOGY IN PIGEON BREEDERS: FIVE YEAR FOLLOW UP
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Background: The immunopathogenesis of pigeon fanciers’ allergic alveolitis is unresolved. Most studies rely on subjects presenting at clinics and proper epidemiological evaluation is lacking. Changes in lung function, immunology, and associated symptoms among a cohort of pigeon fanciers were assessed.

Methods: Forty pigeon fanciers had serial lung function, serum antibody to inhaled avian antigens and symptoms monitored for five years.

Results: Between 1997 and 2002 there was a significant reduction in FEV1 (T = −2.87, p=0.007) and FVC/FVC, F = −3.68, p<0.001). Twenty one subjects were seropositive in 1997 and a further four subjects showed evidence of new sensitisation in 2002 and there was no significant increase in the paired mean titre. The % predicted FEV1 correlated inversely with serum antibody titre (r = −0.380, p<0.019) and peripheral blood CD8 lymphocyte proportion (r = −0.319, p<0.05). The antibody titre also correlated inversely with the CD4:CD8 ratio (r = −0.325, p=0.014). Eleven subjects had symptoms of extrinsic allergic alveolitis in 2002 compared to 13 subjects in 1997.

Conclusion: Serial lung function in statistically determined cohort of pigeon fanciers seems to deteriorate significantly depending on the extent of the humoral antibody response to the inhaled antigens. These changes are associated with underlying immune dysfunction involving the imbalance of T-helper and T-cytotoxic lymphocytes. Subclinical inflammatory changes are common among pigeon fanciers and may be predictive of disease progression.

P71 SERIAL LUNG FUNCTION FOLLOWING PERIPHERAL BLOOD STEM CELL TRANSPLANTATION
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Background: Pulmonary function tests (PFTs) are an established tool in the prediction of respiratory complications following autologous bone marrow transplantation (BMT) for haematological malignancy. Most of these patients are now managed with autologous and allogeneic peripheral blood stem cell transplants (PBSCT), a procedure less toxic than BMT and thought to result in fewer pulmonary complications.

Methods: In this observational study we have followed serial pulmonary function tests in 70 patients up to 8½ years following PBSCT for multiple myeloma (n=35) and leukemia (n=35, 43 % AML, 6 % ALL, 14 % CML, 37 % CLL) to determine whether there were any groups which were particularly susceptible to respiratory complications. The selection of CD34+ cells was performed in 22 cases during the harvesting of peripheral blood stem cells prior to transplantation.

Results: Over the duration of the study there was a notable decrease in TLCO (figure) and an increase in RV (non-significant) in those who received CD34 selected, in comparison to non-CD34 selected grafts.

There was deterioration in lung function data (FEV1 and FVC) in the AML population in comparison to the combined PBSCT population.

Conclusion: Even though PBSCT is associated with fewer pulmonary complications, certain subgroups of patients are more prone to changes in lung function over time. This justifies the performance of serial lung function in these patients.

P72 LUNG REPAIR BY HAEMATOPOIETIC STEM CELLS (HSC) AFTER BONE MARROW TRANSPLANT (BMT)

Introduction: Recent data suggest that HSC contribute to repopulation of the pulmonary parenchyma after BMT (Krause DS, et al. Cell 2001;105:369–77; Kotton DN, et al. Development 2001;128:5181–8). The aim of this study was to define in mice following BMT the phenotype and time course of the appearance of donor-derived cells in the pulmonary parenchyma.

Methods: Six-week-old female recipients were irradiated with 10 Gray as a split dose two hours apart to ablate their BM and then received male wild type whole BM by tail vein injection. Four mice were sacrificed at weekly intervals for six weeks and then at eight and 10 months. Lung sections were hybridised with FITC-labelled Y chromosomes, and CAM5.2 to detect cells of donor origin. For the mouse tissue we combined in situ hybridisation for the Y chromosome with immunohistochemistry for specific markers for macrophages, myofibroblasts, endothelial and epithelial cells.

Results: Y+ cells were widespread in the lung parenchyma a week after BMT, engraftment peaked between four and six weeks, and persisted for at least 43 weeks (figure). Y+ cells were absent from the airway epithelium and the endothelium of venules and arterioles. Y+ cells stained positively with epithelial cell markers T1a, lectin lycoperiscum europaeum, and CAM5.2.

Conclusions: Donor-derived HSC (Y+) cell’s morphology and staining suggests that they become part of the alveolar epithelium. The role of BM derived stem cells in lung repair is unknown but may be a novel target for manipulation or a means of delivering gene therapy to the distal lung.

SJ is supported by a training fellowship from the MRC UK.

Abstract P72

P73 PERIPHERAL BLOOD CHANGES AND CRYPTOGENIC FIBROSING ALVEOLITIS. POSSIBLE MARKERS OF DISEASE?
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Background: Cryptogenic fibrosing alveolitis (CFA) is a disease associated with activated alveolar macrophages at bronchoalveolar lavage. In the peripheral blood, autoantibodies and elevation of the ESR are common but not diagnostic. The prevalence of CFA has increased in the last decade providing more patients for studies.

We have observed a consistent feature (not yet described) of elevation in peripheral blood monocytes (MØ), mean red cell volume (MCV), and serum gamma glutamyl transferase (GGT). In all cases
alcohol intake and drugs were excluded as a cause. Full liver function tests were otherwise normal along with vitamin B12 and folate levels. A bone marrow was examined in three cases confirmed a true macrocytosis without any other myelodysplastic features.

Methods: Ninety one patients [age 41–86 years] presenting with a new diagnosis of CFA had their baseline haematology and biochemistry studied. The results were compared with an age and gender matched reference range obtained from the same laboratory of non-CFA general population controls. The abnormalities at baseline were noted to be persistent throughout the patients treatments.

Results: See table.

Conclusion: Ninety one CFA patients showed a statistical increase in peripheral blood monocytes, MCV, and serum GGT. This observation requires further investigations and may represent a systemic inflammatory response in CFA.

**Poster presentations iii69**
Conclusions: There is presently minimal use of any formal severity assessment and a possible over reliance on intravenous antibiotics. This audit may provide a background on which to investigate the benefits of severity assessment forms in the care of all those admitted locally with possible CAP.

P79 STAPHYLOCOCCUS AUREUS CELL WALL DEFICIENT BACTERIA ARE HIGHLY RESISTANT TO CELL WALL ACTIVE ANTIBIOTICS AND HAVE AN ALTERED PROFILE TO OTHER CLASSES OF ANTIBIOTIC

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Background: Bacteria may lose all or part of their cell walls under certain environmental conditions, including the presence of cell wall-active antibiotics. Cell wall deficient bacteria (CWDB) are hard to detect by light microscopy or culture, but can proliferate in vivo and on specialised media. We investigated whether cell wall deficiency confers stable resistance to penicillin and its effect on the response to other antibiotics.

Method: Staphylococcus aureus cells were cultured in the presence of sublethal levels of penicillin G on various media, including one optimal for CWDB. Minimum inhibitory concentrations (MIC) estimations were performed after three step increases in penicillin concentration and on cells that had been passaged in the absence of penicillin. Cells were examined by gram staining and electron microscopy. Different strains of CWDB were subjected to disc diffusion tests for a range of other antibiotics.

Results: CWDB have a different colony morphology, stain gram negative and have indistinct margins and altered cell morphology on electron microscopy. The MIC for penicillin increased following serial passages, particularly on CWDB optimal media (32 units/ml, compared with 1 unit/ml on DST medium, after 12 passages). After seven passages without penicillin the cell wall was regained, but penicillin resistance was maintained. CWDB were resistant to other cell wall active antibiotics. They also exhibited altered profiles in comparison to the wild type cells for erythromycin, trimethoprim, tetracycline, novobiocin, and nitrofurantoin.

Conclusion: In the presence of sublethal levels of antibiotics and media optimal for CWDB, S. aureus rapidly develops a high degree of stable penicillin resistance. We propose that loss of the cell wall, though rarely demonstrated in clinical microbiology laboratories, is an important cause of antimicrobial resistance to cell wall active antibiotics. Surprisingly these cells show significant alterations in sensitivity to other classes of antibiotics too. This could have profound implications for antibiotic therapy.

P78 IgA1 PROTEASE FROM NON-TYPABLE HEMOPHILUS INFLUENZAE CLEAVES TWO SITES IN HUMAN IgA1 HINGE REGION

D. Mistry, S. He, R.A. Stockley. Lung Investigation Unit, Queen Elizabeth Hospital, Birmingham, UK

Bacterial IgA1 proteases are thought to be important virulence factors in respiratory tract infections. This group of proteolytic enzymes specifically cleave one of several post-proline peptide bonds within the hinge region of human immunoglobulin A1.

We have purified an IgA1 protease with a different cleavage specificity, from a clinical isolate of non-typable Haemophilus influenzae (NTHI), by anion exchange chromatography. Proteolytic assays were carried out with human IgA1, IgA2, and serum albumin. PCR of the NTHI genome was carried out with IgA1 protease sequence-specific primers to identify the gene(s) coding for the IgA1 protease(s) producing this cleavage pattern.

The protease specifically cleaved human IgA1 and did not cleave human IgA2 or serum albumin. However, the IgA1 protease cleaved more than one site within the hinge region of human IgA1. PCR amplification of only one IgA1 protease gene (iga) product. The PCR products contained homologous sequences to other iga genes of the serine-type IgA1 proteases and interspersed between these sequences were new deletions and insertions. The results indicate that the NTHI contains one iga gene sequence that encodes one IgA1 protease, with cleavage at more than one peptide bond in the IgA1 heavy chain. The iga gene sequence may produce the unique cleavage specificity of the NTHI IgA1 protease and further work will require the identification of the residues essential for the IgA1 protease activity, to allow the design of specific inhibitors to this important class of proteolytic enzymes.

P77 ELEVATED NASAL NITRIC OXIDE CORRELATES WITH REDUCED NASAL MUCOCILIARY CLEARANCE IN BRONCHIECTASIS

A. Shoemark, S. Kharitonov, P. Barnes, R. Wilson. Host Defence Unit, Royal Brompton and Harefield NHS Trust and National Heart and Lung Institute, Imperial College of Science Technology and Medicine, London, UK

Effective mucociliary clearance (MCC) is an important first line host defence against infection. Nitric oxide (NO) is also thought to aid in host defence through its antibacterial properties and by increasing ciliary beat (Runer et al. 1998). NO is upregulated in the presence of infection and inflammation (Kharitonov et al. 1995). The aim of this study was to establish the relationship between nasal MCC and NO in patients with bronchiectasis, a disease associated with impaired host defence and infection.

Nasal MCC and NO were measured in 30 non-smoking subjects with stable bronchiectasis confirmed by CT scan, age 25-82 yrs mean 57, male (11), and eight control subjects with no respiratory problems. Eight patients regularly used nasal corticosteroids. Subjects with cystic fibrosis or primary ciliary dyskinesia were excluded as nasal NO is known to be low. NO was measured directly from the nostril during a breath hold using a chemiluminescence analyzer (LR2000 Logan research ltd. Rochester, UK). Three patients could not hold their breath for long enough for the test to be performed correctly. Nasal MCC time was measured by the saccharin test.

In bronchiectasis patients MCC and NO were measured in 30 non-smoking subjects with stable bronchiectasis confirmed by CT scan, age 25-82 yrs mean 57, male (11), and eight control subjects with no respiratory problems. Eight patients regularly used nasal corticosteroids. Subjects with cystic fibrosis or primary ciliary dyskinesia were excluded as nasal NO is known to be low. NO was measured directly from the nostril during a breath hold using a chemiluminescence analyzer (LR2000 Logan research ltd. Rochester, UK). Three patients could not hold their breath for long enough for the test to be performed correctly. Nasal MCC time was measured by the saccharin test.

In conclusion nasal NO is elevated in bronchiectasis patients with delayed nasal mucociliary clearance. This finding may be due to increased inflammation in the upper respiratory tract. Delayed clearance occurs despite any increase in ciliary beat that might occur with increased NO.

P80 STUDY OF EXHALED NITRIC OXIDE IN STABLE BRONCHIECTASIS

L.J. Ozerovitch, A. Shoemark, S. Kharitonov, P. Barnes, R. Wilson. Host Defence Unit, Royal Brompton and Harefield NHS Trust and National Heart and Lung Institute, Imperial College of Science Technology and Medicine, London, UK

We have previously shown that nitric oxide (NO) is elevated in some patients with stable bronchiectasis, but in others levels are normal. Exhaled NO levels are high along with systemic markers of inflammation (CRP and peripheral blood neutrophil count) during an exacerbation and fall after antibiotic therapy. These results suggest that NO is a marker of lung inflammation. The present study was conducted to compare those patients with elevated NO when stable to those with normal levels.

Twenty three patients with bronchiectasis shown on CT scan underwent a protocol of investigation which included full lung function tests, sputum examinations, blood investigations, ciliary studies, sweat test, shuttle walking test, and St George’s Respiratory Questionnaire (SGRQ).

There was no relationship between NO and walking distance nor any component of the SGRQ. There was also no relationship between NO and extent of bronchiectasis on CT scan, blood inflammatory markers, sputum bacteriology, sputum eosinophil count, nor any lung function parameter. There were correlations between gas transfer (% predicted) and walking distance (p<0.05); walking distance and CRP (p<0.03); gas transfer (% predicted) and Total SGRQ (p<0.05); walking distance and Total SGRQ and also the Activities component (p<0.004); and Total SGRQ and FEV1 (% predicted) (p<0.05). In conclusion we do not know why some patients with stable bronchiectasis have elevated exhaled NO. We are continuing to study more patients using the same protocol, and also carrying out a more detailed analysis of the CT scans—for example, airway wall thickness—and a long term study to see if elevated NO influences the subsequent clinical course.
Clinical asthma and the nurse’s role

P81 CHILDHOOD ASTHMA IN THE HIGHLANDS OF SCOTLAND: MORBIDITY AND SCHOOL ABSENCE
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Background: The prevalence of childhood asthma in Scotland is one of the highest in the world. Allergic diseases may cause significant morbidity. The aims of this study were to describe the prevalence of asthma, eczema, and hay fever in the Highlands of Scotland and in the Shetland Isles and to examine factors in relation to quality of life and social deprivation.

Methods: A total population survey of 12 year old children using a parent completed questionnaire.

Results: 86.3% (2658/3080) returned questionnaires. Of the 2549 questionnaires analysed, 476 (18.7%) reported asthma, 362 (14.2%) wheeze in last 12 months, 508 (19.9%) hay fever, and 553 (21.8%) eczema. Of the children reporting asthma or wheeze, 35.4% (229/647) had missed school because of asthma or wheeze, 38.0% (246/647) had missed physical education. Of subjects with lifetime wheeze, 62.5% (354/566) reported sleep disturbance. Deprioritisation measured by DEPCAT scores was associated with maternal smoking and bronchitis in the child but not with allergic diseases.

Conclusion: Compared with previous studies, the prevalence of asthma is unchanged but eczema has increased in Highland adolescents. Allergic disease has a significant impact on school attendance and physical activity. Deprioritisation is associated with maternal smoking and bronchitis in the child but not with allergic diseases. The impact of allergic diseases in rural areas may be different from urban areas.

Acknowledgement: This study was funded by Chest, Heart and Stroke Scotland.

P82 CAN ASTHMA LIAISON NURSES REDUCE UNSCHEDULED CARE IN A DEPRIVED MULTIETHNIC POPULATION? ELECTRA: THE EAST LONDON CONTROLLED TRIAL FOR HIGH-RISK ASTHMA
C. Griffiths, G. Foster, G. Feder, H. Tate, S. Eldridge, N. Barnes, A. Livingstone, T. Coats, for The Electra Group. Dept General Practice and Primary Care, Bart’s and the Royal London Hospital, London, E1 4NS; The London Hospital, London E1, UK

Introduction: Evaluations of specialist nurses have focused on education in secondary care rather than liaison with primary care, and have not been set in multiethnic populations.

Design: Cluster randomised control trial comparing liaison nurse intervention versus best usual practice.

Setting: Forty four general practices in Tower Hamlets, east London Participants: 324 adults and children with asthma recruited after hospital admission or accident and emergency attendance.

Intervention: Intervention practices received two educational visits from liaison nurses to promote care of high risk patients. Participants from intervention practices received asthma education, and self management plans. Following review and or telephone call the nurses read primary care notes and sent a flyer followed by an asthma assessment telephone call by the nurses offering an appointment for a review at the Primary Resource Centre or at one rural practice between 09:00 to 18:00. A letter of invitation was sent if no telephone or if unable to contact. Prior to review and telephone call the nurses read primary care notes and repeated asthma prescription for each patient. The review, taking approximately 45–60 minutes, included asthma education, medication advice, and self management plans. Following review and or telephone call a summary liaison form was sent to the GP.

Results: Telephoned assessments 177/237 (77%), contact time was median 9 (2–29) days. Attended review 62/237 (26%), contact time was median 18 (8–72) days. Refused review 81/237 (34%), 48 (20%) because had hospital/GP review already. Thirty eight out of 237 (16%) defaulted review appointment. Unable to contact 56 (24%) patients. Nurse management recommendations advised for 46/62 (74%) of those reviewed, of which 16 (35%) recommendations were acted on in the practice.

Conclusion: There was a poor response from patients to centralised review. This type of service may not be appropriate for OOH’s attenders.

P83 DEVELOPMENT OF CENTRALISED ASTHMA NURSE SPECIALIST FOLLOW UP SERVICE FOR PATIENTS WHO ATTEND OUT OF HOURS FOR ASTHMA

Background: Local audit of patients attending out of hours (OOH) for asthma highlighted gaps in follow up in primary care. One possible solution was asthma nurse specialists (ANSPs) based in OOH centre, providing a centralised service for reviewing these patients.

Aims: Improvement in primary care management of patients attending OOHs for asthma.

Design: Twenty four practices in two Local Health Care Cooperatives matched by size and deprivation category were randomised to 12 practices whose patients would participate in ANSP service and 12 practices whose asthma care remained the same. Patients, aged 5–60, were recruited over 14 months.

Method: Two part time ANSPs with advanced asthma qualifications were employed. Patients were identified from OOH’s cooperative and Accident & Emergency daily. The Intervention group was sent a flyer followed by an asthma assessment telephone call by the nurses offering an appointment for a review at the Primary Resource Centre or at one rural practice between 09:00 to 18:00. A letter of invitation was sent if no telephone or if unable to contact. Prior to review and telephone call the nurses read primary care notes and repeated asthma prescription for each patient. The review, taking approximately 45–60 minutes, included asthma education, medication advice, and self management plans. Following review and or telephone call a summary liaison form was sent to the GP.

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Conclusion: There was a poor response from patients to centralised review. This type of service may not be appropriate for OOH’s attenders.

P84 WHAT TREATMENT FACTORS INFLUENCE READMISSION AFTER A HOSPITAL ADMISSION FOR ACUTE ASTHMA?
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The most severe forms of asthma attack are the life threatening forms which result in hospitalisation. Once patients have been stabilised as an inpatient, the clinician is faced with the question of what to do with the inhaled therapy of patients admitted with acute exacerbations of asthma? The purpose of this study was to see if discharge medication influenced subsequent readmission rate.

Methods: All patients with a coding diagnosis of asthma were traced through hospital computer system. In 2000 there were 357 patients so labelled. Audit was carried out on 100 patients’ notes. Patients with a greater than 20 pack year smoking history or a diagnosis of COPD anywhere in the notes were excluded unless asthma had been diagnosed by a consultant chest physician. Subsequent to the case note audit, the patients were sent a short questionnaire at the end of 2001, inquiring about admissions to hospitals other than QEH. Steroid use and casualty attendance. Questionnaire letters have been received back from 54 out of 100.

Results: The BTS asthma step of the admitted patients correlated well with the risk of subsequent readmission (r² = 0.89, p=0.01). Patients with step 0 or step 1 asthma treatment had a low asthma readmission rate in the subsequent year (6%). Overall readmission rate was 41% in the year following discharge. Of those readmissions, 25% were to a different trust. Treatment by a respiratory specialist did not decrease the rate of readmission but did result in slightly longer hospital stays (1.2 days p=0.05 Mann Whitney U test).

Conclusion: Asthma liaison nurse intervention reduced unscheduled care in a deprived multiethnic population; white participants benefited but south Asians did not. Interventions are needed that improve asthma morbidity in non-white people with asthma.

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with LAB (27.5 days, p=0.02 Mann Whitney U test). Of patients discharged from hospital, 38% have subsequently been prescribed a long acting β agonist.

Conclusions: The level of treatment received by patients seems to reflect their risk of hospitalisation in this cohort. Readmission rates are high and admission to more than one hospital is common in Birmingham. Specialist care has little effect upon crude readmission rates. The routine use of LAB following hospital discharge needs evaluating in a clinical trial.

**P85** PSYCHIATRIC MORBIDITY IN DIFFICULT ASTHMA

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Introduction: Near fatal/fatal asthma are associated with psychiatric morbidity (PM). Studies have demonstrated PM in asthmatics of varying severity using questionnaire screening tools, but it is unclear how this relates to ICD10 psychiatric diagnosis (gold standard). The aim of this study was to: (1) examine psychiatrist diagnosed morbidity in a population of difficult asthmatics (persisting symptoms/frequent exacerbations despite high dose inhaled steroids/long acting β agonist, and (2) examine ICD10 diagnosis to response to the Hospital Anxiety Depression Questionnaire (HAD), a commonly used screening tool with defined normal values.

Methods: Sequential referrals to a difficult asthma clinic completed HAD questionnaire and were invited to attend for psychiatric interview as part of a systematic evaluation protocol. Psychiatric interview was performed, by an experienced medical liaison psychiatrist, blinded to all clinical information. After interview, an ICD10 diagnosis was recorded and treatment instituted as appropriate.

Results: Seventy eight patients were recruited (seven refused psychiatric assessment but were otherwise protocol compliant, five were non-compliant with the protocol). Of the remaining 66 subjects, 33 (50%) had an ICD10 psychiatric diagnosis; only seven (10%) were psychiatric assessment but were otherwise protocol compliant, five were non-compliant with the protocol). Of the remaining 66 subjects, 33 (50%) had an ICD10 psychiatric diagnosis; only seven (10%) were receiving current treatment. Depression illness (F32) was common (20 (30%) with mainly generalised anxiety disorder (F41) (5 (8%)) plus a variety of other conditions. Anxiety (13.1 (0.82) v 8.5 (0.71)) and depression (10.1 (0.71) v 4.8 (0.47)) scores were significantly higher in subjects with an ICD10 diagnosis (p<0.001). The positive (PPV) and negative predictive value (NPV) for abnormal HADS scores for all psychiatric diagnoses were 60% and 86% respectively and for depressive illness, PPV 76%, NPV 96%.

Conclusions: There is a high prevalence of psychiatric morbidity, particularly depression, in difficult asthmatics, based on psychiatric interview, most undiagnosed at referral. HADS score has poor overall positive predictive value for psychiatric illness but normal depression score virtually excludes the commonest condition, depressive illness. We are currently examining the predictive role of undiagnosed psychiatric disorder in asthma outcome and optimal screening instruments in this population.

**P86** PSYCHOSOCIAL FACTORS IN ADULTS AT RISK OF ADVERSE ASTHMA OUTCOMES: RELATIONSHIPS WITH SYMPTOM CONTROL AND QUALITY OF LIFE

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Background: Despite effective treatments, a proportion of asthmatics suffer from poorly controlled disease and consequent reduced quality of life (QoL), hospital admissions, near fatal, and fatal asthma attacks. This study assesses psychosocial characteristics of adults at risk of such adverse asthma outcomes and examines relationships with symptom control and QoL.

Methods: Ninety two adults with severe asthma (on BTS Step 4/5 treatment and/or with previous admissions for asthma) who exhibited poor compliance (failure to attend clinics or comply with asthma management in other ways) were recruited via hospitals and GP practices in Norfolk and Suffolk. Cross-sectional socio-demographic/socioeconomic data and self report measures of symptom control, QoL, psychiatric morbidity, perceived control over asthma, coping, and aspects of self management were collected via interviews in patients' homes.

Results: In common with those experiencing fatal and near fatal asthma, these patients represent a socioeconomically disadvantaged group (for example, 65% not working, 63% receiving free prescriptions) with reduced QoL (mean 1.17 on a 0 (very good) to 2 (very poor) scale), high levels of psychiatric morbidity (for example, 36% experiencing moderate-severe anxiety, 33% reaching cut off for psychiatric caseness), and inadequate self management (for example, 82% not monitoring asthma, 39% smoking, 61% owning pets). High psychiatric morbidity, low perceived control over asthma and various indicators of low socioeconomic status were significantly correlated with worse hospital control and reduced QoL (all p<0.001). Being overweight, use of coping strategies which involve focussing on asthma (both p<0.05) or hiding asthma and, interestingly, high compliance (both p<0.001) were also associated with poorer asthma morbidity and QoL.

Conclusions: Various mechanisms may explain associations between psychosocial characteristics, symptom control, and QoL in at risk asthmatics and the direction of relationships is likely to be two way. Further psychological research to improve understanding in this area and an intervention study which attempts to address psychosocial issues in improving outcomes for at risk asthma are underway.

**P87** RELATIONSHIP BETWEEN AIRWAY OBSTRUCTION AND SYMPTOM CONTROL IN PATIENTS WITH DIFFICULT ASTHMA

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Introduction: Several studies have demonstrated a poor relationship between symptom control and airways obstruction in patients with asthma. We examined this relationship in a population of difficult asthmatics (persisting asthma symptoms/frequent exacerbations requiring systemic steroids despite maintenance high dose inhaled corticosteroids (ICS) and a long acting β agonist) attending a hospital outpatient clinic.

Methods: FEV₁ and asthma control scores (ACSs) (Juniper et al. 2001) were measured at the first clinic visit and at a follow up visit after a variable period of evaluation and treatment (9 [6.2] months).

Results: Fifty seven patients (37 females; median age 40 years; range 19–72 years; median ICS dose at presentation 2000 µg; range 1000–6400 µg BDP equivalent; median rescue steroid courses 12 months pre-referral = 5). Patients had poor control at the initial visit (mean ACS 4.1 (1.3); FEV₁ 66.3 (22.7)). At the initial visit, FEV₁% was correlated with limitation of activity (p=0.003), shortness of breath (p=0.018), wheezing (p=0.025) and ACS (p=0.018). FEV₁% was significantly improved at the follow up visit (75.3 (22.6), p<0.0001) with an associated improvement in ACS (2.8 (1.3), p<0.0001). However, at the follow up, there was no correlation between FEV₁% and any measured index of asthma control. At the initial visit, 25 patients had severe obstruction (FEV₁% < 60%) and had significantly poorer ACSs (mean 4.6 v 3.7, p=0.003). At the follow up, 15 patients had FEV₁% < 60% but no difference in ACSs (2.7 v 2.8, p=0.9). Best FEV₁% was significantly less in this latter group (62 (21) 96%, 1.6%, p<0.0001) consistent with fixed airflow obstruction. When this group was excluded, FEV₁% at follow up was significantly correlated with night waking (p=0.02), wheezing (p=0.03), and ACS (p=0.036).

Conclusion: FEV₁% correlates well with asthma symptoms in difficult asthma patients with poor control but not when control improves. This loss of relationship is due to subjects with fixed airflow obstruction where good subjective control does not exclude the presence of significant obstruction.


**P88** UTILITY OF HISTORY IN THE DIAGNOSIS OF CHRONIC COUGH

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Background: Patients referred to specialist cough clinics often have a history of prolonged period of cough, multiple investigations, and unsuccessful trials of therapy. It may be that symptoms in these patients are atypical making diagnosis of underlying condition difficult.

Aim: To determine presenting symptoms of patients with chronic cough in relation to their diagnosis.

Methods: In a prospective study based on a therapeutic rather than investigative protocol, consecutive patients with a history of cough for over eight weeks referred to the Hull Cough Clinic were enrolled.

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Assessment was by structured history, physical examination, chest radiograph, spirometry, and reversibility to nebulised salbutamol. From this information a diagnosis was made and patient had an eight week therapeutic trial. Further therapeutic trials were carried out depending on response to treatment and the likely diagnoses. Investigations were carried out in cases of failed therapeutic trials and to exclude specific pathology (in this study lung cancer, localised bronchiectasis and interstitial lung disease).

**Results:** Hundred and eleven (73 female) patients mean (SD) age 56 yr (12.8) were recruited. Initial main diagnoses were gastro-oesophageal reflux disease (GER) 52 (46.9%), asthma 23 (20.7%), and rhinitis 19 (17.1%). Sixty three patients had at least two clinic visits. Of those discharged so far, median (range) duration of cough was 8.2 yr (0.25 to 64) and mean duration of follow up was 14 weeks (2.4 clinic visits). Twenty four out of 63 (38%) patients were discharged at first, second and 10/23 (43%) at their third visit. The main underlying diagnoses at discharge were GER (25.7%), asthma (22.9%), and rhinitis (11.4%). Twenty per cent required investigations to arrive at the diagnosis and exclude other pathology, the rest were managed successfully on the therapeutic protocol. Symptoms associated with diagnosis of asthma were dyspnoea (p=0.007), wheeze (p=0.04) and choking (p=0.03), GER were heartburn (p=0.01) and sour taste in the mouth (p=0.06) and for rhinitis were sneezing (p<0.001), and runny nose (p=0.03). Sixty per cent of patients who were satisfied with treatment, the presenting complex of symptoms is indicative of the underlying cause of their cough. This finding highlights the importance of the history taking in the assessment of patients with chronic cough.

**P87 FACTORS ASSOCIATED WITH POST BRONCHODILATOR FEV1 IN ADULTS WITH ASTHMA**

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Fixed airflow obstruction occurs in a minority of asthmatic patients but is a predictor of overall mortality. Smoking has been identified as a factor associated with airflow limitation in asthma but evidence implicating other factors has been conflicting. In one study ten Brinke et al (Am J Respir Crit Care Med 2001;164:744–8) identified elevated induced sputum eosinophil count as an independant risk factor for persistent airflow limitation in a homogenous population of severe asthmatics. We have investigated factors associated with the post bronchodilator FEV1, in a heterogeneous population of 249 adults with a clinical diagnosis of asthma of variable severity and evidence of airflow variability and/or airway hyper-responsiveness. Patients had either never smoked or were ex-smokers with less than five pack years smoking history. Patients underwent methacholine challenge testing, pre and post bronchodilator spirometry, skin, and radiolallergosorbent testing to commonly encountered aeroallergens and induced sputum analysis. Multiple independent linear regression analysis was used to identify any independent predictors of post bronchodilator FEV1 % of predicted. Duration of symptoms, atopy, dose of methacholine required to cause a 20% fall in FEV1 (PC20), induced sputum eosinophil count and induced sputum neutrophil count were not significant independent predictors of post bronchodilator FEV1, (r2 = 0.060, p=0.162). Patients with post bronchodilator FEV1 of less than 80% predicted had significantly higher induced sputum eosinophil counts (geometric mean 3.95%) than those with FEV1 above 80% predicted (geometric mean 1.88%, mean fold difference 2.10, 95% confidence interval 1.19 to 3.72, p=0.011). Measures of current airway inflammation and responsiveness did not independently predict persistent airflow limitation, as measured by post bronchodilator FEV1 % predicted in a heterogeneous population of non-smoking adult asthmatics. Although sputum eosinophil counts are higher in patients with persistent airflow limitation, sputum eosinophilia is not predictive of airflow limitation and cannot be implicated as causative.

**P90 EMITS: IMPACT OF A CHANGE IN TRANSPORT POLICY ON RESPIRATORY HEALTH IN OXFORD**

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EMITS (Environmental Monitoring of an Integrated Transport Strategy) was established to examine the effects of a change in transport policy on public health as well as on other aspects of life in Oxford. The Oxford Transport Strategy (OTS) was implemented in June 1999 and involved many changes, focused primarily on the city center where all traffic was barred from some streets and private vehicles from others. Between 1998 and 2000, 1386 children aged 6 to 10 were recruited from seven Oxford schools. Schools were visited two to three times a year in different seasons for five day periods. On each day of each visit, research nurses measured the children’s peak expiratory flow and distributed questionnaires enquiring about respiratory symptoms on the previous day. Parents were also sent questionnaires concerning the medical history of the child and the presence of pollutants and irritants in the home. Regression analyses of daily peak flows among all children showed that lung function improved significantly by 5.87 units (std err 0.71, p<0.001) post-OTS after controlling for potential confounders. Similarly, the odds of wheeze decreased post-OTS (OR= 0.84, 95% CI 0.77 to 0.92).

While it is not clear at this stage that these improvements can be attributed solely to the transport strategy, they suggest that traffic management can result in valuable improvements in public health.

**P91 HARIG: ASTHMA CARE IN THE HUNTINGDON PCT 2002**

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**Introduction:** Asthma has considerable impact in terms of morbidity and health care costs. The ACE1 survey suggests that over 30% of patients who report feeling well to their health professional suffer daily asthma symptoms. The HARIG study set out to raise asthma awareness within the Huntingdon PCT and use the results to develop a strategy for asthma care.

**Method:** A shortened version of the “Impact of asthma” questionnaire was used for the study. This was freely distributed in all GP surgeries and given to patients who attended to request repeat scripts and for review. A freepost address was supplied for return of questionnaires.

**Results:** PCT population was estimated at 147 000 patients. 493 responses received, with asthma prevalence estimated at 5%, returns approximately 6.7% of asthma population. Male:male split was 60%;40%. Average duration of asthma was >5 years, with a predominance of sufferers in the 18–65 year age group. Thirty seven per cent of patients reported daily asthma symptoms, with this figure higher than 50% in some GP practices. More than 30% of patients experienced significant night time waking. There was considerable variance in use of reliever medication with 32% of patients reporting use at least once per day but this figure was as high as 67% in one practice. 45% of respondents reported that asthma has at least a moderate effect on their lives, but this did not always correlate with the reporting of other symptoms.

**Conclusion:** Amongst the HARIG questionnaire respondents there is considerable unmet need for asthma symptom control. The results broadly mirror those of the ACE survey carried around one third of respondents suffering continuing symptoms. There may however have been some selection bias in those who responded to the survey and the results may not be a representative sample of the whole PCT population. Within the Huntingdon PCT there may be further opportunity for standardisation of care and sharing of good practice between GP surgeries.

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**P92 IMPULSE OSCILLOMETRY IN SUBJECTS WITH SEVERE ASTHMA**


**Introduction:** Many subjects with severe asthma describe a worsening of symptoms on lying flat. This is felt to be due to an increase in volume of air in the nasopharynx.

**Aims:** (1) To describe airway resistance and capacitative reactance measurements as assessed by impulse oscillometry (IOS) in subjects with severe asthma and to relate them to spirometric parameters. (2) To see whether IOS parameters are affected by posture. (3) To determine whether IOS could identify subjects who clinically had vocal cord dysfunction.

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THE EFFECTS OF ACUTE HYPOXIA ON PROLIFERATION, SUPEROXIDE AND SUPEROXIDE DISMUTASE ACTIVITY IN ERYTHROCYTE SUPEROXIDE DISMUTASE ACTIVITY IN HUMAN FIBROBLASTS FROM THE PULMONARY AND SYSTEMIC CIRCULATIONS

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Introduction: We have previously shown that proliferation and p38 MAP kinase activity in human fibroblasts is increased by hypoxia in animal models (Welsh, et al, Am J Resp Crit Care Med, 1998 and 2001). We now wish to know whether this is true in man. In this study, we have examined the effect of acute hypoxia on human pulmonary and mammary artery (systemic) fibroblast proliferation and p38 MAP kinase activity.

Methods: Fibroblasts were harvested from human pulmonary artery (HPAF) and mammary artery (HMF) obtained from cardiothoracic surgery and utilised between passages 3–10. Cells were quiesced for 24 hours then stimulated by acute hypoxia for 24 hours (PO2=20 mmHg) with or without 0, 0.1, 1, 3, 5, and 10% serum. Fibroblast proliferation was measured by [3H]thymidine uptake and p38 MAP kinase activity was measured by Western Blotting analysis.

Results: [3H]Thymidine incorporation was increased by acute hypoxia (p<0.01) in the HPAF cells, but not in the HMF cells. Acute hypoxia also gave rise to p38 MAP kinase activation in the HPAF cells and to a lesser extent in the HMF cells (results not shown).

Conclusion: Acute hypoxia stimulated the proliferation of HPAF cells but not HMF cells. The increase in p38 MAP kinase activity to hypoxia may suggest a role in the regulation of cell cycle associated events. These results are consistent with our animal findings showing that these effects have racial and species and may be important in man. Chest, Heart and Stroke (Scotland) and British Heart Foundation.

P94 ERYTHROCYTE SUPEROXIDE DISMUTASE ACTIVITY IN INFANTS WITH PERSISTENT PULMONARY HYPERTENSION AND CONGENITAL DIAPHRAGMATIC HERNIA


Introduction: The antioxidant enzyme system is the primary intracellular defence system of the lung against oxygen toxicity. Endogenous SOD is the major mammalian antioxidant enzyme and catalyses the dismutation of superoxide anion to hydrogen peroxide. Reduced SOD activity has been demonstrated in animal models of Congenital Diaphragmatic Hernia (CDH) and in post mortem specimens from infants with persistent pulmonary hypertension of the newborn (PPHN). Erythrocyte SOD activity from live infants with these disorders has not been reported.

Methods: Blood was sampled from seven infants with PPHN and five with CDH. All were near term and mechanically ventilated. Following centrefugation and plasma removal, erythrocytes were stored at −20°C until analysis. SOD activity was calculated spectrophotometrically using the auto-oxidation of pyrogallol. Haemoglobin concentration was calculated using a standard Drabkin’s reagent. Differences in median values were calculated using the Mann-Whitney test.

Results: Median erythrocyte SOD activity of infants with PPHN was 374.15 ± g/Hb (range 1114 to 1791). Erythrocyte SOD activity of infants with CDH was significantly lower (median = 1213.5, range 1016 to 1490.5, p=0.01).

Conclusion: Infants with CDH have lower erythrocyte SOD activity compared to similarly ventilated patients. This gives further evidence to explain the clinical fragility and poor response to inhaled nitric oxide seen in CDH.


P95 SUPEROXIDE AND SUPEROXIDE DISMUTASE IN PULMONARY HYPOTHYROID VASOCONSTRICTION

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Superoxide is known to cause vascular damage and can consume protective NO that maintains a low pulmonary pressure. There is evidence suggesting that hypoxia upregulates NADH/NADPH oxidase and xanthine oxidase in the smooth muscle and endothelial cells of the pulmonary artery, increasing superoxide production. Superoxide dismutase (SOD) is widely distributed in the tissues of the vasculature, destroying superoxide, however, the role of SOD in hypoxic vasoconstriction is unknown. Therefore, the effect of endogenous SOD inhibition and superoxide generation on hypoxic vasoconstriction was investigated.

Male Sprague-Dawley rats were anaesthetised and the trachea and pulmonary artery cannulated. The lungs were ventilated with 20% O2, (normoxia), and perfused with 30 ml of modified Krebs solution. U46619 give preconstriction before a 10min hypoxic challenge (5%CO2, 95% N2). The lungs were allowed to equilibrate for 30 mins, before repeating the perfusate to one containing either: 1 mM DETCA (high affinity Cu2+ chelator that inhibits endogenous SOD) or 10 µM LY83583 (superoxide generator). The lungs were allowed to equilibrate for 30 mins, before repeating the hypoxic and normoxic challenges. The NO donor SNAP (1.7x105 M) was used after hypoxia in the LY83583 experiments.

Hypoxia induced a sustained monophasic increase in pulmonary pressure, that was reproducible (1.8 (0.2) mmHg 1st challenge and 1.7 (0.3) mmHg 2nd challenge, n=5). LY83583 augmented the hypoxic vasoconstriction (3.5 (1.0) mmHg, n=7), and attenuated the SNAP induced vasodilation. These results suggest that superoxide can support or enhance hypoxic vasoconstriction, perhaps by consuming endogenous NO. However, there was a significant reduction of hypoxic vasoconstriction in the presence of DETCA (1.0 (0.3) mmHg, n=7). Overall, these results suggest that hypoxic vasoconstriction can be modified by endogenous superoxide, however this interaction may be dependent on the site of superoxide generation and the concentration of superoxide, as there is likely to be a greater amount of superoxide present in the experiments involving LY83583.

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MICE OVER EXPRESSING THE 5-HT TRANSPORTER: A NEW MODEL FOR PULMONARY HYPERTENSION?

The 5-hydroxytryptamine transporter (5HTT) may play a key role in pulmonary vascular remodelling in primary pulmonary arterial hypertension (PAH) and secondary hypoxia-related PAH. Attenuated hypoxic pulmonary hypertension has been reported in mice over-expressing the 5HT transporter gene and there is 5HTT over-expression in patients with PAH (Eddahbi et al. J Clin Invest 2000;105:1555–62; Eddahbi S et al. J Clin Invest 2001;108:1141–50). Here we examine the development of PAH in mice over-expressing the 5HTT gene (5HTT+ mice) and C57BL/6 x CBA wild type mice (WT mice). Male mice (6 weeks old), exposed to two weeks of hypoxia (0.205 ± 0.005% of 21%); n=8), did not develop a significant pulmonary pressor effect to hU-II alone, but after 2h pre-incubation with the NOS inhibitor L-NAME, there was a significant pressor effect (10.1 ± 0.3 mmHg, p<0.001). In 5HTT+ mice, baseline pressure was significantly lower (p<0.05) and response to hU-II was only uncovered following nitric oxide synthase inhibition. This suggests that hU-II is a significant pulmonary vasoconstrictor with no effect on systemic AOP. Here we investigated the pulmonary and systemic effects of hU-II alone and in the presence of the NOS inhibitor L-NAME in a previously described rabbit model of secondary hypoxia-related PAH. The effects of hU-II were compared with those of ET-1, a pre-constricted system AOP in all groups. In conclusion, hU-II appears to act as a selective pulmonary vasoconstrictor with no effect on AOP.

P97 HUMAN UROTENSIN-II ACTS AS A PULMONARY VASOCONSTRICCTOR IN AN IN VIVO RABBIT MODEL OF PULMONARY HYPERTENSION SECONDARY TO LEFT VENTRICULAR DYSFUNCTION
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The recently cloned peptide, human Urotensin-II (hU-II) has been shown to act as a pulmonary vasoconstrictor in isolated main pulmonary arteries from rats (MacLean, 2000) and in the presence of the NOS inhibitor L-NAME in a previously described rabbit model of secondary hypoxia-related PAH. hU-II appears to act as a selective pulmonary vasoconstrictor with no effect on systemic AOP. Here we investigated the pulmonary and systemic effects of hU-II alone and in the presence of the NOS inhibitor L-NAME in a previously described rabbit model of secondary hypoxia-related PAH. The effects of hU-II were compared with those of ET-1, a pre-constricted system AOP in all groups. In conclusion, hU-II appears to act as a selective pulmonary vasoconstrictor with no effect on AOP.
Results: BMP2 mRNA was expressed in HFLs and binding experiments demonstrated that BMP-2 and BMP-4 competed equi- potency for 125I-BMP-4 binding. BMP-7 was weakly competitive and TGFB1 did not compete. BMP-4 dose-dependently (1-100 ng/ml) inhibited [3H]-thymidine incorporation as well as proliferation of HFLs. FACS analy- sis demonstrated that BMP-4 (50 ng/ml) inhibited cells from exiting the GO/G1 phase of the cell cycle, BMP-4 up-regulated the expression of inhibitors of the GO/G1 phase of the cell cycle, p21, and p27, with a corresponding down regulation in expression of the positive regulators, cyclin D and cdk2. Phospho-Smad1- and phospho-p38were rapidly induced in response to BMP-4.

Conclusion: BMP-4 leads to cell cycle arrest in HFL-1 cells via induction of p21/p27 and inhibition of cyclin D/cdk2. The relative contribution of p38 and Smad1 on BMP-4 induced cell cycle arrest remains to be determined.

Funded: British Heart Foundation and NHMRC of Australia (TK Jeffery).

P100 THE RESPONSE OF FIBROTIC AND NON-FIBROTIC PATIENTS WITH SCLERODERMA ASSOCIATED PULMONARY ARTERIAL HYPERTENSION (SScPAH) TO CONTINUOUS AMBULATORY ILOPROST THERAPY: IS A SIMILAR THERAPEUTIC APPROACH JUSTIFIED?

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Background: It is now accepted that patients with non-fibrotic SSC-PAH respond to epoprostenol therapy in a similar fashion to Primary Pulmonary Hypertension (PPH). We have observed that PHT underlying SSC-associated fibrosis is not predominantly hypoxia-driven and postulated that the mechanisms underlying fibrosis/non-fibrosis-associated PAH in SSC may be similar and thus responsive to the same therapeutic strategy.

Methods: Forty seven patients were initiated on continuous ambulatory iloprost therapy between 1996-2001 as they met the funding criteria for this therapy. Functional impairment was quantified using the Six Minute Walk Test (SMWT).

Findings: Forty seven SSC patients (M:F = 7:40) with a mRAP=10 mmHg, mPAP=42 mmHg, mean SVO2=59 %, and mean CI=1.8 were started on ambulatory iloprost. There was no significant difference in haemodynamic parameters between fibrotics (n=20)/non-fibrotics (n=27). Initial mean SMVT=175m fibrotics/215m non-fibrotics, a mean improvement of 29% in the fibrotics (226m) and non-fibrotics (n=27). Initial mean SMVT=175m fibrotics/215m non-fibrotics, a mean improvement of 29% in the fibrotics (226m) and non-fibrotics (n=27).

Conclusion: In a SSC patient cohort similar in structure in terms of initial hemodynamic findings, treated with ambulatory iloprost, the initial benefit was maintained for >1 year of therapy (14 fibrotics/9 non-fibrotics).

Six month survival was 81%, with 23 (49%) patients surviving non-fibrotics. At 24 weeks this benefit was maintained (272m in fibrotics vs 283m in non-fibrotics, a mean improvement of 29% in the fibrotics (226m) and non-fibrotics (n=27). Initial mean SMWT=175m fibrotics/215m non-fibrotics, a mean improvement of 29% in the fibrotics (226m) and non-fibrotics (n=27).

Of the 21 patients studied, 19 had PAH at rest (mPAP at least 25mmHg). There was a significant correlation between MPAP measured at RHC and P:A ratio, r=0.50, p=0.02. All 16 patients with an elevated P:A ratio >1 had PAH. Patients with a P:A ratio >1 compared to patients with a P:A ratio <1 had a significantly greater MPAP: 43 (13) vs 25 (14) mmHg (95 % CI 2 to 31 mmHg, p=0.02). Using a P:A ratio of >1 to identify patients with PAH at cardiac catheterisation had a PPV of 1.0 and a NPV of 0.4.

In conclusion, an elevated pulmonary to aortic ratio measured using CT scanning techniques predicts the presence of PAH in patients with systemic sclerosis. In these patients undergoing CT scanning of the thorax an elevated ratio should alert the physician to the possibility of pulmonary hypertension.

P101 ELEVATED PULMONARY: AORTIC RATIO IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS

F. Guarasci, D. Manuel, M. Akil, C. Davies, D. Fishwick, E.J.R. Van Beek, D.G. Kiely. Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield, UK

Pulmonary arterial hypertension (PAH) occurs in approximately 15% of patients with systemic sclerosis (SS) and is associated with a poor prognosis. A number of screening regimes using non-invasive techniques are currently used to identify patients for cardiac catheterisation. We have examined whether the pulmonary:arterial (P:A) ratio measured using CT may be a useful non-invasive predictor of PAH in these patients.

Twenty one patients [three male], mean age 60 yrs (range 45–70 yrs) with SS and suspected pulmonary hypertension were studied. Patients underwent HRCT and CTPA in addition to right heart catheterisation. CT scans were interpreted by investigators blinded to the results of the other investigations. The main pulmonary artery and aortic diameter were measured transversely at the same level and the ratio calculated.

Of the 21 patients studied, 19 had PAH at rest (mPAP at least 25mmHg). There was a significant correlation between MPAP measured at RHC and P:A ratio, r=0.50, p=0.02. All 16 patients with an elevated P:A ratio >1 had PAH. Patients with a P:A ratio >1 compared to patients with a P:A ratio <1 had a significantly greater MPAP: 43 (13) vs 25 (14) mmHg (95 % CI 2 to 31 mmHg, p=0.02). Using a P:A ratio of >1 to identify patients with PAH at cardiac catheterisation had a PPV of 1.0 and a NPV of 0.4.

In conclusion, an elevated pulmonary to aortic ratio measured using CT scanning techniques predicts the presence of PAH in patients with systemic sclerosis. In these patients undergoing CT scanning of the thorax an elevated ratio should alert the physician to the possibility of pulmonary hypertension.

P102 THE HAEMODYNAMIC EFFECTS OF “PULSED” INHALED NITRIC OXIDE IN PATIENTS WITH PULMONARY HYPERTENSION

T. Siddons, T.W. Higenbottam, F. Guarasci, I. Armstrong, K. McCormack, D.G. Kiely. Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield, UK

We examined the acute haemodynamic effects of pulsed inhaled nitric oxide (iNO) in patients with pulmonary hypertension. Patients with pulmonary arterial hypertension (n=33), chronic thromboembolic pulmonary hypertension (n=17), and hypoxic lung disease (n=7) were challenged acutely with pulsed iNO at a dose of 1.6 x 10⁸ moles per breath during right heart catheterisation. The iNO was delivered in puls via nasal cannulae using a breath activated device for five minutes. Pulsed iNO significantly reduced mean pulmonary artery pressure (MPAP) 45.0 (14) vs 47.2 (13) mmHg, pulmonary vascular resistance (PVR): 785 (432) vs 878 (456) dynes.s.cm⁻⁵, and increased CO: 4.4 (1.6) v 4.2 (1.5) /min (p<0.001). There was no significant change in mean arterial pressure (MAP): 92 (16) v 91 (14) /min Hg but a significant (p<0.05) fall in systemic vascular resistance [SVR]: 1696 (260) v 1784 (508) dynes.s.cm⁻⁵. We identified four response types (1) Non responder = reduction in PVR <20 %. (2) Pressure response type = reduction in mPAP and PVR > 20 %. (3) Flow response type = reduction in PVR >20% with a reduction in mPAP <10 % and a clinically significant increase in CO. (4) Resistance response type = reduction in PVR >20% with reduction in mPAP between 10-20% and a non clinically significant increase in CO [see table].

Pulsed iNO appears to be an effective acute pulmonary vasodilator. Further work needs to be performed to examine whether these response types predict outcome from therapy or mortality.

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<table>
<thead>
<tr>
<th>n</th>
<th>Response type</th>
<th>Base</th>
<th>During iNO</th>
<th>Base</th>
<th>During iNO</th>
<th>Base</th>
<th>During iNO</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Non-responder</td>
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<td>48.5</td>
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<td>9</td>
<td>Pressure</td>
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<td>33.7</td>
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<td>4.6</td>
<td>8.8</td>
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<td>Flow</td>
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<td>3.9</td>
<td>4.2</td>
<td>10.2</td>
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</table>

P103 COMPASSIONATE TREATMENT OF PULMONARY HYPERTENSION WITH LONG TERM INHALED NITRIC OXIDE AND ORAL SILDENAFIL (VIAGRA®)

T. Siddons, T.W. Higenbottam, K. Amsha, I. Armstrong, K. McCormack, D.G. Kiely. Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield, UK

Despite recent encouraging reports of trials of analogues of prostacyclin and antagonists of the endothelin-1 receptors, many patients with pulmonary hypertension (PH), still receive no treatment as a result of the expense and/or difficulty in administering these therapies. We examined the effects of long term pulsed inhaled nitric oxide (iNO) or oral sildenafil (Viagra®) in eleven disabled patients with PH associated with other disease processes and in two patients with primary PH, who did not receive funding for prostaglandin therapy. Patients were offered compassionate treatment with either pulsed iNO or sildenafil, one patient receiving first pulsed iNO then sildenafil after a wash out period.

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Sildenafil at doses of 25 to 50 mg three times per day resulted in a significant improvement in shuttle walking test 274 (189) m v 201 (114) m at baseline (p=0.045). Two patients discontinued therapy due to deterioration, but six patients continue on sildenafil with a mean duration of therapy of 16 months (range 4–22). In contrast, all patients given pulsed iNO for 12 hours overnight deteriorated, with no patient continuing on therapy for longer than 11 months (mean six months, range 2–11).

In conclusion, although long term nocturnal therapy with pulsed iNO appears to be an ineffective treatment for pulmonary hypertension, sildenafil appears to be an effective and well tolerated form of therapy in this heterogeneous patient population.

**P104** FLOW VELOCITY PROFILES AND HAEMODYNAMICS IN PULMONARY HYPERTENSION: A PILOT STUDY

T. Saba, J. Foster, M. Cockburn, M. Cowan, A. Peacock. Scottish Pulmonary Vascular Unit, Department of Radiology, Western Infirmary, Glasgow, Scotland

Standard assessment of the pulmonary circulation including mean pulmonary artery pressure (MPAP), cardiac output (CO), and pulmonary vascular resistance (PVR) predict prognosis in pulmonary hypertension (PHT) but do not always predict the severity of exercise intolerance. We wondered whether flow velocity profiles, which are likely to reflect haemodynamic response to exercise, would help to explain the differences in symptoms between patients with similar resting haemodynamics.

**Method:** We used cardiac triggered cine MRI to measure mean velocity (MV) and peak velocity (PV) in the right pulmonary artery in three subjects with PHT and one normal subject (see table 1) within two days of cardiac catheterisation and six minute walk testing (6mwt). Studies were performed at rest (R) and after three minutes of straight leg raising exercise (EX).

**Results:** See figures 1 and 2.

**Conclusions:** Resting pulmonary haemodynamics may not predict exercise tolerance in PHT. Exercise MRI is feasible in this group of patients and flow velocity profiles obtained in this way may help to explain the differences in symptoms between patients with similar pulmonary haemodynamics.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>MPAP (mmHg)</th>
<th>CO (l/min)</th>
<th>PVR (Wood units)</th>
<th>6mwt (m)</th>
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</thead>
<tbody>
<tr>
<td>PPH</td>
<td>59</td>
<td>47</td>
<td>3.7</td>
<td>12.7</td>
<td>438</td>
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<tr>
<td>PPH</td>
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<td>15.4</td>
<td>210</td>
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<td>PortoPHT</td>
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<td>41</td>
<td>6.3</td>
<td>6.5</td>
<td>260</td>
</tr>
<tr>
<td>Normal</td>
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<td>16</td>
<td>3.4</td>
<td>4.7</td>
<td>550</td>
</tr>
</tbody>
</table>

**P105** HAEMODYNAMICS DURING EXERCISE ARE A BETTER MEASURE OF VASODILATOR RESPONSE IN HUMAN SUBJECTS WITH PULMONARY HYPERTENSION

R. Syyyd, A.J. Peacock. Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow, UK

Patients with pulmonary hypertension (PHT) are deemed “non-responders” (NR) if they show no response to vasodilators at rest. We therefore decided to investigate the effects of vasodilators on pulmonary haemodynamics during exercise.

**Methods:** We investigated four patients, (two female, two male) with PHT to determine pressure and flow changes over a range of flows. Flow was changed by straight leg raising. A micromanometer tipped continuous pulmonary artery pressure (PAP) catheter was inserted. All four were non-responders to a vasodilator challenge (defined as a reduction of >20% in pulmonary vascular resistance). Resting pressure was noted and then three mins of supine alternate straight leg raising was performed, while the subjects inhaled air or nitric oxide (NO, 40–80 ppm) and oxygen (O₂, 15L min). Cardiac Output (CO) was measured by non-invasive impedance cardiography. Subject data was pooled using the method described by Poon (J Appl Physiol 1998; 84:854–9). The best-fit line for Pressure Flow (P-Q) plots was determined by linear regression. An adjusted two paired student t test was used to compare the line gradients.

**Results:** We found that although total pulmonary vascular resistance as defined as mean PAP/ CO showed no change at rest, the slope of the P-Q plots decreased with vasodilators during exercise (p<0.0005) (see figure).

**Conclusion:** In each of these four subjects, whilst there was no vasodilator response at rest, there was an improving relationship between pressure and flow during exercise whilst receiving the vasodilators NO and O₂. In patients with PHT, the assessment of vasodilator response may be better performed during exercise than at rest.

![Pressure flow changes during exercise](image_url)

**P106** FUNCTIONAL AND HAEMODYNAMIC RESPONSE AFTER PULMONARY THROMBENDARTERECTOMY FOR THROMBOEMBOLIC PULMONARY HYPERTENSION

F. Reichenberger, J. Parameswar, D. Hodgkins, J. Dunning, J. Pepke-Zaba. Papworth Hospital, Papworth Everad, Cambridge, UK

Pulmonary Thrombo-Endarterectomy (PTE) is the treatment of choice in pulmonary hypertension due to proximal chronic thromboembolism. We evaluated the midterm functional and haemodynamic outcome until one year after PTE. The functional capacity was assessed using the six minute walking distance (6MWD). Haemodynamic parameters were obtained during right heart catheterisation with Swan Ganz catheter and cardiac output with thermodilution method. Until March 2002, 88 patients underwent PTE (44 male, 43 female, mean age 52 (18–81) years) at Papworth Hospital. Fifty eight patients completed a three months follow up, and 35 patients 12 months follow up. Two patients were followed up by other centres and two patients did not attend follow up visits. Preoperative functional and haemodynamic data show a severely reduced 6MWD and cardiac index with
increased right atrial pressure (RAP) and mean pulmonary artery pressure (mPAP). Three months after surgery there was a significant increase in 6MWD and cardiac index, and a decrease in RAP and mPAP. These changes were statistically significant (t test p<0.0001).

The functional and haemodynamic improvement sustained also 12 months postoperatively (see table). None of the patients died between three months and 12 months follow up.

Conclusion: Patients have a significant and sustained functional and haemodynamic improvement after PTE with normalisation of haemodynamic parameters in the majority of patients. The main improvement is achieved within three months after surgery.

Cystic fibrosis: Inflammatory consequences of chronic infection

P107 NEUTROPHIL APOPTOSIS AND BACTERIAL INFECTION IN CYSTIC FIBROSIS

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In cystic fibrosis (CF), impaired mucociliary clearance leads to chronic endobronchial bacterial infection and inflammation, mediated by neutrophils. Pseudomonas aeruginosa infection is associated with an exaggerated inflammatory response and colonisation with Burkholderia cepacia is often accompanied by progressive pulmonary deterioration. Apoptosis of inflammatory cells is considered an essential requirement for the resolution of an inflammatory response. It was hypothesised that the number of neutrophils undergoing apoptosis would alter with the agent of infection in CF lungs. The aim of this study was to assess the relationship between levels of neutrophil apoptosis and sputum microbiology in matched clinically stable CF patients. In this preliminary study 29 patients were recruited: six (4M) with no Gram negative infection, 10 (4M) colonised with P aeruginosa, 9 (4M) with B cepacia infection and 4 (3M) with other Gram negative infections such as Stenotrophomonas maltophilia. Sputum was induced as previously described (Kelly, et al 2002). Cells were recovered from sputum plugs. Apoptosis was investigated by staining sputum cells with propidium iodide (PI) and annexin V (AV), were recovered from sputum plugs. Apoptosis was investigated by staining sputum cells with propidium iodide (PI) and annexin V (AV), and subsequent flow cytometric analysis. Non-parametric statistic analyses were used throughout. The % of necrotic granulocytes (AV PI) was significantly higher in the P aeruginosa group (17.1 (2.5%), p=0.008) and the B cepacia group (13.9 (1.3%), p=0.008) compared to those with no Gram negative infection (7.5 (1.6%)). B cepacia patients also had a significantly higher % of secondary necrotic cells (AV PI) than those with no Gram negative infection (13.6 (2.3%), 5.8 (1.9%), p=0.02) whilst those with no Gram negative infection had a significantly higher % of cells which were neither apoptotic nor necrotic (AV PI) than the B cepacia group (7.5 (2%), 58.3 (4.4%), p=0.02). These preliminary results indicate that neutrophil apoptosis is associated with the type of organism colonising the CF lung. The greater number of granulocytes in cell death pathways from patients infected with P aeruginosa or B cepacia suggests that this may be a mechanism of greater inflammation and subsequent lung injury in CF.

Abstract P106

<table>
<thead>
<tr>
<th>6MWD (metres)</th>
<th>RAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>Cardiac index (l/min/qm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>preop (88)</td>
<td>238 ± 115</td>
<td>10 ± 6</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>3 mo postop (58)</td>
<td>386 ± 124*</td>
<td>3 ± 4*</td>
<td>24 ± 9*</td>
</tr>
<tr>
<td>1 year postop (35)</td>
<td>382 ± 123</td>
<td>3 ± 3</td>
<td>22 ± 10</td>
</tr>
</tbody>
</table>

t test: p<0.001.

P108 A COMPARISON OF INFLAMMATORY MARKER LEVELS IN CLINICALLY STABLE CF PATIENTS WITH CHRONIC INFECTION BY UNIQUE AND EPIDEMIC STRAINS OF PSEUDOMONAS AERUGINOSA

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Introduction: There are an increasing number of reports of Pseudomonas aeruginosa colonisation with phagocytosis in CF patients. This study was initiated to determine whether patients with CF bore infection in patients with cystic fibrosis and subsequent flow cytometric analysis. Non-parametric statistic analyses were used throughout. The % of necrotic granulocytes (AV PI) was significantly higher in the P aeruginosa group (17.1 (2.5%), p=0.008) and the B cepacia group (13.9 (1.3%), p=0.008) compared to those with no Gram negative infection (7.5 (1.6%)). B cepacia patients also had a significantly higher % of secondary necrotic cells (AV PI) than those with no Gram negative infection (13.6 (2.3%), 5.8 (1.9%), p=0.02) whilst those with no Gram negative infection had a significantly higher % of cells which were neither apoptotic nor necrotic (AV PI) than the B cepacia group (7.5 (2%), 58.3 (4.4%), p=0.02). These preliminary results indicate that neutrophil apoptosis is associated with the type of organism colonising the CF lung. The greater number of granulocytes in cell death pathways from patients infected with P aeruginosa or B cepacia suggests that this may be a mechanism of greater inflammation and subsequent lung injury in CF.

Poster presentations

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P109 A PSEUDOMONAS AERUGINOSA EXOTOXIN, PYOCYANIN, IMPAIRS PHAGOCYTOSIS AND CLEARANCE OF APOPTOTIC CELLS

S.M. Bianchi, L.R. Usher, D.H. Dockrell, G.W. Taylor, M.K.B. Whyte. Respiratory Medicine Unit, University of Sheffield, Sheffield, UK

Pseudomonas aeruginosa infection in patients with cystic fibrosis and bronchiectasis is characterised by a profound neutrophil inflammation, with neutrophil products [for example, elastases] implicated in tissue injury. We have shown that pyocyanin, a pseudomonas exotoxin, accelerates neutrophil apoptosis (programmed cell death) potentially promoting bacterial persistence (Usher et al. J Immunol 2002:168:1861–8). We hypothesised that accelerated neutrophil death may result in further tissue injury if apoptotic cell clearance was impaired. We therefore studied the effects of pyocyanin on the ingestion of apoptotic neutrophils (APMN) by monocyte-derived macrophages (MDM). All data are expressed as controls versus 24 hour pyocyanin pretreatment. We have observed a time (100%) to 22.7 (7.1%), p<0.001 and concentration dependent reduction in MDM ingestion of APMN in the presence of pyocyanin. We have shown that the reduced interaction is not due to loss of viability (23.2 (2.5%) to 22.7 (1.2) cells/x400 field, p=0.440) or induction of MDM apoptosis by physiological concentrations of pyocyanin (0.6 (0.15%) v 0.93 (0.41%), p=0.108). Similarly we have demonstrated no loss in MDM function as assessed by basal and lipopolysaccharide induced MDM cytokine production. The impairment of phagocytosis has been shown to be specific to APMN as MDM phagocytosis of opsonised latex bead is not impaired (33.3 (4.2%) v 29.7 (2.3%), p=0.312). Also we have determined that the pyocyanin-induced defect is specific to the MDM—APMN killed by constitutive ageing or following exposure to APMN killed by constitutive ageing or following exposure to pyocyanin are ingested similarly by healthy MDM. Using flow cytometry we have shown that pyocyanin is capable of inducing high levels of reactive oxygen species (ROS) within the MDM—however it

international attempts to identify patients most at risk of disease.

A. De Soya1, R. Demarco De Hormaeche1, P. Corris1. Lung Biology and Transplantation group, University of Newcastle upon Tyne, Freeman Hospital and Department of Microbiology and Immunology, University of Newcastle upon Tyne, UK

Cystic fibrosis is a major cause of morbidity in adult cystic fibrosis patient. As compared to those infected with Ps aeruginosa alone the outcomes of Burkholderia cepacia infected patients are poorer. There also appears to be variability in outcomes within the B cepacia infected population (Frangolais, et al. Am J Respir Med 1999). The most striking disease pattern in Cystic Fibrosis Syndrome is a terminal pulmonary fibrosis. There are many host and pathogen factors which may contribute to this variability. The designation of closely related but distinct species, Genomovars I to VII, within the B cepacia complex may offer some insights into this variable pattern. Genomovars III, II, and V are the most prevalent in CF. We have shown poor outcomes in Genomovar III infected patients post-transplant (De Soya, et al. Lancet 2001). As lipopolysaccharide (LPS) is a major mediator of sepsis we have investigated the pro-inflammatory potential of B cepacia LPS.

Methods: We selected three strains of B cepacia after pilot work suggested widely varying biological activity. These strains, GII (LMG 14273 and 13010) and GIII (LMG12614, an ET12 clone), were grown overnight and harvested. The bacteria were sonicated and treated with DNase and proteinase K. LPS extraction using hot phenol was undertaken with final DNA/protein contamination approx 5%. The purified LPS (1–100ng) were added to differentiated U937 macrophages and the tissue culture supernatants were collected at 0 and 24 hrs. Time course experiments were also undertaken up to 48 hrs. The supernatants were tested for IL-6 and TNF using ELISA. We silver stained 16% urea/SDS-PAGE gels to assess LPS structure.

Results: A dose-response was seen. The greatest difference was noted between the purified LPS at a dose of 100ng for TNF induction where LMG 12614 (ET12) was twice as effective at induction as compared to LMG 14273 (GII). LMG 13010 (GII) was as effective as the GII, LMG12614. The gels confirmed that all were of rough LPS chemotype. The two high cytokine inducers LMG12614 and 13010 (GII and GIII) appeared to have the same LPS banding patterns; rough LPS with two distinct bands whilst LMG 14273 did not. LPS knockouts of IL-6 and TNF using ELISA. We silver stained 16% urea/SDS-PAGE gels to assess LPS structure.

Conclusions: The observed differences between B cepacia complex strains LPS may in part explain the variable clinical outcomes. We identified differences between genovar LPSs demonstrating that some of the two most common genovars there is a wide spectrum of activity. One GII strain appears to have the same LPS as the ET-12 GII strain which may explain why some GII patients can develop Cepacia Syndrome. The chemotype of the LPS e.g. rough or smooth may be less important than the structural motifs within each LPS.

LIPOLYMPHOSACCHARIDE STRUCTURAL PROFILES ARE NOT ALTERED IN GENOMOVAR III BURKHOLDERIA CEPACIA QUORUM SENSING KNOCKOUTS

A. De Soya, R. Demarco De Hormaeche, P. Corris. Lung Biology and Transplantation group, University of Newcastle, Freeman Hospital and Department of Microbiology and Immunology, University of Newcastle upon Tyne, UK

Background: Attempts at creating vaccines using isolated bacterial antigens have been relatively unsuccessful for many important pathogens such as Pseudomonas. Gram negative bacteria form biofilms in

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Cystic fibrosis lungs that appear to protect bacteria within the biofilm from antibiotics even at bactericidal levels. The maturation of biofilms is dependent on quorum sensing systems. Quorum sensing mutants produce greatly attenuated infections in animal models and may offer the possibility of an attenuated strain (perhaps with additional mutations in virulence genes) for use as a biological vaccine. Recent data has shown that quorum sensing also controls virulence related genes for proteases and iron binding siderophores. The effect of quorum sensing on a major bacterial pro-inflammatory moiety, lipopolysaccharide (LPS) is less clear. Work with Pseudomonas aeruginosa has demonstrated that a single AAL glycosyltransferase, has a quorum sensing box upstream. There is no data in the Cepacia field assessing the effect of quorum sensing knockouts on LPS structure. Two Burkholderia cepacia quorum sensing mutants, H111-I and H111-R have been created that are defective in the acylhomoserine lactone (AHL) synthase cepall and the AHL receptor ceprr respectively. The effect of these mutations are to impair biofilm formation. These strains therefore may be potentially considered for investigation as starting points for biological vaccines. The effect of these mutations on LPS is however unclear.

Methods: The wild type parent genovar III, strain H111 and the two mutants were kindly gifted (Dr B Huber, University Munich). These were grown in Luria Broth (LB) with appropriate selective antibiotics over 24 hours at 37°C. The organism were then centrifuged and resuspended to a standard optical density at 600nm of 0.2. SDS-PAGE was conducted with subsequent silver staining to assess any changes in LPS profiles.

Results: Silver stained SDS-PAGE gels revealed the LPS of all three strains were of smooth chemotype with multiple bands suggesting variable O side chain lengths. There were however no differences between the three strains in terms of number or pattern of the bands seen on the gels suggesting the O chains of the LPS were not affected by the quorum sensing mutations. There appeared to be no differences in the LPS core. As opposed to data from Pseudomonas spp quorum sensing B cepacia mutants with smooth LPS do not appear to have a change in LPS structure under the above growth conditions.

Conclusions: If quorum sensing mutants are to be considered as starting points for biological vaccines it may be important to create quorum sensing mutants in a wild type genovar III strain with a LPS that has a low inflammatory potential.

Cystic fibrosis: Treatments and outcomes

P114 COMPARISON OF THE HALOLITE® ADAPTIVE AEROSOL DELIVERY (AAD®) SYSTEM WITH A HIGH OUTPUT NEBULISER SYSTEM IN CYSTIC FIBROSIS PATIENTS

R.J. Marsden1, S.P. Conway2, M.E. Dodd2, F.P. Edenborough4, A.S. Rigby2, C.J. Taylor1, P.H. Weller4. Profile Therapeutics, UK; 1St. James’ Hospital, Leeds, UK; 2Wythenshawe Hospital, Manchester, UK; 3Northern General Hospital, Sheffield, UK; 4The Birmingham Children’s Hospital, Birmingham, UK

The HaloLite AAD system (AAD) has been developed to improve inhaled medication delivery by giving feedback during and at the end of treatment. It will not deliver aerosol during nose breathing, talking, or if there is a poor mouthpiece lip seal. A multicentre randomised parallel study (MAL 25–70) comparing AAD with conventional high efficiency nebulisers (NEB) was conducted at CF centres in Australia, Canada, USA, and Europe. Patients established on DNase and inhaled antibiotics were randomised to AAD or NEB within seven days following an exacerbation requiring oral or IV antibiotics. Patients used the study device to take their inhaled medications for 182 days. The primary outcome variable was change in FEV1 from baseline to day 182. Secondary outcome variables were days antibiotic use, exacerbation frequency, time to first exacerbation, safety, adherence to prescribed regimen, and compliance with device (by overt electronic monitoring in 20% of the sample). Patients completed a questionnaire to assess device acceptability.

259 patients were randomised (133 AAD, 126 NEB) median age 17 years, median FEV1 56% predicted. Preliminary analysis of mean change in % predicted FEV1, from baseline to day 182 was –3.5% for AAD and –2.4% for NEB. Difference in means = 1.1% confidence interval = –0.2% to 6.3%, p=0.7. There was no statistically significant difference between AAD and NEB for the secondary outcome variables except for a higher incidence of chest tightness per 1000 days (0.97 for AAD and 0.32 for NEB (p=0.05)). Completed questionnaires showed that compared to their previous nebuliser, 69% of AAD patients felt that they received more dose compared to 30.4% for NEB; 56% of AAD patients felt better compared to 30% for NEB; 82% of AAD patients preferred the trial device compared to 37% for NEB. These differences were significantly different (p<0.001). Fifty one per cent of prescribed doses were taken beyond 90% of the programmed dose for AAD compared with 26% of prescribed doses where the compressor was run for >6 minutes for NEB (p<0.006).

Conclusions: There were no differences in the efficacy outcome variables between the devices. A higher incidence of chest tightness for AAD may be indicative of more successful delivery of antibiotic to the lung. Patient acceptability of the device was better for AAD than for NEB. Patients take more doses to an acceptable level using AAD.

P115 COMPLIANCE IN CYSTIC FIBROSIS PATIENTS USING TWO DIFFERENT AEROSOL DELIVERY SYSTEMS

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CF patients may use conventional high output nebulisers (NEB) for up to an hour a day to aerosolise therapies aimed at preserving lung function. Poor techniques such as nose breathing, talking and inadequate lip seal compromise the time spent breathing correctly on the mouthpiece and hence the amount of drug delivered to the lungs. HaloLite (AAD) has been designed to generate aerosol only whilst patients breathe correctly through the mouthpiece. The system provides feedback to the patient during treatment. Patients start/by the number of doses prescribed) and “compliance” (the % of doses taken correctly) were recorded. For AAD a correctly taken dose was defined as delivery of >90% of the pre-programmed dose, and for the NEB when the Porta Neb® PLS compressor was run for >6 minutes. “True compliance” is adherence X compliance. FEV1 was recorded on day 0 and 28. The use of oral or IV antibiotics was recorded on day 0 and 28. The sample included 30 AAD and 20 NEB patients. Provisional data shows that adherence was 62% for AAD and 47% for NEB (p=0.05). Compliance was 84% for AAD and 43% for NEB. “True compliance” was significantly higher for AAD (51%) compared to NEB (27%) (p=0.006). For NEB there was no correlation between true compliance and % change in FEV1, after 28 days, neither was there a correlation between true compliance and % change in FEV1, for the subgroup of patients who did not need oral or IV antibiotics for an exacerbation there was no correlation between % change in FEV1 and true compliance for AAD (n=17) (R=0.53) (p<0.03).

Conclusion: These data show that the AAD system increases true compliance and may contribute to the maintenance of FEV1.


P116 PORTACATH COMPLICATIONS IN CYSTIC FIBROSIS PATIENTS


Introduction: Cystic fibrosis (CF) patients requiring repeated intravenous antibiotic courses eventually benefit from insertion of percutaneous vascular catheters such as a Portacath. There is little information on complications arising from such procedures, which need to be taken into consideration when discussing the relative merit with patients and parents.

Patients: Over a 12 year period out of a population of 78 patients 18 (six male, 12 female) have received 30 Portacaths. Ten patients were <18 years old; 11 have only needed one Portacath to date, three have required two, two have needed three, and two have received four Portacaths.

Results: Average length of use: 36.7 months. Longest surviving Portacath: 8 years 10 months. Reasons for failure: Catheter...
disconnection one, systemic/infective complications three, lung collapse one, leakage four, blockage with pain six. Short survival of the first Portacath is a marker for failure with subsequent Portacaths.

**Discussion:** Complications are relative frequent and unpredictable. Our findings are similar to others in CF and oncology patients. Needle-phobia is a common experience in CF Clinics but the use of Portacaths needs full discussion with families and should not be entered into lightly.

**P117** ANTIBIOTIC RELATED RENAL IMPAIRMENT IN ADULT CF PATIENTS

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Colonisation with multiresistant *Pseudomonas aeruginosa* (Pa) in CF results in repeated use of a limited number of antibiotics to which the organisms are sensitive, increasing the risk of toxic effects. In Liverpool, we have a multidrug resistant strain colonising many CF patients that is only sensitive to aminoglycosides and polymyxins, antibiotics that are known to cause renal damage. In this study, we compare the number of Pa strains in patients with a normal Pa level and those colonised with a multiresistant strain. Overall, 52 patients (32 multidrug resistant) were studied (mean age (range): multidrug resistant 23.6 years (15 to 42) v sensitive 24.9 (18 to 37); FEV1 % predicted: 61.3 (16 to 95) v 61.8 (17 to 115); BMI: 21.6 (18 to 28) v 20.4 (14 to 27); CF related diabetes: v 4 (all Pa=NS). During exacerbations, all patients had aminoglycoside levels measured and adjusted after the 4th dose as per protocol and no episodes of acute toxicity were noted. Renal function was measured by estimation of serum urea and electrolytes and 24 hour urinary creatinine clearance when patients were in a stable clinical state. Patients produced satisfactory 24 hour urine collections, measured by sufficient urine volume and total urinary creatinine excretion. All patients had serum creatinine and urea levels within the normal range, but those colonised with multidrug resistant strains had a lower creatinine clearance (mean 75 ml/min [range 11 to 112] v 101 ml/min [28 to 171]), p<0.002, and had received more IV aminoglycoside courses (mean 23 per patient (range 0 to 100)) v 8 (0 to 30), p<0.007), and more IV colomycin courses (22 (0 to 80) v 7.4 (0 to 50), p<0.006). Also, the total number of IV courses correlated with aminoglycoside renal function (r=0.39, p<0.001). We conclude that repeated dosing with these potentially nephrotoxic drugs has damaged the renal function in those patients colonised by Pa strains, and in some patients we can now no longer conclude that repeated dosing with these potentially nephrotoxic antibiotics is suitable patient segregation.

**P118** VARIATION IN REPORTED INTAKE OF PANCREATIC ENZYME REPLACEMENT THERAPY IN ADULTS WITH CYSTIC FIBROSIS

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**Background:** Pancreatic Enzyme Replacement Therapy (PERT), the number of enzymes taken with food, is assessed as part of the annual review. In this centre both the doctor and dietitian review independently, however it is the amount each patient reports to the doctor which is recorded on the UK National Cystic Fibrosis (CF) database.

**Aim:** To investigate whether reported intakes of PERT capsules differ when assessed by dietitian, doctor, or using a food diary.

**Methodology:** Patients attending their annual review at the CF Centre between July 2000 to May 2002 were asked the number of PERT capsules they consumed with meals, snacks, nutritional supplements, drinks etc daily. This is the recall method and is recorded by the dietitian (in conjunction with diet history) and the doctor on the same day. Patients are also requested to complete at least a three day food diary (two weekdays and one weekend day). They record the quantities and types of food, fluid and PERT consumed on those days. The numbers of PERT recorded by each method were compared.

**Results:** There was significantly less PERT intake reported using the recall method by dietitian, 3.6 ± 10.3 enzymes (p=0.04, t Test) compared to the database documented value (doctor).

The number of enzymes recorded on the food diary was also lower than the database documented value (doctor), 3.8 ± 9.1 enzymes but was not significant (0.07, t Test). In addition, there is considerable variation in the number of PERT capsules reported using each method (table).

**Conclusion:** The actual over reporting of enzyme intake for the UK CF database is slight overall, however for an individual patient the report can vary by over 100% difference. It is also shown that 40% of patients are more than 25% inaccurate in their reporting. This may have implications for their individual enzyme assessment and monitoring. In light of this evidence we suggest that consideration is made to the method of assessment used.

**P119** INTRAVENOUS ANTIBIOTICS INCREASE EXHALED NITRIC OXIDE IN CHILDREN WITH CYSTIC FIBROSIS

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**Introduction:** Data on the effect of intravenous (IV) antibiotics on exhaled nitric oxide (NO) in CF and on correlation of NO with lung function are conflicting because of lack of standardisation for the measurement of NO.

**Aims:** To assess the effect of IV antibiotics on exhaled NO in CF children and to correlate NO with lung function. Methods: Exhaled NO was measured on line during a slow exhalation according to ATS guidelines using an exhalation flow of 50 ml/s (NIOX, Aerocrine,) in CF patients admitted for IV antibiotics. Pulmonary function was measured according to ATS guidelines (MasterScreen, Jaeger). Measurements before and after treatment were compared with Wilcoxon Signed Ranks Test. Spearman correlation tests were used to assess correlation. A value of p<0.05 was considered significant.

**Results:** Fourteen CF subjects (10 female), median age (range) 12.1 years (5.9 to 16.0) were studied. Genotypes were as follows: ΔF508/ΔF508, n=10; ΔF508/N1303K, n=1; ΔF508/−, n=3. Reasons for admission were: infective exacerbation, n=4; routine quarterly antibiotics, n=10. Cough swab or sputum culture on admission: *Pseudomonas aeruginosa*, n=6; *Staphylococcus aureus*, n=6 (one had coliforms and one had *Stenotrophomonas maltophilia* in addition); no growth, n=2. Median (range) length of treatment was 8.5 (6 to 15) days. There was a significant improvement in mean (SEM) %FEV1 from 60.0 (6.3) to 68.0 (5.4) (p=0.02) and %FVC from 66.3 (5.2) to 75.1 (4.9) (p=0.003). There was a significant increase in NO following treatment (median (range): pre; 5.8 ppb (2.0 to 14.3), post; 9.2 ppb (0.8 to 25.1), p=0.02). There was no correlation between NO and %FEV1 or %FVC.

**Discussion:** NO is raised in lung diseases with an inflammatory component, however this is not true for CF, and is further supported by these results. Various hypotheses have been proposed to account for this. These include: entrapment in sputum; degradation by superoxide production from activated neutrophils; NO reductase in *P aeruginosa*; reduced inducible NO synthase expression in epithelial cells. Our results support these hypotheses as it is likely that antibiotic treatment results in a reduction in *P aeruginosa* colony forming units, neutrophil activation and airway sputum volume.

**Conclusion:** IV antibiotics increase exhaled NO in CF. However, NO does not correlate with lung function and is not a useful marker of lung disease in CF.

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**Abstract P118**

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FACTORS DETERMINING DIAPHRAGM STRENGTH IN INCREASED ENERGY EXPENDITURE DUE TO Coughing in Patients with Cystic Fibrosis (CF)

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Respiratory failure is the major cause of death in patients with cystic fibrosis (CF). Although the diaphragm is the most important muscle of inspiration, it is unclear as to whether there are any alterations in diaphragm strength in patients with cystic fibrosis (CF). In the current study, we hypothesised that diaphragm strength would be determined by airflow obstruction and pulmonary hyperinflation, gas exchange impairment, inspiratory muscle load, and nutritional status of the patient. 20 patients with CF were studied (mean age 15.1 (2.8) years). We measured twitch transdiaphragmatic pressure (Tw Pdi) in response to bilateral anterior magnetic phrenic nerve stimulation to quantify diaphragm strength; forced expiratory volume in 1 sec (FEV1) and functional residual capacity (% Pred FRC) as estimations of airflow obstruction and hyperinflation; and diaphragm pressure time index (PTI) as an indicator of diaphragm load. Nutritional status was evaluated using body mass index adjusted for age and sex (BMI z-score), fat free mass (FFM) and arm-muscle circumference (AMC). These were determined from measurements of height, body weight, mid-arm circumference (AC), and skinfold thickness (SK) at four different sites (biceps, triceps, subscapular, and suprailiac). FM and FFM were calculated from SK and weight. AMC was calculated from the formula: AMC = 0.134 * biceps SK – 2 + triceps SK/2 - FM. FFMM, and AMC were expressed as percent predicted for statural age (% Pred.). Results are expressed as mean (SD). Tw Pdi was 24.3 (5.5) cmH2O, % Pred FEV1 was 44.5 (21.4), % Pred FRC was 158.9 (40.9), PaO2 was 9.5 (1.5) kPa, PaCO2 was 5.5 (0.6) kPa; and PTI was 0.05 (0.03). Univariate regression analysis demonstrated Tw Pdi correlated with % Pred FRC (p=0.001; r = +0.68); % Pred FRC (p=0.005; r = -0.65); Po2 (p=0.001; r = +0.68); PaCO2 (p=0.03; r = -0.50); BMI z-score (p=0.003; r = +0.63); % Pred., AMC (r = +0.47; p=0.04). There were no correlations between Tw Pdi and % Pred., FM (p=0.1 and PTI, p=0.2). In conclusion, in children and young adults with CF, diaphragm strength falls as airways obstruction and hyperinflation increases, gas exchange impairment worsens, and nutritional status declines. However, load does not have effect of diaphragm strength.

Dr N Hart was supported by the Scadding-Morrison Davies Joint Respiratory Medicine Fellowship, a European Respiratory Society Long Term Fellowship and a grant from the Association Française Contre Les Myopathies.

INCREASED ENERGY EXPENDITURE DUE TO COUGHING IN ADULTS WITH CYSTIC FIBROSIS

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Patients with Cystic Fibrosis (CF) have increased resting energy expenditure (REE). We hypothesised that frequent coughing, occurring spontaneously and during physiotherapy in most patients, adds to the REE and overall energy expenditure (EE), which may contribute to weight loss. We measured breath by breath REE (K4b2, Cosmed) in 12 clinically stable patients and 10 healthy subjects. A steady state baseline was recorded and each subject coughed voluntarily three times after breathing to TLC. A further 10 patients had REE measured on repeated occasions by the same method. During 45, 10minute recordings of REE 144 spontaneous coughs occurred. The REE before coughing occurred and after each coughing episode was recorded. The mean recovery time (VE, /min back to baseline) after the three voluntary coughs (41 seconds) was used to calculate the EE after spontaneous coughing as the area under the curve after each cough by locally designed software. We also compared the REE after spontaneous coughs to the baseline REE, because the duration of the baseline record was variable (mean 106, minimum 371, minimum 8 seconds). There was no difference in EE after three coughs (ratio to baseline), between patients and healthy subjects (p=0.05). The FEV1 (patients) was inversely related to EE after three coughs, r = -0.58, p=0.04. Recovery time was similar to the healthy subjects. Spontaneous coughs in patients increased the EE by a mean (95% CI) 7.9 (2.7 to 13.3) % compared with baseline, mean (95% CI) 32.63 (30.51 to 34.75), and 30.66 (28.59 to 32.73) kcal/kg/min, p<0.01. The REE (area under curve over time) with spontaneous coughs was greater than REE recorded when spontaneous coughs were removed from the 10 minutes measurement in CF patients compared with baseline REE in healthy subjects (28.4 to 31.3) and 21.5 (16.8 to 24.3), respectively, p=0.016.

Cough increased the REE in adults with CF. For accuracy REE measurements in CF should include any spontaneous coughs that occur. Due to the frequency of coughing, the energy costs are likely to increase the negative energy balance in some patients.

Sponsored by the Cystic Fibrosis Trust UK.

SEQUENTIAL SINGLE LUNG TRANSPLANTATION FOR SEPTIC LUNG DISEASE: A SINGLE CENTRE COMPARISON BETWEEN CF AND NON-CF BRONCHIECTASIS

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Background: The outcomes for transplantation for septic lung conditions including Cystic Fibrosis (CF) and non-CF bronchiectasis have been comparable to those for non-septic lung conditions despite the additional risks associated with these conditions. Given the current organ donor shortage it is important to compare outcomes for each pre-transplant outcome within a single centre to allow appropriate allocation of organs. It is recognised that certain pre-transplant indications such as Pulmonary Fibrosis and Pulmonary Hypertension are associated with poor transplant outcomes. We have not previously compared the outcomes of Cystic Fibrosis and non-CF Bronchiectasis at this centre.

Methods: We identified all patients receiving lung transplants at this centre for septic lung diseases through our transplant database. A survival table was constructed and the two groups were compared using the log rank (Mantel-Cox) test for real survival. Pre-transplant recipient characteristics were also compared including pre-transplant body mass index, pre-transplant FEV1, need for non-invasive ventilation and median time post transplant.

Results: We have transplanted 96 CF patients and 26 non-CF Bronchiectasis (NCFBr) over 10 years. Median age at transplantation CF group 25.4 yrs (range 16 to 49.5) and NCFBr median 48 yrs (range 25 to 56) p<0.05. Survival was comparable between groups at one year CF 81%, NCFBr-76.5% p=0.46. At five years survival was 70% for CF, and 72% for NCFBr p=NS. Pre-transplant FEV1% predicted was similar between groups median in the CF group =19.1% (range 8 to 35%) and NCFBr 18 (9 to 49%) p=NS. In each group early deaths were predominantly related to sepsis: The early deaths were due to sepsis in the CF group (9/96) and also in the NCFBr group 13% (4/29) Fishers exact test p=0.3. Median pre-transplant Body mass index (BMI - kg/m2) was 17.8 (range 12 to 24) for CF and NCFBr =23 (range 16 to 32), Mann Whitney, p<0.01. No patient in the Bronchiectasis group required non-invasive ventilation pre-transplant whilst 11/96 CF patients had NIV pre-transplant Fisher exact test p=0.11. Similarly there were 12/96 CF patients infected with Burkholderia cepacia complex organisms whilst no NCFBr were infected with this organism p=0.11 pre-transplant Fisher exact test p=0.11.

Conclusions: Cystic Fibrosis patients had poorer pre-transplant nutrition and were more likely to be infected with B cepacia complex. There were however no statistical differences in post transplant survival noted. We conclude that despite these features CF patients are as likely to benefit from pulmonary transplantation than older non-CF bronchiectasis patients.

RECOMBINANT SENDAI VIRUS-MEDIATED CFTR cDNA TRANSFER

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To assess applicability for Cystic Fibrosis (CF), recombinant Sendai virus (SeV) carrying the CFTR gene was tested on different models of airway epithelial cells. In vitro CFTR activity was assessed at two days

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GENE SILENCING THROUGH RNA INTERFERENCE AS INFECTION OF THE MURINE LUNG WITH Sendai virus carrying mouse interleukin 10 cDNA (SeV-IL10) infects

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Gene silencing through dsRNA-mediated RNA interference (RNAi) has been described in C. elegans and Drosophila. We, and others, have recently described RNAi in mammalian cells mediated by small dsRNAs of 21–23 nucleotides (nts) termed short interfering RNAs (siRNAs) (Caplen NJ, PNAs 2002). Here, we provide preliminary proof of principle that gene silencing through RNAi can be achieved in lung vivo. Balb/C mice (female 6–8 weeks) were simultaneously transfected with pcDNA3CAT (80µg/mouse) and 22 nts siRNA corresponding to CAT (40pg/mouse) or an irrelevant control siRNA, each complexed with the cationic lipid GL67 (n=12 in both groups). Forty eight hours after transfection the lungs were harvested and CAT activity assayed. CAT expression was reduced by 90% in animals treated with control siRNA, when compared to controls (control siRNA: 736±437 pg CAT/mg protein, CAT siRNA: 80.1±31.4 pg CAT/mg protein). A potential confounding factor is the co-transfection of the plasmid and siRNA, allowing for a non-posttranscriptional silencing mechanism of action. To address this, we compared the silencing of the green fluorescent protein (eGFP) using a siRNA against eGFP either in cells co-transfected with eGFP plasmid and siRNA or cells stably expressing a destabilised version of eGFP (eGFPd2) transfected with siRNA alone. The degree of silencing in both cases exceeded 90%. We have recently shown that, in contrast to the liver, uptake of DNA into the nucleus of airway epithelial cells is extremely inefficient in vivo. However, cytoplasmic transfection can be readily achieved. RNAi has been shown to primarily act within the cytoplasmic compartment and so may offer a major advantage over conventional transfection techniques that have been proposed for the treatment of respiratory tract disorders. Although the pathophysiology in CF is not completely understood, several proteins may provide good targets for gene silencing, including the epithelial sodium channel (ENaC), as well as several pro-inflammatory cytokines, such as IL-8 and chaperones, which retain delta F508 CFTR within the endoplasmic reticulum.

P124 GENE SILENCING THROUGH RNA INTERFERENCE AS PUTATIVE THERAPY FOR CF

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Gene silencing through dsRNA-mediated RNA interference (RNAi) has been described in C. elegans and Drosophila. We, and others, have recently described RNAi in mammalian cells mediated by small dsRNAs of 21–23 nucleotides (nts) termed short interfering RNAs (siRNAs) (Caplen NJ, PNAs 2002). Here, we provide preliminary proof of principle that gene silencing through RNAi can be achieved in lung vivo. Balb/C mice (female 6–8 weeks) were simultaneously transfected with pcDNA3CAT (80µg/mouse) and 22 nts siRNA corresponding to CAT (40pg/mouse) or an irrelevant control siRNA, each complexed with the cationic lipid GL67 (n=12 in both groups). Forty eight hours after transfection the lungs were harvested and CAT activity assayed. CAT expression was reduced by 90% in animals treated with control siRNA, when compared to controls (control siRNA: 736±437 pg CAT/mg protein, CAT siRNA: 80.1±31.4 pg CAT/mg protein). A potential confounding factor is the co-transfection of the plasmid and siRNA, allowing for a non-posttranscriptional silencing mechanism of action. To address this, we compared the silencing of the green fluorescent protein (eGFP) using a siRNA against eGFP either in cells co-transfected with eGFP plasmid and siRNA or cells stably expressing a destabilised version of eGFP (eGFPd2) transfected with siRNA alone. The degree of silencing in both cases exceeded 90%. We have recently shown that, in contrast to the liver, uptake of DNA into the nucleus of airway epithelial cells is extremely inefficient in vivo. However, cytoplasmic transfection can be readily achieved. RNAi has been shown to primarily act within the cytoplasmic compartment and so may offer a major advantage over conventional transfection techniques that have been proposed for the treatment of respiratory tract disorders. Although the pathophysiology in CF is not completely understood, several proteins may provide good targets for gene silencing, including the epithelial sodium channel (ENaC), as well as several pro-inflammatory cytokines, such as IL-8 and chaperones, which retain delta F508 CFTR within the endoplasmic reticulum.

P125 INFECTION OF THE MURINE LUNG WITH NON-TRANSMISSIBLE RECOMBINANT SENDAI VIRUS EXPRESSING THE SECRETED PROTEIN INTERLEUKIN 10

U. Griesenbach1, T. Shiraki-Iida1, S. Ferrari1, H. L. Gautrey5, X. Hout1, A. Iida1, D. M. Geddes1, M. Hasegawa1, E. W. F. W. Alton1. 1Department of Gene Therapy, Faculty of Medicine, Imperial College, London, London, UK; 2DNAVEC Research Inc., Tsukuba, Ibaraki, Japan

We have previously shown that a transmission-competent recombinant Sendai virus carrying mouse interleukin 10 cDNA (SeV-IL10) infects the airways efficiently. A second generation, and for human use potentially safer SeV has recently been generated, in which the gene for the membrane fusion protein (F protein) has been deleted from the viral genome (SeV/ΔF) (Li et al. J Viroal 2000;74:6564–9). The F protein is essential for virus entry into the cell and is supplied in trans during viral production. However, following infection and virus replication of the vector genome in vivo the virus cannot infect neighbouring cells. Here, we assessed the efficiency of F-defective SeV (SeV-IL10/ΔF) in lungs of mice and in primate trachea. The lungs of C57B/6 mice were transfected by placing SeV-IL10/ΔF or a SeV-LacZ control virus (7×105–7×106 CIU/mouse) as a single 100µl bolus into the nasal cavity and the solution was snuffed into the lungs. Lung tissue and serum was harvested 2, 7, and 14 days after infection. IL10 production was measured in lung homogenate and serum using standard ELISA. In lung homogenate expression was measured two days after infection and was up to 7 logs above control levels for 7×106 and 7×107 CIU/mouse, respectively. At day seven expression in mice transfected with the higher dose had dropped to 1.3% of the day two levels, but only to 15% in the lower dose. At day 14 the lower dose still showed low but significant IL10 expression, whereas the higher dose was not longer different from control levels. High levels of serum IL10 were detected two days after infection with 7×107 CIU/mouse, but in not animals infected with 7×106 CIU/mouse, and were still significantly increased seven days after infection (SeV-IL10/ΔF: 3500 ± 429, 7×106 CIU/mouse; and 28. SeV-mCFTR (n=9) was used as control. Two days post-infection, NPĐlow values in animals treated with SeV-CFTR 23–3/23–4 ± 0.11 (0.07) mV were significantly (p<0.05) higher (that is, towards non-CF values) than those observed in animals treated with SeV-mCFTR (3.25 ± 0.73 mV). NPĐlow in animals treated with SeV-CFTR 23–3/23–4 remained significantly (p<0.05) higher at day 7 (0.20 ± 0.73 mV as opposed to −1.55 ± 1.23 mV in controls). Baseline values at day seven for animals treated with SeV-mCFTR (30.8 ± 3.6 mV) were not different to untreated CF mice, but in mice treated with SeV-CFTR 23–3/23–4 they were not different from those observed in wild type mice (12.1 ± 1.5 mV) as p<0.01 compared to controls. Baseline and low chloride values had returned to typical G551D CF mouse values. In conclusion we have shown that SeV can mediate CFTR gene transfer both in vitro and in vivo.

P126 PILOT DATA: PULMONARY REHABILITATION IN RESTRICTIVE LUNG DISEASE

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Introduction: Pulmonary rehabilitation is a proven therapy for patients with obstructive pulmonary disease, however little is known concerning the effects in patients with restrictive disease. This study reports on data from an seven week, ×2 weekly, “real life” programme of exercise and education in patients with both restrictive and obstructive disease were admitted.

Methods: Outcome measures were baseline spirometry. Exercise tolerance using Shuttle Walk Test (SWT), health related quality of life using St George’s Hospital Respiratory Disease Questionnaire (SGRQ), mood state using Hospital Anxiety and Depression Scale (HAD).

Results: Sixty seven patients completed the course. Of these patients, 57 had baseline spirometry from which 48 were classified as obstructive; mean FEV1, 1.09 (0.4), FVC 2.5 (0.7) l and 9 restrictive, patients, 57 had baseline spirometry from which 48 were classified as obstructive; mean FEV1, 1.42 (0.4), FVC 1.8 (0.5) l.

Both obstructive and restrictive patients showed a statistically significant effect of rehabilitation on SWT; mean difference (SD) 47.8 (86.9) (p=0.0005), 91.1 (64.1) m (p=0.0022) respectively. However, the difference between the groups (43.3 m was not significant (p=0.16)). There were statistically significant improvements in SGRQ (p<0.001) and depression (p<0.001) for the obstructive group and a trend in response for the restrictive group.

Conclusion: Low power means we cannot rule out the possibility of type II error for difference in SWT between the groups. Data from an uncontrolled “real life” study indicates that patients with restrictive disease may show greater improvements in exercise tolerance than...
obstructive disease. This report highlights the need for baseline spirometry in the assessment and thorough evaluation of pulmonary rehabilitation in differing populations.

**P127** **OXYGEN COST SCORE FOLLOWING 4 STEP COPD PROGRAMME AND COMMUNITY BASED PULMONARY REHABILITATION**

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Since January 2000 Wyre PCT has been implementing a 4 step COPD Health Improvement Programme (HImP) to ensure correct diagnosis and optimal, guidelines led, therapy. The programme, developed in collaboration with Blackpool Victoria Hospital Chest Clinic, involves spirometry assessment by a mobile spirometry service visiting all General Practices with further assessment and patient management by COPD trained Practice Nurses. Following diagnosis (step 1), inhaled steroid trial (step2), anticholinergic trial (step3), and long acting β2 trial (step4), community based pulmonary rehabilitation (PR) is now (since July 2001) offered to those patients motivated to attend. PR, led by a Physiotherapist and a Respiratory Nurse, is offered at two sites in the PCT; a Local Authority Sports Centre and a Village Community Centre. Patients attend for two hours twice a week for eight weeks and are then invited to attend one hour a week for ongoing supervised exercise. The Oxygen Cost Score (OCS) is used to assess breathlessness by functional ability at each stage of the HImP and PR programme.

Data from 55 COPD patients (10 mild, 21 moderate, and 30 severe using BTS criteria for severity) were examined for dyspnoea, measured by OCS; before entering the 4 step programme (stage 1), on completion of the 4 step programme and before entering PR (stage 2), on completion of the eight week PR programme (stage 3).

The mean OCS (±SD) is shown in the table.

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>MI</th>
<th>Stage 3</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>3.25 (1.25)</td>
<td>4.75 (0.25)</td>
<td>4.50 (0.5)</td>
<td>5.35 (0.95)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.35 (0.5)</td>
<td>4.4 (0.5)</td>
<td>5.35 (0.95)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3.66 (0.5)</td>
<td>1.63 (0.5)</td>
<td>1.73 (0.9)</td>
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</tbody>
</table>

Conclusions: These preliminary data suggest that COPD patients demonstrate an improvement in functional ability following a four-step community based HImP with further improvement gained by attending community PR. Patients with moderate and severe COPD appear to demonstrate greater improvement from PR than from the 4 step programme. The number of mild COPD patients referred for PR are too small to be meaningful.

**P128** **BREATHLESSNESS AND ANXIETY MANAGEMENT COURSE FOR PATIENTS WITH COPD UNSUITABLE FOR CONVENTIONAL PULMONARY REHABILITATION**

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Pulmonary rehabilitation is known to improve health status, symptoms, and exercise tolerance in patients with COPD. Particularly in secondary care, many COPD patients are unsuitable for conventional PR due to concomitant disease or extremely limited mobility. This breathlessness and anxiety management course, run by COPD nurse specialists, was designed specifically for these patients. All are receiving optimal medical therapy and are clinically stable at entry and have been deemed unsuitable for conventional PR. Patients attend once a week for 2 hours over a six week period. Individual assessment is made and anxiety management, breathing control, relaxation techniques, partially supervised physical exercise, and support and practical advice tailored as appropriate. There were 41 patients referred to the course, but only 19 attended for initial assessment (12 not motivated, three transport problems, three repeated COPD exacerbations, four misc). Assessment at visit one and final visit consisted of resting pulse and respiratory rate, 6MWD (with and without Borg scores), SGRQ, HAD, and MRC dyspnoea scale. Patients who exacerbated were allowed to continue if well enough, those patients who did not complete the course were not reassessed. Mean (SD) age 69 (7) years, 11 (58%) female, FEV, 1.03 (0.48) litres, % pred FEV1 36.9 (11.9), pH 7.39 (0.04), pO2 10.4 (2.3) kPa, pCO2 4.8 (0.7) kPa (an acute upon chronic hyperventilation).

Nine patients did not complete the course (six repeated COPD exacerbations, two worsening of pre-existing arthritis, one developed lung cancer).

There was no significant difference in age, sex, lung function, or exercise tolerance between those patients who completed the course and those who did not. There was a significant improvement in resting respiratory rate (18.4 to 15.6, p<0.05), change in Borg score after 6MWD (4 to 3.1, p<0.05), HAD depression score (7.5 to 5.7, p<0.05) and the Activity (82.5 to 73.3, p<0.01) and Impacts (60.9 to 51.0, p<0.05) of SGRQ. Although the 6MWD was not significantly improved in this small group there was a trend to improvement (202 to 280m).

Individually tailored programs are time consuming and drop out rate is high. However, those that do complete the course benefit in terms of health status and symptoms. Although numbers are small these results are encouraging and merit further study.

**P129** **DIFFERENT EXERCISE RESPONSES IN SUBJECTS WITH IDIOPATHIC HYPOVENTILATION**

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Hyperventilation may occur as an acute and a chronic phenomenon. In addition, it may occur in isolation (idiopathic) or may co-exist with other disease processes. There is very little data on homogeneity within any of these subgroups.

We have studied 40 subjects referred through our chest clinics with symptoms suggestive of idiopathic hyperventilation (IH) and normal lung function. IH was confirmed by resting arterial hypocapnia and sustained hypocapnia during ramp-incremental exercise. Further analysis of the ventilatory response to exercise revealed that 11 of the 40 subjects demonstrated acute upon chronic hyperventilation at exercise onset (defined as RER >1.0), six of the 40 subjects demonstrated acute upon chronic hyperventilation at rest which continued during early exercise. Twenty three of the 40 subjects did not demonstrate acute hyperventilation in addition to their chronic hyperventilatory state.

There were no differences between the three groups in the Hospital Anxiety and Depression scores, Nijmegen Questionnaires, and St George’s Respiratory Questionnaires or in maximally achieved parameters during cycle ergometry and in breath—hold tolerance both on 21 and 100% O2. Resting respiratory rate was higher (mean (SD) 33.7 (6.7) br/min) in the chronic group compared to the those demonstrating acute hyperventilation in addition to their chronic hyperventilation (mean (SD) 27.7 (8.33) (p<0.02). There was a significant correlation between breathing rate, resting PETCO2 and SGRQ, in the chronic group.

These data demonstrate that within this population of seemingly homogenous subjects with IH, there are different responses to exercise. This does not appear to alter the overall symptomatology of the groups or their other physiological indices. Whether the different responses to exercise relate to chronicity of symptoms needs further study.

**P130** **THE DAILY EXPERIENCES OF PATIENTS LIVING AND COPING WITH LONG TERM OXYGEN THERAPY (LTO)**

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**Aim:** To describe experiences of patients who had been using oxygen at home for at least one year.

**Patients:** Five women and two men (mean age 58yrs) were identified from a hospital register of known oxygen dependant patients.

**Inclusion criteria:** diagnosis of chronic respiratory disease, using oxygen >1hrs daily and able to communicate verbally.

**Design and methods:** A phenomenological method was used to describe the daily problems encountered by patients with LTOT.
and how they coped. Unstructured audio-taped interviews lasting approx 60 minutes were conducted in the patients’ home. Interviews were directed by the patients. Tapes were transcribed verbatim, checked for accuracy, and analysed using Colazilii’s method.

**Main Findings:** Themes which emerged included that of feeling unprepared, living life on a lead, feeling stigmatised, and no longer your own person.

Feeling unprepared related uncertainty about the purpose of treatment, and impact on lifestyle. Descriptions ranged from nervousness to fear about the equipment and oxygen as well as a sense of being left to “get on with it” unsupported. All were unprepared for the timing of the introduction and felt disappointed that it had come “too soon in life”. Living life on a lead referred to restrictions caused by physical attachment to the equipment, lack of spontaneity, and pre-planning activities around oxygen. Feeling stigmatised related to a sense of shame or embarrassment felt if seen in public with cumbersome cylinders and visible tubing. Coping descriptions referred to “camouflage” to conceal equipment outside, “brazening it out”, or “just going without”. No longer your own person related to descriptions of reduced autonomy, changes in status and role, and reliance on family or others. Coping descriptions related to social support and spiritual belief.

**Conclusions:** The patients in this small study would have benefited from the support of a respiratory nurse to provide counselling and support prior to the introduction of LTOT as well as follow up. Sense of stigma prevented some patients from using oxygen for outdoor activities. In the light of the ongoing review of domiciliary oxygen services, the experiences of these patients may have a bearing on the process of assessment and counselling prior to provision of LTOT and lightweight oxygen systems.

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**P131 A SURVEY OF THE PHARMACOLOGICAL MANAGEMENT OF THE SYMPTOM OF DYSPNOEA**

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**Background:** The symptom of dyspnoea is an increasing clinical problem, with rising incidence and longevity of patients with respiratory diseases. The current evidence base for treatment is sparse and often contradictory.

**Aims:** To determine current clinical practice in the symptomatic pharmacological management of dyspnoea, when disease related treatments are optimised, in patients with malignant and non-malignant diseases. To compare practice in two groups: respiratory and palliative medicine consultants.

**Methods:** Postal survey to consultant members of British Thoracic Society and Association of Palliative Medicine, with letter from the “Respiratory Centre” accompanying the anonymous survey. Data was analysed using nonparametric statistics to compare the results from the two groups.

**Results:** 896 surveys were sent. Of these 46% were returned: 37% useable (32% respiratory (R), 45% palliative medicine (PM)), 13% analysed using nonparametric statistics to compare the results from the Society and Association of Palliative Medicine, with letter from the palliative medicine consultants.

The majority of both groups (R 72%, PM 61%) agreed that there is not enough evidence available to support the use of their choice of drug.

PM physicians used significantly more: Lorazepam (p<0.0001), Cannabinoids (p<0.0001), Levomepromazine (p<0.0001), and nebulised saline (p<0.0001). Oxygen was used more frequently by R (p<0.002).

PM physicians were more likely (p<0.02) to prescribe the same drugs for non-malignant as for malignant diagnoses. R physicians were significantly more concerned about respiratory depression with opioids in patients with non-malignant disease, compared to PM.

**Conclusions:** The data shows there are significant differences in the prescribing practices of PM and R physicians. It highlights concerns regarding lack of evidence base for practice and over 95% of the total sample felt more research was needed in this area.

Supported by an Educational Grant from Link Pharmaceuticals Ltd.
conditions such as cardiovascular disease. This is especially important as many of the ARVs induce significant metabolic complications such as hyperlipidaemia. We sought to characterise smoking habits within an HIV infected population, using a questionnaire-based evaluation linked to our prospective HIV database. Over a six week survey period, 394 ambulant subjects were enrolled (85% male, median age 34 - IQR 29–39, 30% previous clinical AIDS diagnosis, 73% using ARVs). Forty five per cent were current smokers and 24% ex-smokers. The current smokers were heavy users with a median pack year consumption of 15, IQR 6–25, and 75% reporting the first cigarette of the day within one hour of waking. They had a significant increased self reported incidence of chest infections compared to ex-smokers and non-smokers. Of the current smokers, 74% had tried to quit. Nicotine replacement and no cessation aids were the two most frequently used methods (44% each). The majority of ex-smokers stopped without specific cessation aids (49%). Cardiovascular risk factors were common, with elevated blood lipids reported in 20%. 30% of individuals had a family history of heart disease, and up to 10% drank more alcohol than the current recommended upper limits. Our study, the largest undertaken in Britain so far, reveals high levels of cigarette smoking within individuals who demonstrate considerable risk factors for smoking related disease. Smoking cessation work should target this at risk population.

Rationale: Peer smoking is associated with starting smoking in childhood, but this effect may be biased by smokers’ selection of smoking peers and their overestimation of smoking among their peers compared to non-smokers. We have prospectively investigated the effect of tutor group smoking prevalence (an objective, unbiased measure of peer smoking) on the uptake of smoking in Nottinghamshire school children.

Methods: A questionnaire survey of past and current smoking behaviour, parental, and sibling smoking histories was performed in pupils in Years 9 and 10 (aged 13 to 15) in 10 secondary schools in Nottinghamshire, UK in 2000, and repeated in 2001. Data were linked to identify all children who started smoking between the two surveys (incident smokers). We calculated the prevalence of current smokers in each pupils school tutor group in 2000. The independent determinants of incident smoking were analysed by multiple logistic regression and multilevel modelling.

Results: We obtained paired data on 2109 pupils in 2001 (73% follow up). Of the 1766 non-current smokers in 2000, 267 (15%) were incident smokers by 2001. Tutor group smoking prevalence was a significant risk factor for incident smoking after adjusting for female sex, parental and sibling smoking; the risk of incident smoking was independently greater for those in the highest quartile v lowest quartile of tutor group smoking (19% v 12% respectively, adjusted odds ratio 1.78, 95% Confidence Intervals 1.20 to 2.65). Multilevel modelling showed a negligible effect of schools.

Conclusions: Tutor group smoking prevalence is an important, independent, and unbiased determinant of incident smoking in teenagers.

Funded by the Wellcome Trust.

[PT34] THE EFFECT OF SCHOOL TUTOR GROUP SMOKING PREVALENCE ON THE RISK OF INCIDENT SMOKING IN SECONDARY SCHOOL CHILDREN: A LONGITUDINAL STUDY

A.W.P. Molyneux1, S.A. Lewis1, M. Antoniak1, W. Browne1, A. McNell1, R.J. Madeley1, C.A. Godfrey1, R. Britton1. 1City Hospital; 2University Hospital; 3The Zone Youth Project, Aspley, Nottingham; 4New Leaf Smoking Cessation Service, Nottingham, UK

Rationale: We conducted a questionnaire survey of 11 to 20 year olds. The Zone Youth Project, a voluntary sector project in one of Nottingham’s most deprived areas, over a month period at all drop-in cafes, dance sessions, schools outreach, and sexual health sessions. A measurement of exhaled carbon monoxide (CO) was performed in consenting individuals.

Results: 264 valid questionnaires were returned and 75% of respondents consented to exhaled CO measurement. The median age of respondents was 14.0 (11–21) with 42% male. 49% were self reported current, regular smokers. Amongst the smokers the median CO reading was 8ppm (1–32) median Fagerstrom score 3.0 (0–7) and median number of cigarettes smoked per day 10. Most smokers obtained their cigarettes from newsagents, friends, or “faghouses” (contraband) and 94% came from households with at least one smoking adult. Of those who smoked, 65% would like to quit smoking and 85% had made previous unsuccessful attempts, giving up for an average of 0–3 weeks. 84% said that they would like the chance to use some kind of NRT with a preference for gum amongst the girls and patches amongst the boys. Family support and willpower rated highest amongst non-pharmacological aids with one to one support from a counsellor also scoring highly.

Conclusions: Our survey confirms the expected high prevalence of smoking in this group but the proportion of those young smokers who would like to quit and who have previously tried and failed was higher than expected. Views expressed will guide the design of specific smoking cessation services in this group.

Funded by Cancer Research UK.

[PT35] SMOKING CESSATION SERVICES FOR YOUTH SMOKERS: QUALITATIVE AND PILOT INTERVENTION STUDIES

A.W.P. Molyneux1, S.A. Lewis1, T.J. Coleman2, A. McNell1, R.J. Madeley1, C.A. Godfrey1, J.R. Britton1. 1City Hospital; 2University Hospital Nottingham; 3St George’s Hospital, London; 4Centre for Health Economics, University of York, UK

Rationale: Most adult smokers started smoking as adolescents. Half of adolescent smokers would like to stop smoking and 70% have tried unsuccessfully to give up. There is little provision of smoking cessation services for teenagers. We carried out a study in secondary schools to investigate teenagers’ views of how smoking cessation help should be provided to them, and developed and piloted a prototype school-based smoking cessation intervention based upon these findings.

Qualitative Study Methods: We invited teenage smokers (aged 13 to 16, previously identified by a questionnaire survey), from six secondary schools in Nottinghamshire, UK, to attend focus groups to discuss smoking behaviours, knowledge, and attitudes to smoking cessation, delivery of smoking cessation services to teenagers, and barriers and motivators to use of such services. Group discussions were recorded and transcribed. Transcripts were coded, sorted and indexed using a framework and discussed by three researchers. Emergent themes are presented.

Results: 135 smokers participated in 25 groups. Teenage smokers would prefer help with cessation that is non-judgmental, confidential, and delivered by trained counsellors to individuals or small friendship groups, at school in school time, with the opportunity to use Nicotine Replacement Therapy.

Pilot Study Methods: We conducted an uncontrolled pilot study of a prototype cessation intervention in three schools. We invited smokers (aged 14 to 16, identified by a survey) to attend the intervention alone or in small friendship groups, receiving six weekly smoking cessation counselling sessions delivered by a trained counsellor, with a six week course of Nicotine Replacement Therapy (NRT) given as appropriate under medical supervision. Self reported abstinence was validated by an exhaled carbon monoxide of ≤ 5 ppm. Results 158 smokers were screened and 155 enrolled, 91 (59%) female, mean age 15, smoking mean 10 cigarettes per day. One hundred and forty nine (96.1%) participants set a quit date, 138 (89%) used some NRT, of whom 47 used a six week course. At the final visit 21 (14%) were abstinent and 82 participants (53%) attended.

Conclusions: This study suggests that this school based smoking cessation intervention is acceptable to teenagers, that is feasible and associated with reasonable cessation rates.

Funded by the Wellcome Trust.
**P137** AN ASSESSMENT OF SMOKING IN ACUTE MEDICAL INPATIENTS

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**Aim:** To investigate the epidemiology and smoking habits of hospital inpatients and to assess the willingness of smokers to quit.

**Study population:** Inpatients of acute medical wards of the Pamela Youde Nethersole Eastern Hospital, Hong Kong.

**Method:** A questionnaire survey was prospectively administered before admission of all patients to the acute medical wards between 15th April and 22nd April 2002. Data collected included age, gender, smoking status/history, and an assessment of willingness to quit. Patients who could not provide such information were excluded.

**Results:** There were 446 admissions to six acute medical wards over the one week period. Out of the 418 (93.7%) questionnaires returned, there were 208 males (49.8%). Mean ages were 66.2 (17.5) years (males) and 69.7 (18.0) years (females). 171 (41.1%) patients had ever smoked (135 males). Males smoked more than females (29.8 (22.7) v 15.9 (14.2) pack years (p=0.0001)) and started smoking at a younger age (35.8 (17.4) v 45.5 (16.3) years (p=0.008)). 57 (13.6%) current smokers (47 males) had smoked 25.4 (22.4) pack years. Of these, 35 (61.4%) had ever thought of quitting, 33 (57.9%) acknowledged a willingness to quit, and 26 (45.6%) accepted help towards quitting. Neither current age, at which smoking commenced, nor overall consumption in pack years was related to attitude towards smoking cessation, although those who had smoked less tended to be more willing to quit. Males had thought more about and were significantly more willing to quit than females however, an equal proportion of both sexes accepted help with cessation. 114 (27.3%) ex-smokers (89 males) had quit for 12.5 (11.4) years, having smoked 28.5 (21.7) pack years.

**Conclusions:** 41.1% of medical inpatients surveyed had ever smoked. 13.6% were current active smokers and of these 45.6% agreed to intervention with help in smoking cessation. The hospital inpatient setting provides a good opportunity to assess smoking status with a view to assisting smokers to quit.

### The therapy of asthma

**P138** BODIPY-TMR-CGP 12177: AN IRREVERSIBLE FLUORESCENT PROBE FOR THE HUMAN β2-ADRENOCEPTOR WITH AGONIST PROPERTIES

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Current methods to study native receptors in cells from patients are thwarted by the need for large numbers of cells. Fluorescent techniques offer an opportunity to work at the single cell level. BODIPY-TMR-CGP 12177 (BOD-CGP) is a fluorescent analogue of the hydrophilic β2-adrenoceptor (β2-AR) antagonist CGP 12177. It can stimulate cAMP accumulation (EC50 = 28.2 (4.0) nM, n=3) and gene transcription (EC50 = 22.3 (3.6) nM, Emax = 47% of the maximum isoprenaline response) in CHO-K1 cells expressing the human β2-AR and a cAMP response element reporter gene (CHO-β2 cells). Studies using [3H]-CGP 12177 indicated that BOD-CGP was able to displace the specific binding of this radioligand to the human β2-AR with an apparent Kd of 15.8 (3.0) nM, n=4. Pretreatment with BOD-CGP (100nM) reduced the maximal specific binding of [3H]-CGP 12177 by 50%, even after the fluorescent ligand had been washed out two hours previously. This provides strong evidence that BOD-CGP is effectively irreversible over this time period. Visualisation of the binding of the fluorescent BOD-CGP to single living cells (CHO-β2) using confocal microscopy demonstrated clear membrane labelling at concentrations of 30nM BOD-CGP and above. Analysis of the total pixel intensities of each image enabled an estimate of the KD for BOD-CGP to be determined from saturation analysis (27.6 (6.4) nM, n=4). The binding of 50nM BOD-CGP to living cells was also inhibited by increasing concentrations of the β2-antagonistICI 118551 (IC50 = 4.30 (0.86) nM, n=4) and CGP 12177 (0.76 (0.40) nM, n=3). Simultaneous imaging of the binding of this red fluorescent ligand (BOD-CGP) to a β2-AR-Green Fluorescent Protein fusion protein in CHO-K1 cells indicated that BOD-CGP did not induce receptor internalisation. A similar observation was made with the low efficacy agonist salbutamol, whereas the full agonist isoproterenol caused substantial receptor internalisation. We have concluded that it has fully characterised a novel fluorescent ligand for the human β2-AR and shown that it can be used to visualise receptors in single living cells. The irreversible nature of this ligand should make it readily applicable to the study of β2-ARs in acutely isolated native human cells in health and disease.

JGB is a Wellcome Trust Clinical Training Fellow.

### Small Airway Reticular Basement Membrane (RBM) Thickening in Clinically Stable Lung Transplant Recipients (SLTR) Is Not Affected by Three Months Treatment With Inhaled Corticosteroids (ICS)

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**Introduction:** Recent publications have demonstrated potentially pathological changes in clinically stable lung transplant recipients (SLTR), with frank airway remodelling demonstrated in allograft recipients with established BOS. In asthma RBM thickening has been demonstrated at an early stage and it is suggested that ICS treatment reduces this. There is no such data regarding RBM thickening in small airways sampled at transbronchial biopsy (TBB) of lung allografts.

**Hypotheses:** RBM thickening exists in small airways of lung allograft recipients. ICS treatment may decrease small airway RBM thickening.

**Methods and Results:**

**Abstract P140.** *Normal large airway RBM (Ward, et al. Am J Respir Crit Care Med 2001; 164:1718–21).*

![Image of RBM thickness measurement](http://thorax.bmj.com/Thorax: first published as 10.1136/thorax.57.suppl_3.iii48 on 1 December 2002. Downloaded from http://thorax.bmj.com by guest. Protected by copyright.
Methods: Thirty one SLTR >3 months post transplantation, randomised to three months 400µg CFC BDP bid or a formulation designed to yield at least an equivalent small airway dose (200µg HFS BDP bid Autohaler). Bronchoscopy BAL and TBB pre and post ICS. TBB were fixed in 10% buffered formalin, embedded in paraffin and H+E stained. Assessment of airway Rbm thickness was carried out at image analysis from serial stepwise sections by a blind experienced observer, exceeding ERS criteria (>1mm Rbm always scored). Ethical considerations required the use of a normal range for Rbm thickness in large airway biopsies (Ward, et al. Am J Respir Crit Care Med 2001;164:1718–21). Rbm is thought to be systematically thicker in large airways. See figure.

Conclusion: Small airway Rbm thickening exists even in SLTR, but its significance with regard to the subsequent profound remodelling in BOS (1) is not known. three months of moderate ICS did not affect Rbm thickening. Further longitudinal studies, including the effect of anti-remodelling strategies are possible.

Rapid Effects of Single Dose Fluticasone Propionate on Allergen-Induced Early Asthmatic Responses in Man

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Background: There is no evidence to date to suggest that inhaled glucocorticosteroids (GCS) affect the early asthmatic response (EAR) following allergen inhalation in sensitised asthmatic subjects. This is perhaps surprising as we have previously demonstrated that single dose inhaled fluticasone propionate (FP) attenuates airway responsiveness to the mast cell stimulus adenosine 5'-monophosphate (AMP) within two hours (Ketchell, et al. J Allergy Clin Immunol 2002; in press). Objectives: The aim of this study was to assess the effect of inhaled FP on allergen-induced airway narrowing.

Methods: In a randomised, double-blind placebo controlled, cross-over study in mild steroid-naive asthmatics, 12 subjects with a known EAR to inhaled allergen, underwent two constant-dose allergen challenges separated by 3-4 weeks. Each challenge was preceded two hrs earlier by a single dose of inhaled FP 1000µg or matched placebo via an accuhaler™. The EAR was measured as the % change in FEV1, from baseline at 5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes following allergen challenge and the area under the curve during the first two hours (AUC0–2hrs).

Results: FP 1000µg significantly attenuated the EAR compared to placebo with a 45.1 (12.2) % reduction in AUC0–2hrs, p=0.04. A reduction in FEV1 was observed at each time interval, although differences were not significant until the 90 minute point (p=0.01). The mean maximal % fall in FEV1, was observed at the 15 min time interval and was 18.9% following a single dose of FP 1000µg and 21.6% following placebo (ns)

Conclusions: This study confirms rapid anti-inflammatory effects of inhaled FP in man. The time interval of protection suggests an effect on mast cell mediator responses such as increased microvascular permeability and/or mucosal blood flow rather than on mast cell degranulation and immediate smooth muscle responses. Inhaled GCS may provide additional beneficial topical effects in the management of acute allergic asthma.

Four Month Adjustable or Fixed BD Dosing with Budesonide/Formoterol in a Single Inhaler Reduces Symptom Severity

P. Indi, J. Haughney*, D. Price*, J.P. Rosen*, J. Kennedy*, Hammersmith Hospital, UK; *University of Aberdeen, UK; †AstraZeneca UK, Luton, UK

Aims(s): To evaluate the efficacy of budesonide/formoterol combination (B/F; Symbicort Turbohaler) administered as either adjustable or fixed bd dosing.

Methods: Patients (mean age 48 years) were randomised to adjustable maintenance (n=782; B/F two inhalations bd for four weeks, thereafter 1–4 inhalations bd depending on asthma symptoms for 12 weeks) or fixed B/F dosing (n=771; two inhalations bd for 16 weeks). Primary efficacy variables were reduction in symptom severity (according to GINA definitions) and total exacerbations.

Results: Changes in symptom severity are shown in the table. Ninety four per cent of patients (both groups) reported no exacerbations. The average number of daily inhalations was 15% lower in the adjustable dosing group.

Conclusions: Patients treated with both adjustable and fixed-dose B/F demonstrated a reduction in symptom severity as shown by the marked shift from moderate to mild intermittent. Overall there was a 46% reduction in patients graded as moderate persistent and a doubling of patients categorised as mild intermittent. A reduced overall daily dose was observed in the adjustable arm.

Symbicort Used in a Guided Self Management Plan Provides Additional Enablement to Asthma Patients Compared with Fixed Dosing

J. Haughney*, D. Price*, J.P. Rosen*, K. Morrison*, †University of Aberdeen, UK; ‡AstraZeneca UK, Luton, UK

Aims: To assess the effect on patient enablement of a guided self management plan compared with fixed dosing in asthma patients prescribed Symbicort.

Methods: After a four week run-in on budesonide/formoterol two inhalations bid, patients received adjustable dosing (n=124) or fixed dosing (n=104) for 12 weeks. Patients completed a validated Patient Enablement Instrument (PEI) within eight weeks of the last clinic visit. The PEI has six questions ("As a result of your treatment do you feel you are: Q1: able to cope with life; Q2: able to understand your illness; Q3: able to cope with your illness; Q4: able to keep yourself healthy; Q5: confident about your health; Q6: able to help yourself"). Patients' responses are scored 0 ("same or less" or "not applicable") to two ("much better"). A mean difference in total score of ≥0.8 between groups, or an individual's total score of ≥6 is considered to reflect a relevant treatment benefit.

Results: The baseline and demographic characteristics of the two groups were well matched. The total PEI scores were (mean (SD)) 6.24 (3.73) and 5.44 (3.84) in the adjustable and fixed dosing groups, respectively, difference 0.8 (95% CI 0.2–1.8), p=0.12. A statistically significantly greater proportion of patients receiving adjustable dosing had a score of ≥6 compared with fixed dosing (57% v 43%, p=0.04). There were no significant differences between responses to Q1, Q3, Q5, and Q6.

Conclusions: Guided self management with Symbicort provides a greater level of patient enablement than fixed dosing.

AIRWAY DRUG DELIVERY: SIZE MATTERS—BIGGER IS BETTER

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Current inhaler devices are inefficient as the dose delivered is a poly-disperse distribution of drug particle sizes, and only 20% reaches the lungs. Aerosol particle size influences drug deposition and in vitro models conclude 2–6µm as optimal. Monodisperse aerosols are the appropriate research tools to investigate particle size effects, as the dose is within a narrow size distribution. We hypothesised that engineering such aerosols of salbutamol would identify the ideal bronchodilator particle size and improve inhaled therapeutic drug delivery.

We previously described our use of a spinning top aerosol generator to produce such aerosols, and reported larger particles were significantly more potent bronchodilators in asthmatics—6µm > 3µm > 1.5µm, at 1/10th standard MDI doses. The 6µm particles achieved equivalence with 200µg MDI salbutamol. No adverse effects were observed. We then hypothesised the differences were a result of the deposition characteristics of each particle size, in that larger particles were better matched to their target site of action.

We therefore undertook to assess lung and extrathoracic deposition patterns using 2D planar imaging and 11C-labelled monodisperse salbutamol (30µg dose) aerosols, in 12 asthmatic subjects with simultaneous measurements of clinical efficacy. The smaller particles achieved greater total lung deposition; 1.5µm (56%), 3µm (50%), 6µm (46%), however the larger particles were more efficacious 6µm > 3µm > 1.5µm (FEV1, p<0.05). We quantified regional deposition in the lungs and found more of the larger particles in the central-intermediate zone; 6µm (75%), 3µm (66%), 1.5µm (56%). The penetration index confirmed greater peripheral lung penetration of the smaller particles; 1.5µm (0.79), 3µm (0.60), 6µm (0.36); p<0.05.

The data support our hypothesis that for β2-agonists, regional airway targeting to the conducting airways is more important than alveolar deposition. Particles in the higher part of the respirable range achieve the greatest clinical response and we advocate small doses, when correctly delivered, may improve the therapeutic index. We now aim to investigate the effects of inspiratory flow and respiratory disease severity on aerosol deposition. With resurgence of interest in inhalation drug delivery as a means of systemic therapy, we must take the opportunity to research basic aerosol science to enhance the efficiency of clinical airway drug delivery.

The size distribution by number of a range of pMDIs [including Qvar (3M), Salbutamol (GSK), Fluticasone (GSK), Budesonide (AstraZeneca)] was measured to determine the proportion of particles in the sub-micrometer range. Measurements were made by Electrical Low Pressure Impactor (size range 30nm–10µm) and a Scanning Mobility Particle Sizer (size range 10–100nm). All devices tested yielded high numbers of fine and ultrafine particles, the number being greater for HFA than for CFC propelled MDIs. (%<100nm, HFA-Qvar:76%, HFA-Salbutamol:75%, HFA-Fluticasone:76%, CFC-Budesonide:65%, CFC-Budesonide:57%). We suggest that the number of fine and ultrafine particles, the concentration of drug per particle, the molecular properties and the hydroscopic properties of the drug, may all influence MDI potencies. See figure.

This work was supported by an academic grant from 3M Pharmaceuticals.

PD20 TO METHACHOLINE IS PREDICTED BY AIRWAY INFLAMMATION AND REMODELLING: A SYSTEMATIC, LONGITUDINAL, STEROID INTERVENTION STUDY OF AIRWAY BIOPSY (Ebb) AND BAL PARAMETERS

C. Ward1, D. Reid1, M. Pois1, B. Orsida1, B. Feira1, R. Buhl1, D. Johns1, E. Haydn Walters1.1 Lung Biology and Transplantation Group, University of Newcastle upon Tyne and The Freeman Hospital, UK; 2University of Tasmania and Monash University, Australia.

Introduction: We have recently shown that PD20 may be predicted from a model including terms measuring airways remodelling: (reticular basement membrane (Rbm) thickening) and inflammation quantified at BAL. In this study we have refined our paradigm, including information on large airway biopsy (e bb) inflammation and the effect of inhaled corticosteroid treatment.

Hypothesis: Ebb provides complimentary inflammatory indices to BAL, which supports a link between inflammation, airway remodelling and PD20.

Methods: A double blind, randomised, placebo-controlled, parallel group study of inhaled fluticasone propionate (up to 12 months FP 750µg bd) in 35 symptomatic, mild to moderate atopic asthmatics with previously described BAL inflammation, Rbm thickening and PD20. Quantification of ebb inflammation by immunohistochemistry/image analysis. Matrix analysis of individual univariate correlations, with subsequent “best subsets” multiple regression.

Results: Cross sectional, multiple regression analysis explained 56% of the variability in BHR, 23% related to log EG2 (eosinophil) counts, 19% to log Rbm thickness, and 14% to BAL epithelial cell counts improving our previous model (overall 40%; 1). Following three months FP ebb inflammatory cell counts fell significantly, with no further FP effect, for example, baseline median ebb EG2 count 8/mm basement membrane (mm), (range 0–32), three month; 2/mm mm (0–22, p<0.01 v baseline), 12 month median 2/mm mm (0–72, NS v 3 months). Changes in ebb inflammation preceded an effect on Rbm thickness and the maximal effect on BHR (at 12 months FP, 1).

Conclusion: Ebb and BAL are complimentary, and further support the view that PD20 to methacholine reflects airway remodelling and inflammation in asthmatic subjects. A lack of specificity for any one part of asthma pathophysiology may represent a strength of BHR testing.

Chris Ward is an ERS research fellow.


RELATIONSHIP BETWEEN AdHERENCE TO PRESCRIBED REGIMENS AND ASTHMA CONTROL IN PATIENTS WITH DIFFICULT ASTHMA

S. Aburuz2, J. McElnay1, J. Millership1, J. Gamble3, L. Heaney2.1School of Pharmacy; 2Department of Medicine, Queen’s University Belfast; 3Regional Respiratory Centre, Belfast City Hospital, Belfast.

Introduction: Non-adherence with prescribed therapy is a major problem in the management of chronic illness. The aim of the present study was to examine the relationship between asthma control and adherence to oral therapy (prednisolone (P) and theophylline (Th)) and high dose inhaled steroids (HIDS) in a population of difficult asthmatics (persisting asthma symptoms/frequent exacerbations requiring systemic steroids despite maintenance high dose inhaled corticosteroids plus a long acting β agonist).

Method: A range of parameters was used to assess adherence and asthma control in patients, with difficult to control asthma, attending a
hospital outpatient clinic. Plasma P was measured by HPLC. Plasma T was measured by fluorescence polarization immunoassay. Urinary Cortisol (C) was measured by HPLC and corrected for creatinine (UCC ratio). Non-adherence was recorded if (a) Prednisolone: no plasma P detectable; (b) Theophylline: no plasma T detectable. Adherence to HDIS was recorded if morning UCC ratio was suppressed below 8.0 ng/ml/μmol creatinine. Asthma symptom control scores (ASCoS) were recorded using the Juniper Asthma Control Questionnaire. Results: Eleven (25%) patients of 44 patients taking T and 14 (56%) of 25 patients taking P were non-adherent. Of 43 patients taking HDIS (median 2000 μg; range 1000–4000 μg BDP equivalent), 31 (72%) had suppressed UCC ratio. ASCoS, wheezing a morning symptoms were significantly lower (p<0.05) in patients with UCC suppression. There was no relationship between FEV1% and suppression of urinary cortisol. Asthma control did not vary with adherence with theophylline or prednisolone.

Discussion: There was a high prevalence of non-adherence with prescribed oral therapy in patients with difficult asthma. Asthma control was related to the presence of urinary cortisol suppression in patients receiving HDIS, which may reflect non-adherence with inhalated therapy. Failure to suppress urinary cortisol can be used as a marker of possible non-adherence to HDIS in this population.


P149 EARLY ANTIBIOTIC PRESCRIPTION AND ALLERGIC DISEASE IN UK ADULTS

P. Collison, J.M. Harris, P. Mills, S. Maffot, C. White, F. Figg, A. Moon, A.J. Newman Taylor. Occupational & Environmental Medicine, Faculty of Medicine, Imperial College of Science, Technology and Medicine, London, UK

To investigate any association between treatment with antibiotics in early life and subsequent atopic or allergic disease, we studied a population of adults in southeast England. 1063 men and women (93% of those eligible), parents of a birth cohort based in Ashford, Kent, agreed to participate. Allergic diseases were defined by responses to a questionnaire; atopy was measured by responses to skin prick tests with common aeroallergens. Prescription information for antibiotics in the first five years of life was successfully obtained from the general practice records of 746 (70%) subjects. There were no important differences in the rates of atopy or allergic disease between those whose records were or were not available for examination.

Thirty percent of adults were atopic; 14% reported a history of asthma and 29% hay fever, 564 (76%) had at least one antibiotic prescription in the first five years of life. The median age at first prescription was 1.5 years. Older subjects were more likely not to have a prescription record, indicating a temporal increase in prescription patterns. There was a clear association with family size, whereby adults with fewer siblings were significantly more likely to receive at least one antibiotic prescription by the age of five years (p<0.001). There was no evidence of any association between atopy and total antibiotic prescriptions in total (adjusted OR 1.01, 95% confidence interval (0.97 to 1.05) per prescription), a pattern which did not alter at any age or by antibiotic class. Asthmatics—with or without atopy—were more likely to receive an antibiotic prescription by the age of five years (adjusted OR 1.08 (1.03 to 1.13) per prescription). This relationship increased with age at prescription (adjusted OR 1.02 per prescription by age 1, 1.18 age 1–2; 1.4 age 2–3; 1.23 age 3–4; 1.32 age 4–5). A similar but less marked pattern was observed for hay fever, again with or without evidence of pollen sensitisation. These findings do not rule out a positive association between antibiotic use and subsequent allergic disease; but are more probably explained by a protopathic bias.

P149 IS A TWO WEEK TRIAL OF ORAL PREDNISOLONE PREDICTIVE OF TARGET LUNG FUNCTION IN PAEDIATRIC ASTHMA?

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The optimum length of a steroid reversibility trial in children is not known. We have used a two week trial of oral prednisolone to determine target lung function for subsequent asthma therapy. The aim of this study was to determine whether in fact on subsequent visits some children actually exceeded this "target lung function".

Methods: Twenty five severe asthmatic children (median age 13 (range 6–16) years) were studied. Severe asthma was defined as persistent symptoms despite treatment with ≥1600 μg/d of inhaled budesonide or equivalent, long-acting β-agonist ± regular steroids. FEV1 was measured following high-dose systemic steroids (oral prednisolone 40 mg/day for 14 days) and compared with the highest FEV1, obtained in subsequent visits during the following year. Results: The mean (SD) FEV1, as a percentage of the predicted value following the formal steroid trial was 74.28 ± 19.66 (range 38–103). A total of 8 (32%) children actually obtained an increase of >10% above their "target" FEV1, during the following year at routine clinic spirometry. There were no important changes in prescribed asthma medications (for example, cyclosporine, methotrexate, s.c. terbutaline), which might have accounted for this in these eight children. In 17/25 (68%) children FEV1, measured in subsequent visits remained stable or declined. The mean age of both patient groups was equal, and it was not possible to predict which children would exceed "target lung function" from baseline characteristics or post-steroid FEV1.

Conclusions: A two weeks course of prednisolone is not necessarily predictive of target lung function. Further studies are needed to find out whether a higher dose or longer duration of the steroid trial is more predictive, or whether adding an acute inhalation of β-agonist at the end of the trial may increase predictive power.

P148 EARLY ANTIBIOTIC PRESCRIPTION AND ALLERGIC DISEASE IN UK ADULTS

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P145 TRENDS IN TUBERCULOSIS CASE FATALITY IN ENGLAND AND WALES 1988–2000

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To determine trends in tuberculosis (TB) case fatality in England and Wales according to age and disease site we analysed published notification and mortality data for TB from 1988–2000 [see table overleaf]. In contrast to 1974–1987, (1) case fatality for TB of all sites and age groups combined fell over this period despite increasing incidence of disease. Declining case fatality is likely to be due to changes in TB epidemiology: younger patients with higher rates of extra-pulmonary disease and lower case fatality rates accounted for an increasing proportion of TB cases over the study period. Improvements in TB notification rate, under-diagnosis of TB at post mortem and improved case management may also have contributed to the decreasing case fatality rates observed.

Abstract P151

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**P152 ERRORS IN THE NOTIFICATION OF TUBERCULOSIS**

C. Seehra1, F.A. Drobniewski2, P.G. Mare3, D.C.S. Hutchinson1. 'Lambeth, Southwark & Lewisham Health Authority (LSLHA); 2PHLS Mycobacterium Reference Unit, Dulwich; 3Respiratory Medicine, King’s College Hospital, London, UK

**Introduction:** In the UK, clinical disease with *Mycobacterium tuberculosis (MTB)* is notifiable by law, whether cases are MTB culture positive or culture negative treated as MTB. Notification initiates contact tracing and provides epidemiological data. Two main sources of error exist: (1) Under notification (failure to notify cases of MTB infection). (2) Over notification (notification of cases not due to MTB infection). Both errors can occur and we have examined local procedures, with emphasis on over notification.

**Methods:** We have studied notified patients treated at King’s College Hospital (KCH) and resident in LSLHA. Over notification in 1996 to 2000 inclusive was defined for this audit by comparison of notified cases with microbiologically confirmed cases. Under notification (limited to 1999) was detected by search of KCH Pharmacy data base for patients prescribed anti-tuberculosis chemotherapy, but not notified as TB.

**Results:** In 1996 to 2000, 279 cases were notified as tuberculosis, 229 (82%) being MTB culture positive. Forty culture negative cases were notified, 32 being clinically probable MTB and nine probably not. Nine cases were culture positive with non-MTB mycobacteria. Thus 18 notified patients definitely or probably did not have MTB. One hundred and forty two patients with MTB infection were erroneously notified as MTB.

**Conclusion:** Combining under and over notification rates for 1999 yields a net under notification rate of 7/45 or 15.6% (CI 7 to 29). The over notification rate of 4/45 or 8.8% (CI 2 to 20).

**P153 UPDATE ON AN OUTBREAK OF ISONIAZID MONO-RESISTANT TUBERCULOSIS IN NORTH LONDON**

M. Ruddy1, A.P. Davies1, M.D. Yates2, S. Yates3, S. Balasagunathan1, B. Patel1, S. Lozewicz1, S. Sen1, M. Bah1, E. James1, M. Lipman1, Y. Drabu1, J. Watson1, M. Piper1, F. Dronniewski1, H Maguire1, on behalf of a Londonwide Incident Committee. 1PHLS Mycobacterium Reference Unit, King’s College Hospital (Dulwich); 2North Middlesex University Hospital Trust; 3PHLS Communicable Disease Surveillance Centre; 4Barnet, Enfield & Haringey Health Authority; 5Camden & Islington Health Authority; 6Barnet & Chase Farm Hospital Trust; 7Royal Free Hospital Trust; 8Department of Health Prison Policy Unit

Since January 2000 an outbreak of isoniazid mono-resistant *Mycobacterium tuberculosis* has been investigated. Typing of suspected isolates has been performed at the PHLS Mycobacterial Reference Unit using a new rapid PCR-based method (RAPET), with confirmation by RFLP IS6110 typing showing a distinctive 15 band pattern. Case finding has been performed by initial retrospective and continuing prospective analysis of isoniazid mono-resistant isolates from the source and neighbouring hospitals, and all isoniazid mono-resistant isolates in London from January 2000 onwards, along with comparison of the fingerprint to RFLP IS6110 databases. The earliest case detected was a Nigerian student resident in London in 1995. Epidemiological links were established by questionnaire in face to face interviews. Outbreak control is coordinated by an Incident Control Committee at the PHLS Communicable Disease Surveillance Centre. To date 97 patients’ isolates have demonstrated the RAPET pattern. Eighty three microbiologically confirmed cases have been identified in London, with 14 clinically proven cases in their contacts and nine epidemiologically linked cases outside London. Contact tracing so far has suggested a higher than predicted transmission rate (11%). Thirty contacts have been placed on chemoprophylaxis. The epidemic curve suggests that the peak of the outbreak may not yet have been reached. A wide range of racial and social groups have been involved in the outbreak with 17 of the cases associated with prisoners including one prison staff member. The investigation has revealed the first documented case of transmission in a UK prison. Nosocomial transmission has occurred involving staff and patients. The involvement of IDUs and sex workers along with documented compliance problems in 38% of cases has made control of the outbreak difficult.

**P154 MISSED DIAGNOSIS OF TUBERCULOSIS IN THE ACCIDENT AND EMERGENCY DEPARTMENT**

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In our district many patients present with illness first to the accident & emergency department (A&E) at our hospital rather than to primary care. This is a result of several factors such as poor understanding of the primary care system in the UK, and poor access to primary care. The aim of this study was to ascertain how many patients with tuberculosis in our district present to the A&E department, and how well they are diagnosed at presentation.

Of the 243 notified cases of tuberculosis (TB) in Newham during 1999, 121 (50%) patients were seen at A&E prior to notification. Of these 121 patients, 62 had pulmonary disease; their median age was 32 years (range 1 to 88 years). Fifty one patients attended the A&E department more than once (total 211 visits). The number of attendances: number of patients, was as follows: 1 attendance: 70 patients, 2:30, 3:9, 4:8, 5:3, 6:1. Of the 171 visits for which A&E attendances: number of patients, was as follows: 1 attendance: 70 patients, 2:30, 3:9, 4:8, 5:3, 6:1. Of the 171 visits for which A&E patient information cards were traced: 143 (84%) were for TB related episodes, 12 (7%) were episodes unrelated to TB, and 16 (9%) did not wait after being triaged.

Records for the TB related episodes (143 visits) were divided into those in whom TB was suspected when seen in the A&E department (37 visits), and those in whom TB was not suspected (106 visits). All patients where TB was suspected had one or more symptoms suggestive of the diagnosis (cough, haemoptysis, night sweats, breathlessness, lymphadenopathy, and fever). However, in the 106 A&E visits where TB was not suspected, 61 (58%) cases had one or more symptoms suggestive of TB.

Of the 37 visits at which TB was suspected, the number of cases and the department of the clinician who raised the suspicion were: 29 A&E clinician, five general medicine, two surgical, one gynaecology. Of the cases that were unsuspected, the majority of cases were seen by A&E clinicians. In all cases where presenting symptoms may
have suggested TB (98 visits), 19 (19%) patients had a chest x-ray performed and nine (9%) had sputum taken for acid-fast bacilli. Those patients that were not followed up later presented to A&E or another hospital department where the correct diagnosis was eventually made.

Many TB patients attended A&E where the diagnosis was unsuspected. In our district, with a high incidence of TB, A&E staff need better education about the diagnosis of TB.

Methods: During a period of three months all adults (age ≥15years) admitted to one of six South African hospitals and put on anti-tuberculous treatment for suspected or confirmed pulmonary tuberculosis were eligible. This at the treatment was initiated the performance status was recorded by the doctor or the nurse in charge. The vital status of the patient (alive or dead) was determined two months after initiation of treatment (table).

Results: 347 patients were admitted to hospital and started on TB treatment during the study period. For nine patients performance status was not obtained and so analysis has been restricted to the remaining 338 patients.

Discussion: Performance status at the time of diagnosis appears to be a powerful predictor of mortality in this population.

Supported by TB Alert.

## P156 Performance status on admission to A&E departments: an opportunity to diagnose tuberculosis (TB) early?

A. Smith, A. Goodburn, A. Story, R. Miller, G. Scott, H. Booth. TB Clinic, Middlesex Hospital, University College London Hospitals (UCLH), UK

TB is a major health problem in London, accounting for more than 40% of the national total. North Central London Sector has seen the highest rate of increase in TB since 1998 (155%), and is also the epicentre of an ongoing outbreak of isoniazid resistant TB. Early case finding remains an essential part of TB control.

**Aims:** (1) To identify the rate of usage of A&E to access healthcare in our TB patient population. (2) To identify whether A&E attendances present an opportunity to diagnose TB early.

**Methods:** TB notifications between the period from January 2001 to March 2002 (15 months), were cross referenced against A&E and microbiology records for the six month period prior to each notification.

**Results:** There were 171 TB notifications during this time. Of these, 48 (28%) patients were seen in A&E a total of 69 times prior to their diagnosis. Thirty two patients had pulmonary TB (19 smear positive) and 10 were HIV positive (one previously undiagnosed). Thirty five patients were admitted from A&E of which 27 were diagnosed as a direct result of their admission. Four patients were discharged from A&E with TB clinic follow up. Seventeen (eight admitted) of the 48 patients did not have TB diagnosed or considered at the time of their A&E attendance(s).

**Conclusions:** A third of our patients with subsequent TB diagnoses had attended A&E within the six month period preceding notification. This may reflect the difficulties that this patient population has in accessing healthcare by other means. It also serves to emphasise the key role A&E staff have to play in TB case finding among this population.

Thirty five out of 48 patients with TB were admitted, suggesting that these patients were systemically unwell on presentation, and emphasising the importance of liaison between acute general medical and TB services. In 17 out of 48 cases the diagnosis of TB was either not made or considered, representing a potential missed opportunity to diagnose TB early.

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TUBERCULOSIS: A CHEAP DISEASE?

NO BOOSTER EFFECT IN BCG IMMUNISED

TUBERCULOSIS AND HEALTH BELIEFS IN THE BANGLADESHI COMMUNITY OF EAST LONDON

We investigated the understanding and recognition of symptoms of TB, any associated stigma, use of alternative practitioners and attitudes to medication amongst Bangladeshi patients with TB in Tower Hamlets, east London. Forty three newly diagnosed subjects were approached and 41 took part. Twenty six were male and 15 female, aged 20–85 (median 36). 19 had pulmonary and 22 extra pulmonary TB. Each underwent two interviews, of c.1 h duration, the first within a few days of diagnosis, the second after 1–3 m treatment. Interviews were semi-structured, for analysis with NVivo software after transcription.

Strikingly, only two subjects admitted to knowing that TB could infect organs other than the lungs. Twenty four of the 41 associated cough, haemoptysis, and weight loss with TB, but the significance of fevers and night sweats was largely unrecognised. Most were afraid to discuss their diagnosis outside their close family, with 31 subjects believing there was significant stigma associated with TB and five stating that TB affected a sufferer’s prospects of marriage. While most (27) expressed no concerns about medication, the others were unhappy with size and/or number of tablets and duration of treatment. Only six admitted to pluralistic health practices: while adhering to standard therapy, they consulted religious leaders and took herbal remedies.

Seven subjects admitted to being not literate in any language. Adherence, assessed semi-objectively (including tablet counts and urine checks) was not related to literacy, proficiency in English, nor educational attainment, and the least compliant patient was UK university educated. Fear of TB, the desire for cure and respect for medical staff were the most commonly expressed reasons for adherence.

Our findings of lack of awareness of TB symptoms and of substantial stigma must give rise to concerns both about delays in presentation for medical care and regarding contact tracing. Culturally appropriate health education initiatives may help address these problems. We keep in mind, however, that our findings might not necessarily have been significantly different had we studied UK born white TB patients.

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status and were excluded from the analysis. In 34 cases, the grade of the 2nd Heaf test was unequivocally higher than the grade of the 1st Heaf test. In the remainder (101 cases) it was not. 27/119 (22.7%) of those with previous BCG demonstrated an increase in Heaf grade, compared with 7/16 (43.8%) of those with no evidence of previous BCG (table).

These results do not support the contention that boosting is more common in BCG vaccinated subjects.