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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 cytospins 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 glycol-methacrylate 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(IL4) 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 (cellular and extracellular in 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 (NE−/−) 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 NE−/− 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 NE−/−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 NE−/− mice (p<0.05 v WT). No differences in inflammatory cellularity, alveolar-capillary leak, TGF-β, or TGFB1 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 injury or damaged alveoli. In contrast, staining for active TGF-β in bleomycin-treated NE−/− lungs was minimal, and limited to peribronchial and perivascular locations. In conclusion, TGF-β activation was diminished in alveolar fluid from bleomycin-treated NE−/− 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 outpatient 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 £1755 (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 TGF-β5 INTERNEXIN 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 TGFβ5 is a feature of the most poorly differentiated SCCs, while an increase in TGFβ5 is associated...
with invasiveness and metastatic spread [Watt, Dev Suppl 1993:1 B5–92]. Epithelial cells normally undergo apoptosis on detachment from their extracellular matrix (anoikis), 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 anoikis.

Methods: αv or α4 integrin subunits were transfected into H357 and SCC4 cells using the pBabe-puro retroviral vector giving high expressing polyclonal populations. Anoikis was assayed 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. Anoikis activation was examined using a chimeric molecule with the cytoplasmic domain of Jβ attached to the extracellular domain of β6.

Results: The αv subunit formed a functional heterodimer with β5 as measured by FACs and adhesion to vitronectin. Anoikis 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). Anoikis was not increased in αvβ6 expressing cells. The pathways involved in αvβ5 induced anoikis include a suppression of activation of the survival factor Akt/ PKB, possibly via the cytoplasmic domain of Jβ 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 anoikis via the αvβ5 heterodimer. Both the intrinsic and extrinsic apoptotic pathways are required, and a cell survival mechanism of activating Akt/PKB is suppressed.

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 11y (9.5-16y)) and 21 non-CF children (median age 11y (9.5-15y)) and 21 non-CF children of impaired nMCC. Saccharin clearance times were measured in 18 children with CF and non-CF (CS−) subjects (CS− n=12: 18 (11; 24) mins; CS− n=16: 14 (6; 16) mins; p<0.05). IL-8 was significantly higher in the CF CS− group than in the healthy adult group (CF CS+45 (15; 76) pg/ml NLF; healthy adults: 10 (1; 64) pg/ml NLF; p<0.01) and there was a trend with regards to the CF CS− group (15 (1; 39) pg/ml NLF; p=0.06). In conclusion, the delayed MCC reported in the CF nose was not seen in a group of young children, but became apparent in adult patients with chronic sinus disease. This suggests a role for mucosal inflammation in the aetiology of delayed MCC in the upper and proximal airways but not distal airways where the ciliated epithelium is more sparse, and low volume ASL may be more detrimental on the clearance process.


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Phosphodiesterase 4 (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 PDE4D expression, but gain PDE4A and PDE4B isoforms. I hypothesised important roles for PDE4 isoforms in macrophage behaviour.

Methods: RAW 264.7 cells were treated with 10ng/ml LPS +/− the PDE4 inhibitor rolipram, PDE3 inhibitor cilostamide or signal transduction inhibitors. Cyclo-oxygenase 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 COX2 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 COX2, PGE2, and iNOS while inhibiting TNFα. TNFα inhibition is not due to increased PGE2 production. Complex crosstalk between the cAMP and MAPKsignal cascade 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 MAPKsignal.
Lung cancer outcomes

[51] 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 34.5%, Stable Disease 32%, and Progressive Disease 17.1%. Overall 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.

[52] 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 0–0.5%) 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 (48.6%) 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=0.09).

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.

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 IIB) with concurrent radical radiotherapy using a tumour dose of 52.5 Gy given in 20 daily fractions over four weeks, together with cisplatin 20 mg/m² concurrent with fractions 1–5 and 16–20. Thirty four patients received 2–4 courses of chemotherapy after concurrent chemoradiation. 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 IIB disease treated with concurrent chemoradiotherapy 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.

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 suffering from lung cancer 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 years (range 30–94), 133 had a pathological diagnosis—27 had small cell tumours and 106 had non small cell cancers. 59 patients were excluded from radical treatment by performance status, a further 62 by stage of disease, a further 15 by inadequate pulmonary function and 8 by other co-morbidity. Thirty-one (16%) remained and were potentially operable for radical treatment.

Conclusion: In this study only 16% of patients were potentially curable at presentation. On the basis of these figures targets for surgical resection rates running 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

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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 (8.75) yrs, FEV1 1.24 (0.88) l, FEV1/VC 0.65%, PaO2 8.8 (1.2) kPa, PaCO2 5.4 (0.6) kPa, PaO2 46.2 (3.18) pack years of smoking, MRC dyspnoea score 3 (0, 10), 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=0.032). An inverse relationship was seen between numbers of intraepithelial EG2 positive cells per high-powered field also increased with increasing daily inhaled steroid dosage (rho=0.850, p=0.032). An inverse relationship was seen between numbers of intraepithelial EG2 positive cells per high-powered field also increased with increasing daily inhaled steroid dosage (rho=0.850, p=0.032). An inverse relationship was seen between numbers of intraepithelial EG2 positive cells per high-powered field also increased with increasing daily inhaled steroid dosage (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 daily inhaled steroid dosage (rho= –0.714, p=0.047). Patients with symptoms of daily dyspnoea 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 daily inhaled steroid dosage (rho= –0.714, p=0.047).

Conclusion: Given that neutrophil (PMN) recruitment, and subsequent transmigration, is central to the development of COPD, it is possible that PMN from smokers who develop the disease are primed to migrated 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. 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 (82.1 (10.0) v 47.0 (19.3), p=n.s.). To assess endothelial adhesion and migration, PMN were perfused at a physiological flow rate over intercellulin-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);
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 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 smoking 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) > 47.4 (15.7), p=0.004, SGRQ impact 46.1 (16.1) > 34.1 (17.3), p=0.013, SGRQ symptoms 70.3 (14.8) > 60.5 (21.4), p=0.003, SGRQ activity 76.8 (17) > 63.2 (20.4), p=0.004. SF-36 vitality and role physical limitation were also worse in this group.

The PPMs group had an exaggerated airway inflammatory response, mean (SD): sputum supernatant log IL-8 (nM) 0.01 (0.35) > -0.29 (0.41), log IL-1B (nM) 0.32 (0.33) > 0.07 (0.40), p=0.008, Log TNF-α (pM) -0.15 (0.78) > -0.78 (0.56), p = 0.001, NE (µM) -1.27 (1.01) > -2.04 (0.52), p=0.001 and NC [% IMLP] 70.4 (19.1) > 54.6 (19.0), p=0.001. There were increased numbers of sputum neutrophils (absolute count) but this was not statistically significant (p=0.038). Fibrinogen levels (µM) 1.4 were greater in the PPMs group: 3.21 (0.87) > 2.85 (0.64), p=0.05.

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.

**Smoking cessation, attitudes, and examples**

**A survey of published curriculum content on smoking and smoking cessation in UK medical schools**

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**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 cessation. We identified keywords such as “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%) made no references to smoking or smoking cessation in their published curriculum material. Most of the references made to the importance of taking a smoking history, and to the occurrence of tobacco-related diseases. Four medical schools (17%) offered 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.

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**Attitudes of General Practitioners and Patients Towards Smoking Cessation Advice in Primary Care**

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Despite compelling evidence for the effectiveness of smoking cessation advice from a GP, rates of provision of such advice remain persistently sub-optimal (Frehel 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 advice? 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 content they believe would be effective (Butler CC, et al. BMJ 1998;316:1878–81). Is there is 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.

**S13**  
**“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**

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**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.


**S14**  
**EXAMPLE OF AN EFFECTIVE SMOKING CESSATION SERVICE WITHIN A PRIMARY AND SECONDARY CARE TRUST**

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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 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 care 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 those 612 (52%) were not smoking at 4 weeks with CO validation, 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 and mocking smoking 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.

**S15**  
**12 MONTH QUIT RATES OF A “SPECIALISED” HOSPITAL BASED SMOKING CESSATION SERVICE**

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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 and 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 recommended 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

THE UPPER AIRWAY IN PREGNANCY AND PRE- ECLAMSIA

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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 in 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-eclamptics (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 preeclampsia 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 preeclampsia which may further increase blood pressure.

Study supported by the Cunningham Trust.

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

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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 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 (apnea index 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 1–1.5 water 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: pre treatment 54.0 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’s standard OSA treatment.

Abstract S19 Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post CPAP</th>
<th>p Value</th>
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<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 (4–20)</td>
<td>13 (4–20)</td>
<td>&lt;0.005</td>
</tr>
<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, Vitality</td>
<td>25 (0–100)</td>
<td>75 (0–100)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SF-36, Physical Limitation</td>
<td>30 (0–45)</td>
<td>55 (0–100)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SF-36, Mental Health</td>
<td>68 (4–100)</td>
<td>84 (28–100)</td>
<td>&lt;0.005</td>
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**THE MULTIDIMENSIONAL FATIGUE INVENTORY (MFI-20) IN OBSTRUCTIVE SLEEP APNEA (OSA): EFFECTS OF NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)**

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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 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 (67%, 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 PH > 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.

**PULSATION PRESSURE PREDICTS MORTALITY IN PULMONARY ARTERIAL HYPERTENSION**

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**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 (PHT). Of the 80 patients 19 (11 female, 8 male) had PPH, 18 (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<0.001) and Kaplan Meier survival curves revealed a 100% probability of survival at 2 years for PP<30 mmHg compared to 85% probability of survival for PP 30–40 and 46% 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.

**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.
Abstract S22 (A) Breathlessness and cardiac index. (B) Kaplan-Meier curve: breathlessness.

series but found the reality to be the opposite. We have previously found cardiac index (CI) to be an important predictor of survival so we correlated duration of breathlessness and CI.

Methods: We examined admission data in all our patients with PPH. We included demographic variables (sex, age) medical history (duration of breathlessness, NYHA class), haemodynamic data (mean pulmonary artery pressure, cardiac index). Kaplan-Meier (KM) survival curves and regression analysis were used to examine the correlation between these variables and survival.

Results: For our 25 patients with PPH, the probability of survival at 12 months after diagnosis was 100% for those 8 patients with a history of breathlessness ≥3 years and 51% for those with breathlessness <3 years (12 patients). There was also a positive correlation coefficient of 0.6 between cardiac index and duration of breathlessness (we excluded 2 patients with breathlessness longer than 6 years as outliers).

Conclusion: A longer duration of symptoms at diagnosis may represent a slower progression of disease and better survival prospects, reflected by the improved cardiac index.

Abstract S23 SCREENING FOR EARLY PULMONARY ARTERIAL HYPERTENSION IN PATIENTS WITH SYSTEMIC SCLEROSIS (SScPAH): RATIONALE FOR AN INVASIVE APPROACH

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Aims: To document the accuracy of echocardiography to identify early pulmonary hypertension (PH) in a high-risk Systemic Sclerosis (SSc) cohort, we identified 140 patients who have had echo and cardiac catheter within ±3 months of either investigation. Previous studies have documented under-estimation of tricuspid gradient (TG) compared to catheter results, with only a few studies reporting echo over-estimation of this parameter.

Method: Echo-estimated TGs and the catheter-measured TGs were correlated and a linear regression was derived to predict catheter-measured mean Pulmonary Artery Pressures (mPAPs) from echo estimated TGs.

Results: N=140, (F:M=119:21), mean age=56 (7) years. Haemodynamic parameters: mPA Systolic Pressure=47 mmHg, mPA diastolic Pressure=18 mmHg, mPAP=34 mmHg, mRAP=4 mmHg, mean echo estimated TG=42 mmHg. Echo-estimated TG showed a positive correlation with catheter-measured TGs in 140 patients (r=0.44, p<0.005). By linear regression, echocardiography was sufficiently accurate at moderate/ high pressures (echo TG ≥45 mmHg) identifying >80% of patients correctly. In contrast, at lower pressures where early diagnosis is critical, echo was less accurate—at both under-estimated the catheter-measured mPAPs in 30% and over-estimated the catheter-measured mPAPs in 32% of cases. The latter inaccuracy may lead to a potential for over-diagnosis in unaffected patients.

Conclusions: Though echo accurately identified a poor prognostic group of PH patients (mPAP >35 mmHg on cardiac catheter), reliability on the present technique to accurately identify early PH in an “at risk” SSc cohort is inadequate. In its current form, echo-estimated TGs demonstrate a tendency to both under and over-estimation at the lower end of the spectrum of pulmonary artery pressures—with the subsequent risk of exposing a patient with either no or mildly elevated pulmonary pressures to over-investigation. This latter finding is particularly relevant when applied to low prevalence PH populations where the false positive rates are proportionately higher and in such scenarios the accuracy of echo is further diminished.

Abstract 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 embolism (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/minute (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.

Abstract S25 OUTCOME AFTER PULMONARY THROMBOENDARTECTORGY FOR CHRONIC THROMBOEMBOLIC 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 infections despite 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 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 bronchodilation 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). Conclusion: 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 (800µg) 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 BUDERONIDE 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 quadratic 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 (p<0.05) 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

M. Masoli, M. Weatherall, S. Hold, R. Beasley. Medical Research Institute of New Zealand

**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, β2-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.

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 that the dose-response relation of fluticasone in children be studied in greater detail, we recommend that fluticasone should be routinely prescribed in children with asthma in doses of up to 200 µg per day.

### S30 STANDING DOWN INHALED CORTICOSTEROIDS IN ASTHMA: A RANDOMISED CONTROLLED TRIAL


**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. We aimed to determine whether a 50% reduction in the dose of inhaled corticosteroid could be undertaken in patients with chronic stable asthma, whilst maintaining 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 the inhaled corticosteroid dose (control) or a 50% reduction in their dose if they met criteria for stable asthma. After a 1 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 (0.1 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. Fluticasone was the next most efficacious treatment with similar improvements in morning PEF (17.5 l/min, 95% CI 4.0 to 31.0).

**Conclusions:** 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.

### S32 THE BRAVELUNG STUDY: BRONCHIOLITIS RSV AUDIT INTO VACCINATING FOR EARLY LUNGS

J. McCormick, M. Almaghrabi.

**Background:** Each winter season there are pervasive outbreaks of respiratory syncytial virus (RSV) bronchiolitis. Premature infants with CLD who are re-admitted with RSV utilise greater health service resources in the first two years of life after birth. Palivizumab, the humanised RSV monoclonal antibody has been shown to cause a relative reduction in readmission rates in infants born at <35 weeks group by 55%.

**Objectives:** To audit current protocols and practice into Palivizumab prescribing and Palivizumab funding in Scotland and Northern Ireland over the winter 2001—2002 season.

**Design:** Retrospective postal questionnaire.

**Methods:** Targeted questionnaire to lead neonatal or paediatric consultants in 27 units in Scotland and Northern Ireland following the end of the RSV season in late March/early April 2002.

**Results:** Response rate was 100% from units responsible for an estimated 72 400 births. 200 babies received a course of Palivizumab over the winter season (1 per 362 births) at an estimated cost of £490 000. Important regional variations were demonstrated; 1 in 179 babies born in Northern Ireland compared to 1 in 538 babies born in Scotland receive RSV prophylaxis. Six units using agreed guidelines prescribe 49% of the palivizumab in Scotland. Only 63% of respondents had an agreed protocol for palivizumab administration. Inclusion criteria for receiving palivizumab included; chronic lung disease (76%), home oxygen (71%), congenital cardiac abnormality (59%), specific gestation (53%), and consultant discretion (35%). The source of funding was described as Trust (50%), Health Board (32%), Directorate (14%) and 4% from winter pressures money. There were three reports of “breakthrough” RSV infection (3% of treated babies) following immunisation.

**Discussion:** Palivizumab is prescribed 3 times more in Northern Ireland than Scotland. Should UK guidelines for palivizumab administration (like the US) now be the goal?


### S31 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 (0.1 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. Fluticasone was the next most efficacious treatment with similar improvements in morning PEF (17.5 l/min, 95% CI 4.0 to 31.0).

**Conclusions:** 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.
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 252 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, 147 at 12 months, 103 at six years and 176 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 (n=0.24, n=65, p=0.05). Atopy at six years of age was positively associated with grade of AR χ²=6.2, n=93, p=0.03. Atopy at six months and at 11 years of age was positively associated with the grade of AR aged 11 years 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=32, 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=0.18, n=174, p<0.001) and current atopy (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). The TNFα secretion is influenced by single nucleotide gene polymorphisms in controls with a group of infant wheezers, and childhood asthma, the DRS at six years of age was related to the urinary cotinine concentration aged 12 months (r=0.45, n=32, 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.

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 controls. 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 SF, 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.

Conclusion: The LCI can be used to assess airway function from infancy to adulthood and has potential for monitoring CF lung disease.

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 asthma, as 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 all 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 2 (4.1–128) 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%.

In the wheezy infants, nasal TNFα levels were not influenced by RSV status. Levels were significantly lower in the presence of a TNF2 gene (p=0.006), which was the opposite of that expected, and there was a trend (p=0.08) to higher levels if the LTα A gene was present (as expected).

Conclusions: The TNF2 allele is associated with wheezing whereas the LTα G gene had a protective effect. Clearly the TNF gene polymorphisms may be important. We compared the TNFα and LTα polymorphisms in controls with a group of infant wheezers, and childhood asthma, as 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.
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 upper and lower respiratory tract secretions from infants with bronchiolitis and reach the airways along chemotactic gradients. Our aim was to compare the pulmonary chemotactant 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 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 for the first time the term and preterm infants ventilated with RSV bronchiolitis with that from a control group.

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 [OcTal 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 <6 using prescription data, 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 (BDPI (dry powder inhalers)).

Results: 1031 asthma patients identified who had been prescribed SFC, F, S 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 vs 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

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 influenced by emotional well-being. 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 anxiety and depression. Mean PaO2 was 8.6 (9.7), mean Pco2 5.2 (6.5). Oxygen saturation at rest was 93.4% (3.29) in patients. Percentage of predicted FEV1/FVC ratio was 45.8% (12.4). 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 = −2.98, 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); and immediate memory with PaO2 (r = 0.33, p<0.05); divided attention with PaCO2 (r = −0.34, p<0.05) and with FVC (r = −0.27, p<0.05). Independent t tests showed patients scored significantly higher than 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 hypoxic 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.

RESPONDER ANALYSIS OF PULMONARY REHABILITATION

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Introduction: Research has shown improvements in exercise tolerance (ET) and health related quality of life (HRQoL) after...
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 SGQR 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 statistically significant improvement in SWT mean change; 52 m (84.4) (p = 0.0001) and in SGQR; 5.2 (10.6) (n = 67). Responder analysis, based on a change >30m for SWT and >4 points for SGQR, showed that 37 patients were responders (R) for ET and 33 for HRQoL. 18 patients were characterised as non responders (NR). However both HRQoL and 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 SGQR was large; 12 (71.4)m and 12 (6.2) respectively. There was a significant difference for SGQR between R and NR; 57 (14.6) and 47 (14.4), p = 0.04 with Rs showing poorer QoL, similarly for depression 7.5 (3.2), 5.6 (2.4), p = 0.04. Rs showed a larger initial SWT compared to NR; 270 (139.2) and 217 (94.6) m although the difference was not statistically (p = 0.04). Baseline cycle ergometry (ECE), on four separate visits, Patient difference, R and NR, mean (SD): 1.1 (0.5) (n = 17) and 1.1 (0.5) (n = 15).

Conclusion: These data generate the testable hypothesis that greater exercise tolerance and poor HRQoL are associated with better improvements in pulmonary rehabilitation. Prospective randomised trials are warranted.

Abstract 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 exercise 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 (72M:28F, 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 cycle ergometry (ICE), and endurance cycle ergometry (ECE), on four separate visits. Patients were asked to name the predominant symptom limiting further exercise: shortness of breath (SOB), leg fatigue (LF), 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 therapeutic interventions on exercise-induced dyspnoea.

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

Abstract S41

ASSESSING THE DETERMINANTS OF INCREMENTAL SHUTTLE WALK TEST 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 measures 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.

Methods: Incremental shuttle walking test was carried out. Spirometric and anthropometric measurements were recorded including Forced Expiratory Volume (FEV1), weight, and four sites skinfold thickness. Perceived health status, personal cognitions of illness and affect were assessed using the Chronic Respiratory Disease Questionnaire (CRQ), 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 (SD) = 52.7 (15.6); fat free mass index (mean (SD) = 17.6 (2.6)); CRQ (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) = 18.0 (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=0.02)) 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.

Abstract 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 × weekly outpatient programme (OP) as part of “real life” clinical service.

Methods: After the 7 week outpatient programme, 30 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 Shuttle Walk Test (SWT) and St George’s Hospital Respiratory Disease Questionnaire (SGQR) were made at the end of the 7 week outpatient period and after the 6 month period (n = 25).

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

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.

Abstract 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
known which aspects of PR (e.g. exercise versus education versus social support) are found to be most helpful by 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 reduced fear of dyspnoea, leading to new activities; perceived 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 extra-curricula 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

**S44 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 pneumonia 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 case (n=133). 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 Epi-Info 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, 0.32; 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 0.59 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.

**S45 INCREASED SERUM LEVELS OF MUCIN KL-6, SURFACTANT PROTEIN-D(SDP) AND ANTIBODY TO DIETARY ANTIGENS SUGGEST ALTERED MUCOSAL PERMEABILITY AMONG PIGEON FANCYERS**

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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 immuno- assay in 60 pigeon fanciers.

**Results:** The serum KL-6 levels in pigeon fanciers was (median, IQR) = 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 not 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.

**S46 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 lead 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 [336% above control levels (n=3)]. 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=3). 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 [3H]-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 upregulate 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.

**S47 COLLAGENASE 1 (MATRIX METALLOPROTEINASE 1, MMP1) IS INVOLVED IN THE DEVELOPMENT OF CRYPTOGENIC FIBROSING 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.

**Spoken sessions iii15**
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 25 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.

**Abstract S49**

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**A DOUBLE BLIND RANDOMISED PLACEBO CONTROLLED PILOT STUDY OF SEPTRIN IN THE TREATMENT OF CRYPTOGENIC FIBROSING ALVEOLITIS**

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**Background:** 14 patients with end stage pulmonary fibrosis were openly treated with oral Seprtin. All made a dramatic clinical recovery and were discharged from the natural home. This prompted a double blind randomised placebo controlled pilot study in earlier stages of the disease when cough, dyspnoea and oxygen desaturations on exercise were present.

**Method:** 20 patients with pulmonary fibrosis (aged 49–84 years) underwent a detailed assessment of arterial blood gases, lung function, progressive shuttle walking tests with oxygen saturation monitoring, quality of life and diary cards etc. Randomisation was to Seprtin or identical placebo for 3 months followed by 6 weeks of pulmonary rehabilitation (rehab) before decoding. 2 weekly reassessments of shuttle walk (etc) were made throughout the study.

**Results:** The first 16 cases have been decoded (8 Seprtin, 8 placebo). The remaining patients will complete by September 2002.

**Conclusion:** Seprtin produced a significant improvement in shuttle walking distance with improved arterial oxygen values, lung volumes and quality of life assessments. A fully decoded study by October 2002.

**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/µl respectively for 0.2 and 0.4 ml/kg OA compared to 0.2 (0.03) in the PBS control group). Albumin was also detected in BALF from all OA-treated animals (0.2 (0.0) µg/µl). Total cell numbers (1.1 (0.3) µg/µl) increased for the two doses compared to 0.4 (0.1) x 10^6/µl in control and the marker of cell damage, lactate dehydrogenase (LDH) activity (156 (40) and 446 (117) U/l compared to control 49 (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.

**CHARACTERISATION OF A MURINE MODEL OF OLEIC ACID-INDUCED ACUTE LUNG INJURY**


1 Department of Gene Therapy, Faculty of Medicine at the National Heart and Lung Institute, Imperial College, London, UK; 2 Department of Anaesthetics and Intensive Care, Faculty of Medicine at the Chelsea and Westminster Hospital, Imperial College, London, UK

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**THE DEVELOPMENT OF LUNG FIBROSIS IN TRANSGENIC TGF-β1 MICE**

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TGF-β1 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 TGF-β1 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 TGF-β1 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 TGF-β1 bioassay). We then analysed their lungs histologically after bleomycin injection (3000 IU intraperitoneal), and after administration of herpesvirus (4 × 10^5 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 0–5, based on an previously published grading system (Ashcroft et al. J Clin Pathol 1988;41:467–70).

The Tr+ mice were confirmed to have higher circulating levels of active TGF-β1 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 TGF-β1 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 TGF-β1 into lung tissue. Therefore lung injury may be of primary importance and individual susceptibility a secondary phenomenon.
compared to control. OA treatment resulted in substantial hypoxia (PaO₂, at Fco₂, 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 density parameters revealed a 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.

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 inhibit apoptotic cell death in neutrophils cultured in vitro. This may be of physiological importance given the significant role of hypoxia in tissue oxygenation 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 +/- 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 apoptosis in human neutrophils from 5% 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-1α and TNFα. Furthermore, the hypoxic inhibition of neutrophil apoptosis was unaffected by the TLR kinase inhibitors LY294002 (10 µM), oxapaxidoxin or cytochrome c, and was independent of extracellular apoptosis-inducing factors.

Discussion: 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. Further studies are required to identify the oxygen sensing mechanisms that are operative in vivo and to determine the mechanisms by which hypoxia can inhibit neutrophil apoptosis.

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

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ARDS is a lung condition commonly associated with septic. Recently the toll-like receptor family has been 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-signal in response to LPS with TLR-4. TLR-2 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 isolated 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 (above isotype control) on monocytes was 15.44 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 expression. However, monocytes from ARDS patients had significantly lower levels of TLR-2 mRNA (83% of 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 have a high expression 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 IPS for TLR-4 receptor ligation and signalling.

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 versus controls in plasma (45.9 [27.9] ng/ml vs 23.6 [13.4] ng/ml, p<0.002) 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-8 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 survivors 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.

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

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Previous work in our laboratory suggested a role for VEGF in the pathogenesis of ARDS [Thickett DR et al. Am J Resp Crit Care Med...
Asthma mechanisms I

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

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**Introduction:** Transforming growth factor beta (TGF-β) is an immunomodulatory cytokine regulating the proliferation and differentiation of various cell types. It also contributes 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 rt-PCR, 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 TGF-β1,-2,-3 were obtained from R&D Systems. TGFβ isoforms mRNA were measured by rtPCR using primers designed from the human sequences of TGFβ1-3 genes and GAPDH as the control. The presence of bioactive TGFβ in HASMC-conditioned medium was determined using a bioassay that is based on the ability of TGFβ to inhibit proliferation of the Mv1Lu cells. Immunohistochemical localisation of TGFβ1-3, in normal lung sections was assessed using avidin-biotin-peroxidase and antibody to the TGFβ Biologos.

**Results:** Messenger RNA transcripts for TGFβ1-3 were all expressed in the HASMC. The conditioned medium shows presence of a bioactive TGFβ 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 TGFβ1 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 TGFβ bioactivity was significantly abrogated by panspecific antibody to TGFβ. Immunochemistry showed that all three isoforms of TGFβ were detected in the epithelial cells, smooth muscle cells, and macrophages.

**Conclusion:** This study demonstrates the expression of TGFβ isoforms in the lung, and suggests that autocrine/paracrine release of TGFβ 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

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Airway smooth muscle infiltration by mast cells is a key feature of asthma and non-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 unknown.

We have undertaken a comparative immunohistochemical study in bronchial biopsies from 14 subjects with asthma, 10 with eosinophilic bronchitis and 8 normal control subjects 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 (ADP9)+ 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 (0–1.7), 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+ (ADP9) in the airway 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 (ADP9).

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 activators 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 10nB10(M), for 1 hour prior to lipopolysaccharide (LPS) stimulation. Secreted cytokines (GM-CSF, TNF-α, IL-1ra and IL-10) were quantified by ELISA.

**Results:** Addition of formoterol or salmeterol to steroid gave greater suppression of LPS-induced GM-CSF and TNF-α release 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 IL-1α and TNF-α release. The action of the LABA differed with IL-10, 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 cytokines towards inflammatory cytokines.

This study was sponsored by Innovanta Biomed Ltd.

**S58** LEUKOTRIENE RECEPTORS ON HUMAN EOSINPHILS

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CysteinyiHeukotrienes are potent bronchoconstrictor mediators and eosinophilic toxins released by mast cells and eosinophils within the airway. These actions are thought to be mediated by CysLT receptors, with vascular effects mediated by CysLT 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 CysLT, than for CysLT, receptors, with vascular effects mediated by CysLT receptors. CysLT receptor expression on 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 CysLT, than for CysLT, receptors, with vascular effects mediated by CysLT receptors.
during 22 hours culture from a median fluorescence intensity (MFI) of 4.96 (0.50) to 2.87 (0.23) arbitrary units (p<0.009; n=9). This decline was not observed in the presence of dexamethasone (1µM), with an MFI value of 4.01 (0.36) at 22 hours (p=0.044 v untreated). Theophylline (0.1mM) provided similar protection but this did not achieve statistical significance (p=0.056). In contrast to CysLT1, no CysLT2 expression was detectable by flow cytometry on the surface of live eosinophils, although these cells transcribed mRNA for CysLT2. The signal transduction pathways that lead to chemotaxis of human eosinophils are incompletely understood but are believed to involve the LT-synthesising enzymes (Cowburn, et al. J Immunol 1999;163:456–65). Secondly, while CysLT1 mRNA may be processed, the receptor protein does not appear to be expressed on the surface of blood eosinophils from healthy donors.

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To understand the mechanisms underlying eosinophilic airways inflammation in asthma, it is necessary to characterise the chemotaxants mediating eosinophil recruitment. The CC chemokines eotaxin (CCL11), eotaxin-2 (CCL24), RANTES (CCL5) and monocyte chemotactic protein-3 (MCP-3) are potent eosinophil chemoattractants and are believed to play an important role in eosinophilic inflammation (Kita & Gleich. J Exp Med 1996;183:2421). Of these, eotaxin and eotaxin-2 act exclusively via the CC chemokine receptor CCR3 upon a restricted set of cells: namely eosinophils, basophils and Th2 lymphocytes. We have investigated the role of eotaxin in the eosinophil chemotactic activity of asthmatic airway secretions using a specific anti-eotaxin antibody, CAT-213.

Sputum samples were collected from 60 volunteers: 11 healthy controls, 12 mild asthmatics, 12 stable moderate asthmatics, 12 unstable moderate asthmatics and 12 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 the presence of untreated supernatants and eotaxin-neutralising antibodies.

Eotaxin expression was detectable by flow cytometry on the surface of autologous blood monocytes and T-cells. We conclude firstly that dexamethasone may upregulate eosinophil chemotactic activity of asthmatic sputum.

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The aim of this study was to use a case control design to describe the characteristics of CF patients isolating SM in sputum, to assess risk factor for acquisition of SM and to assess clinical outcomes. Data were collected on patients and controls between 1991 and 1999. A control patient had never isolated SM in sputum and was matched for age, sex and FEV1. The following data were collected: FEV1, FVC, height and weight; sputum culture and antibiotic sensitivity; antibiotic use; oral steroid use.

Results: 63 patients isolated SM at least once. Controls were found for 52 patients. Prevalence of SM rose from 3.3 to 15% by 1999. Isolation of Aspergillus fumigatus (AF) was much more frequent in SM patients than controls, 51% vs 8.9% (p=0.001, OR 5.9 [95% CI 2.0–17.8]. The effect of AF was independent of steroid use. Past acquisition there was no difference between the two groups in mortality, antibiotic use, lung function or nutritional status. Antibiotic treatment had no impact on future isolation of SM.

Conclusions: This is the first documentation of an association of SM with AF isolation. We also can reassure patients that SM acquisition is unlikely to cause accelerated decline in clinical status.

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The signal transduction pathways that lead to chemotaxis of human eosinophils are incompletely understood but are believed to involve protein tyrosine kinase(s) and MAP kinase(s), but not protein kinase C (Schweizer et al. J Leukoc Biol 1996;59:347; Kampen et al. Blood 2000;95:1911). As MAP kinase activation by eotaxin in human eosinophils has been shown to occur downstream of phosphatidylinositol 3-kinase (PI-3K) activation (Miki et al. J Leukoc Biol 2000;67:117), we investigated a possible role for PI-3K in the induction of eosinophil chemotaxis using the inhibitors wortmannin and LY294002 in human eosinophils stimulated with platelet-activating factor (PAF) or eotaxin (CCL11).

Eosinophils were isolated from the blood of atopic, non-asthmatic donors and chemotaxis was evaluated in a fluorescence-based 96-well blind-chamber assay. Calcein-labelled eosinophils (2H10) were pre-incubated for 30 min at 37°C in the absence and presence of wortmannin (0.1–100 nM) and located in the upper wells of the chemotaxis chamber. Migration through 8-µm pore-size PVC-coated polycarbonate filters in response to PAF or eotaxin (both at 30 nM in the lower wells) was measured after 1 h as cell-associated fluorescence (λex=485 nm, λem=530 nm) in the lower wells.

PAF and eotaxin caused chemotaxis of eosinophils (geometric mean 19,140 [14,060–26,060] and 27,010 [15,310–47,640] cells well−1, respectively, above the background level of migration; n=12). Wortmannin caused concentration-dependent inhibition of PAF-induced eosinophil chemotaxis (IC50=1.24 nM [0.092–16.6 nM]; n=6), with significant inhibition observed at 1 nM (P<0.0001), while responses to eotaxin were inhibited substantially less potently (IC50=17.6 nM [1.06–292 nM]; n=6), with significant inhibition observed only at 100 nM (P<0.05). LY294002 also inhibited PAF-induced chemotaxis (IC50=0.76 µM [0.026–22.1 µM]; n=6) but had no effect on responses to eotaxin (>50% inhibition at 100 µM; n=6).

We conclude that, although PAF and eotaxin both induce MAP kinase activation and chemotaxis in human eosinophils, PAF-induced chemotaxis is dependent upon the activation of PI-3K while the response to eotaxin involves PI-3K to a much lesser extent. This may indicate alternative pathways of activation of MAP kinases and chemotactic responses.

Ongoing management issues in cystic fibrosis


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.

Methods: The aim of this study was to use a case control design to describe the characteristics of CF patients isolating SM in sputum, to assess risk factor for acquisition of SM and to assess clinical outcomes. Data were collected on patients and controls between 1991 and 1999. A control patient had never isolated SM in sputum and was matched for age, sex and FEV1. The following data were collected: FEV1, FVC, height and weight; sputum culture and antibiotic sensitivity; antibiotic use; oral steroid use.

Results: 63 patients isolated SM at least once. Controls were found for 52 patients. Prevalence of SM rose from 3.3 to 15% by 1999. Isolation of Aspergillus fumigatus (AF) was much more frequent in SM patients than controls, 51% vs 8.9% (p=0.001, OR 5.9 [95% CI 2.0–17.8]. The effect of AF was independent of steroid use. Past acquisition there was no difference between the two groups in mortality, antibiotic use, lung function or nutritional status. Antibiotic treatment had no impact on future isolation of SM.

Conclusions: This is the first documentation of an association of SM with AF isolation. We also can reassure patients that SM acquisition is unlikely to cause accelerated decline in clinical status.

S61 STENOTROPHOMONAS MALTOPHILIA ACQUISITION IN CYSTIC FIBROSIS; A COMPLICATION OF ASPERGILLUS FUMIGATUS?

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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 fingerprinting 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 the Sheffield MR strains already are known to become multiresistant from the paediatric unit, but the Sheffield strain is our own and is transmissible. If MR confers poor prognosis we believe these groups should be segregated from each other.

METHOD:

A retrospective review of case notes using the OGTT and Hba1c databases. 242 patients were identified but 91 patients excluded due to pre-existing CFRD at 01/03/2000 (n=52), referred after 01/03/00 (n=13), care transferred to other centre (n=18), post-transplant (n=7), not CF (n=1).

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.


RE-AUDIT OF THE SCREENING PROTOCOL FOR CYSTIC FIBROSIS RELATED DIABETES (CFRD) IN AN ADULT CENTRE

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INTRODUCTION: The average age of onset of CFRD is 18–21 years and is associated with a 6-fold increase in mortality and associated comorbidity. Yung et al described annual oral glucose tolerance testing (OGTT) as being time and resource consuming for patients and staff. An earlier audit at our centre, using these selective screening criteria for OGTT testing found that, the identified incidence of 1.9% was significantly less than the expected (4–6%) and concluded that only 52% of patients with CFRD would have been identified. Hence all patients were offered routine annual OGTT testing.

AIMS: To assess whether all patients received annual OGTT between 3.00–3.01. To assess the true incidence of CFRD at the Centre. To identify the CFRD patients who would have been “missed” if the old screening protocol were still in place. To calculate the sensitivity and specificity of the selection criteria in our population.

METHOD: A retrospective review of case notes using the OGTT and Hba1c databases. 242 patients were identified but 91 patients excluded due to pre-existing CFRD at 01/03/2000 (n=52), referred after 01/03/00 (n=13), care transferred to other centre (n=18), post-transplant (n=7), not CF (n=1).

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 1998–2002. 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. Group C: 17 non-CF/non-bronchiectatic (emphysema, fibrosing alveolitis or obliterative bronchiolitis) 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 cardiopulmonary bypass times; post-op haemorrhage; times to extubation, ITU discharge and hospital discharge; FEV1 at 6 months; 30 day mortality; and adhesions 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 obliterative 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.

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PULMONARY ARTERY PRESSURE AND RIGHT VENTRICULAR FUNCTION IN CYSTIC FIBROSIS ADULTS

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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 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 by measurement of RV dimensions and tricuspid long axis motion (TLAM) and diastolic function via measurements of RV diastolic function 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) v 90.1 (9.7) (p<0.001) and FEV₁ percentage predicted (FEV₁ %) 47.0 (21.7) v 98.1 (9.8) (p<0.001) respectively. 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. TLAM(cm) was reduced in CF patients compared to controls 21.5 (0.4) v 25.0 (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 v control): Avel(cm/sec) 45 (13) v 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<0.001; r=-0.432, p=0.001) and TLAM (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, kjoule (kJ)/kg/min) was calculated from breath by breath O₂ uptake and CO₂ output measured with a mask (K4b, 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 (46.4 (29.9 to 60.1) and 21.6 (10.9 to 32.3) seconds, p=0.02) and stepping (70.7 (47.2 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). FMFI was inversely related to EE during HG, (r=−0.38, p<0.005).

Adults 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

N.M. Wilson¹, J.C.W. Mak², J. Lampriil, H. Bilakiar, J.R. Clarke, A. Bush, M. Fischer-Semenov¹, ²Department of Paediatrics and Respiratory Medicine, Royal Brompton Hospital, Imperial School of Medicine, London, UK; ³Department of Child Health, University of Leicester, Leicester, UK

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 at 10 yr. VmaxFRC varied according to aa27 genotype (ANOVA p=0.023). It was significantly increased in the homozous 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 homozous 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 EMPIEYA

K.M. Eastham¹, R. Freeman¹, A. Kearns², G. Eltingham³, J.P. Leeming³, J. Clark³, D.A. Spencer¹.¹Freeman Hospital, Newcastle Upon Tyne, ²Newcastle Public Health Laboratory, ³Bristol Public Health Laboratory, ⁴Newcastle General Hospital, Newcastle Upon Tyne, UK

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

 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.

 Methods: 43 pleural fluid specimens, negative for pneumococcus beyond 4 years was strongly related to atopy and increased BR at 10 yr.

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

<table>
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<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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</table>

*p<0.05; **p<0.01

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Results: The median age was 5.6 years (0.6–16.9 years). All pneumococcal DNA positive specimens were penicillin sensitive.

Conclusions: Pneumococcus is the major pathogen in childhood empyema, accounting for 75% of culture negative cases. Capsular antigen detection indicates that 63% of are serotype 1, paralleling culture-based studies. These data have implications for vaccine development strategy, as the new 7-valent pneumococcal vaccine does not prevent against serotype 1. Penicillin resistance does not appear to be a problem in our population.


Abstract S68

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<th>Bx MEX</th>
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<td>1.12*</td>
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</table>

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

Abstract S69

Respiratory disease in chronic granulomatous disease

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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. 85 episodes of probable pneumonia were recorded with x ray changes documented in 65 (77%) of these. Organisms were isolated in 37 cases (44%). However Staphylococcus aureus and Burkholderia, respiratory pathogens previously reported in other series, only accounted for 2 cases. Aspergillus was isolated in 10 and suspected in a further 12 cases. Of the 11 documented cases of lung abscess, Staphylococcus species and Aspergillus species were isolated in 4 cases, however Streptococcus milleri was also isolated from 2 patients. 4 patients suffered from their first episode of pneumonia 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.


Exercise limitation in CF and non-CF bronchiectasis

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

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 testing using cycle ergometry and respiratory mass spectrometer were performed at a time of disease stability. We measured effective pulmonary blood flow (Bx), 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 10.6–17.1) median FEV1, 74% predicted (range 47–90%). Data are expressed as mean ± s scores derived from normal values at rest and at maximum exercise (MEX) in 106 normal children.

Conclusions: In both groups Geff 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 Geff 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 ESTIMATES OF PLETHYSMOGRAPHIC FRC EXCEED THOSE BY GAS DILUTION IN INFANTS WITH CYSTIC FIBROSIS (CF) BUT NOT IN HEALTHY CONTROLS

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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\(_{\text{pleth}}\)) and multiple breath inert gas washout (FRC\(_{\text{mbw}}\)) in infants with recently diagnosed CF and healthy control infants.

**Methods:** 21 infants with CF, median age (range) 36 (10–83)w, and 20 healthy control (HC) infants 42 (5–91)w were studied during quiet sleep. FRC\(_{\text{pleth}}\) was measured using a respiratory mass spectrometer with SF\(_6\) 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\(_{\text{mbw}}\) was measured immediately afterwards according to ERS/ATS guidelines (ER/ATS 2001; 17:302–12) using commercially available equipment (Jaeger MasterScreen BabyBodyplethysmograph).

**Results:** The mean within-subject coefficient of variation for FRC\(_{\text{pleth}}\) and FRC\(_{\text{mbw}}\) 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\(_{\text{mbw}}\) when comparing HC and CF. In infants with CF, however, the FRC\(_{\text{mbw}}\) was significantly elevated not only compared to HC (p=0.001), but also compared to FRC\(_{\text{pleth}}\) 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 sensitivity, 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 (nmol/L) causing 2 (C2) and 5 (C5) coughs, (2) cough visual analogue score (VAS; 0–100 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 (physiological, 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) mm; logC2: 0.57 (0.08); logC5: 1.41 (0.18) nmol/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 (8.8). 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 B0.34 respectively). In conclusion, we found no relationship between quality of life or symptom scores and capsaicin cough reflex sensitivity in patients with chronic cough. Our results suggest factors other than a heightened cough reflex are important in how a patient perceives the severity of their cough, or how it impacts on their quality of life. These measures assess different aspects of cough and therefore may provide complimentary 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 an isolated chronic cough using a KoKo Digidoser and 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 capsain concentration that causes 2 coughs (C2) SD 1.2 (0.8) and 5 coughs (C5) SD 2.7 (1.8) µmol/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 µmol/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 0.3 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) µmol/L; intraclass correlation coefficients 0.9 and 0.9 respectively), and patients with chronic cough (mean of difference [within subject SD]: logC2: 0.1 (0.2), logC5: 0.3 (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 discriminatory test. We have also demonstrated an effect of gender but not age on capsaicin cough reflex sensitivity measurement highlighting the importance of matching subjects when making comparisons using this test. Coughs capsaicin 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 in 14 healthy subjects and 14 subjects with a chronic cough (cough subjects were predominantly female (81%) and the cause of cough were idiopathic chronic cough (11), cough variant asthma (1), rhinitis (1) and rhinitis and gastro-oesophageal reflux (1). Glottic stop sensitivity 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
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 matched healthy subjects (mean glottic reflex sensitivity threshold: 483 v 1029 ppm; mean difference 546ppm, [95% Confi- dence Interval 137 to 954], p=0.01; logC2: 0.3 v 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=0.006). 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.


SMOKING, SALBUTAMOL, AND THE COUGH REFLEX

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Background: Smokers have an increased prevalence of chronic cough, but the mechanisms of GOR related cough are not fully understood.

Aim: To determine the association between cough and reflux 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 (IGR) 55 (49–62) yr with cough duration 8 (1–5–10) yr underwent 24-h pH monitoring during Ambisense® cough and reflux events were recorded. GOR related cough was diagnosed when pH<4 was recorded for >4% of total time and when cough improved with subse- quent antireflux therapy. A reflux event was defined as a drop of pH<4 for >12 sec. Cough was considered associated with reflux when it occurred within 5 min from reflux.

Results: 29 patients had GOR related cough. The other 31 patients had normal 24-h pH monitoring, and cough was either due to asthma or rhinosinusitis or was idiopathic. The total number of coughs did not differ significantly between patients with GOR (9 [5–17]/24 hr) and without GOR (8 [6–16]/24 hr). Patients with GOR related cough had 20 (10–31)% of coughs associated with reflux, compared with 0 (0–7)% in patients without GOR (p<0.001). In patients with GOR related cough, 7 (1–10)% of total reflux events occurred within 5 min after cough, compared with 1 (0–2)% in patients without GOR (p<0.001). In patients with GOR related cough 6 (4–6)% of reflux events occurred within 5 min after cough, compared with 3 (0–2)% in patients without GOR (p=0.002).

Conclusions: In GOR related chronic cough, reflux and cough events are frequently associated. In patients with other causes of chronic cough, in contrast, this association is infrequent.

ASSOCIATION BETWEEN COUGH AND REFLUX: EVENTS IN PATIENTS WITH CHRONIC COUGH WITH AND WITHOUT GASTRO-OESOPHAGEAL REFLUX

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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 reflux 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 (IGR) 55 (49–62) yr with cough duration 8 (1–5–10) yr underwent 24-h pH monitoring during Ambisense® cough and reflux events were recorded. GOR related cough was diagnosed when pH<4 was recorded for >4% of total time and when cough improved with subse- quent antireflux therapy. A reflux event was defined as a drop of pH<4 for >12 sec. Cough was considered associated with reflux when it occurred within 5 min from reflux.

Results: 29 patients had GOR related cough. The other 31 patients had normal 24-h pH monitoring, and cough was either due to asthma or rhinosinusitis or was idiopathic. The total number of coughs did not differ significantly between patients with GOR (9 [5–17]/24 hr) and without GOR (8 [6–16]/24 hr). Patients with GOR related cough had 20 (10–31)% of coughs associated with reflux, compared with 0 (0–7)% in patients without GOR (p<0.001). In patients with GOR related cough, 7 (1–10)% of total reflux events occurred within 5 min after cough, compared with 1 (0–2)% in patients without GOR (p<0.001). In patients with GOR related cough 6 (4–6)% of reflux events occurred within 5 min after cough, compared with 3 (0–2)% in patients without GOR (p=0.002).

Conclusions: In GOR related chronic cough, reflux and cough events are frequently associated. In patients with other causes of chronic cough, in contrast, this association is infrequent.

Issues in non-invasive ventilation

A SURVEY OF HOME MECHANICAL VENTILATION IN THE UK

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As part of a European-wide Project, a survey of custom and practice in Home Mechanical Ventilation (HMV) was carried out in the UK. 80 known and possible HMV centres were targeted with initial requests, of which 65 responded. 13 of these did not have any HMV users. Full surveys were received from 47 centres (at least 70% response rate). 7 of these were paediatric centres. The answers reflected the situation on the 1st July 2001. A total of 2842 HMV users were identified in the
Severe respiratory acidosis \( ([H^+] > 55 \text{ mmol, pH} < 7.26) \) predicts mortality in exacerbation of chronic obstructive pulmonary disease (COPD). Non-invasive ventilation (NIV) is an effective alternative to intubation and mechanical ventilation and is justified in milder respiratory acidosis \( (pH 7.35 \text{ to } 7.26) \) associated with exacerbation of COPD. To assess use in the first year since introduction \( [\text{to December 2001}] \), we have retrospectively audited our management of patients with hospital discharge codes for COPD or respiratory failure. Where results from arterial blood gas (ABG) samples were available \( (n=239, 46\%) \), 60 had type 2 respiratory failure complicated by acidosis. Of the others, 74 had type 1 respiratory failure. 48 had compensated type 2 respiratory failure, 10 had metabolic acidosis, 2 had hyperventilation, and 45 had no respiratory failure. Of those with respiratory acidosis \( (n=60) \), 15 were excluded from NIV, reasons included patient preference, respiratory depressant drugs with pain, pneumothorax, brainstem stroke, and immediate self-correction of acidosis. Of the remaining 45, 24 had a review by the anaesthetists (ITU) who further excluded four as inappropriate, offered NIV to 17 patients and intervention with mechanical ventilation to three. Of those initiated on NIV, 11 satisfied criteria for mild acidosis with six others more aci- 

**RESULTS:** 

Whilst minute ventilation increases linearly with set pressure, minute leak increases exponentially, particularly above 20cmH\(_2\)O. Some patients will benefit from increased minute ventilation at higher pressures, but may suffer intolerable leak.

JT is funded by NHS Northern & Yorkshire Executive.

**FACTORS WHICH MIGHT INFLUENCE MEDIUM TERM PROGNOSIS IN SUBJECTS WITH ACUTE VENTILATORY FAILURE TREATED WITH NON-INVASIVE VENTILATION**


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 \( (\text{Mean age 72 (7) years, 24 males, 38 main diagnosis COPD, mean pre NIV arterial blood gases } pH 7.23 (0.09), PaCO\(_2\) 72 (2.4), Paco\(_2\) 11.8 (2.5), bic 35 (8) \text{ [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 FEV\(_1\), reported exercise tolerance, diagnosis, etc were compared between those still alive and those dead at any time point, 2–3 years post treatment and one year post treatment, using Wilcoxon an \& \chi^2.

Survival at one year was 60%. There was no difference between survivors and non-survivors in terms of age \( (71 (8) \text{ vs } 73 (7) \text{ p}=0.3, \text{ sex (53 vs 54% males), mean } \% \text{ predicted FEV}1 45 (21) \text{ vs } 35 (16) \text{ p}=0.08 \text{ or severity of initial ventilatory failure } pH 7.24 (0.1) \text{ vs } 7.23 (0.08) \text{ p}=0.22} \text{ or by diagnosis (33 of those still alive } 66% \text{ of dead subjects did not have COPD as the cause of their ventilatory failure, p=0.08). The only factor which significantly varied between the two groups was reported exercise tolerance 150 (230) \text{ vs } 54 (79) \text{ metres, p=0.016. At the end of a mean follow up of 26 months } 45\% \text{ of subjects were still alive. There was no difference between those who survived and those that did not in terms of sex or initial blood gases } pH (p=0.22), \text{ Paco}_2 (p=0.14), \text{ bic (p=0.5). However the difference almost reached significance in terms of age 70(6.7) } \text{ vs } 73.5 (7) (p = 0.057 and } \% \text{ predicted FEV}1 4.5 (17) \text{ vs } 39 (7) \text{ p=0.058. There were significant differences in terms of reported exercise tolerance 180 (255) \text{ vs } 57 (84) \text{ metres, p=0.022 and diagnosis, all patients who did not have COPD being dead at the end of follow up compared to } 45\% \text{ of patients with COPD being dead. In summary in the medium term survival in this group was related to the subjects usual chronic state} \)
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.

**S83** 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 orthopnoea due to respiratory muscle weakness. Maximum inspiratory pressure (Pmax), Pco2, Pao2, bulbare 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, Pmax, Pco2, bulbare score, and limb and axial muscle score were evaluated by univariate and multivariate analysis. Multivariate analysis 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=0.042) and upper limb muscle score (r=0.67, p<0.05), and showed a trend towards correlation with ALSFRSr bulbare 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 (p<0.05).

**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.

**S84** 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 run by a critical care outreach team. However, patients referred to them were documented as not for intubation/ventilation (n=26; 74%), of whom 12 (46%) survived. Seven of nine patients (78%) for full reabsuscitation 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 those 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

**S85** EFFECT OF NEUTROPHIL PRIMING AND ACTIVATION ON 18F-DIDEOXYGLUCOSE (18FDG) UPTAKE IN VITRO

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Priming describes up-regulation of the neutrophils response to a secretagogue agonist following prior exposure to a priming agent. 18FDG is used in PET to identify areas of infection and inflammation. This study addresses the mechanisms underlying 18FDG accumulation in vitro in human neutrophils and monocytes. Time courses of 18FDG accumulation for both reversible priming peptide platelet activation factor (PAF) and priming/activating agents GM-CSF and IMLP were undertaken. 18FDG 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 supernatant were compared.

**Results:** Neutrophils took up more 18FDG than monocytes. In neutrophils incubated for 35 mins 18FDG 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. 18FDG 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 18FDG 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 18FDG 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 18FDG accumulation in line with their demonstrated priming efficacy.

**S86** DIMINISHED NEUTROPHIL RESPONSES IN MICE LACKING THE REGULATORY SUBUNIT OF PHOSPHOINOSITIDE 3-HYDROXYKINASE (p13Kγ)

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From infection is conferred by the coordinated and regulated response 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) and bronchiectasis. 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 (p13Kγ). The isoform p13Kγ, activated by G-protein linked agonists such as activated complement (C5a) and bacterial formylated peptides (IMLP), is thought to mediate 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 p13Kγ. Analysis of...
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 bronchovascular lavage (BAL 3×30mL) and large airway endobronchial biopsy.

Results: BAL showed a significant neutrophilia (4%±0.8) compared to normal controls (n=34) (1.6%±0.2) (Means±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.
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 now shown that CS stimulated the transcription and release of EGFR ligands from NCI-H292 bronchial epithelial cells (Richter, et al. Am J Respir 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 epithelia such as chronic inflammation and goblet cell hyperplasia.

EGFR ligands are cleaved from transmembrane precursors by Zn2+-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;2:297–322). 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. We then 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 immunosay to determine the concentration of EGFR 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 EGFR 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 EGFR 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 COI**

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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 pathogens. As sepsis develops, endothelial and vascular smooth muscle become activated to express 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 hyporesponsive 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 to stimulate nitrite, measured by Griess assay) in RAW 264.7 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).
HEM OXYGENASE INDUCTION IN ISOLATED NEUTROPHILS STIMULATED WITH LPS, OR FROM PATIENTS WITH SEPSIS 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 induction 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 (10µg/ml) in 6 well plates at a concentration of 5 x 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 x 10⁶ cells were harvested and lysed. HO-1 and HO-2 protein expression was measured as before.

Contrast: in vivo, HO-1 levels were elevated 8 hours after LPS by comparison to baseline and unstimulated cells (199.2% ± 42%, n=9, p<0.05). HO-1 levels in cells 16 and 24 hours after LPS were not significantly different from levels in untreated cells because of non-specific induction of HO-1 in the unstimulated cells (n=11, 0.9 (21.1), n=9 and 1.14 (0.55), n=9 respectively). HO-2 levels were not significantly altered at any of the timepoints between the LPS stimulated and non-stimulated cells.

Conclusion: HO-1 production can be induced by LPS in neutrophils, and is also present in neutrophils from patients with septis. However, HO-1 levels in septic patients are lower than controls. The anti oxidant potential of HO-1 may therefore be reduced in this 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 SERIOUS 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 bacterial load 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 38 (16.8), FVC 2.57 (0.93) l, Paco₂ 10.2 (1.1) kPa, Paco₂ 6.22 (0.9) kPa, age 67.4 (11.8) yrs, m 40, 28 current smokers] completed daily diary cards of respiratory symptoms were followed up for 12 months and reported symptoms of exacerbation to our study team. Sputum was initially sampled in the stable state and later within 48 hours of the onset 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, (11%) 31% of exacerbation samples (2), Streptococcus pneumoniae (11%) 9%, (2) 11%, Haemophilus parainfluenzae (11%) 12.5%, (2) 2%, Branhamella catarrhalis (11%) 7%, (2) 13% and Pseudomonas aeruginosa (11%) 5%, (2) 5% with Non specific growth in (1) 48% and (2) 25%. The mean [SD] stable bacterial load was 10⁹ (10³) cfu ml⁻¹ rising to 10¹⁰ (10⁹) cfu ml⁻¹ at exacerbation p=0.001. The mean [SD] stable FEV₁ was 0.99 (0.38) l falling to 0.90 (0.31) l at exacerbation. The percentage fall in FEV₁ at exacerbation was related to the rise in airway bacterial load rho=0.411 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 increased at exacerbation. Exacerbation severity was 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.

THE 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 fewer 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 sarcina, tuberculosis or non-CAP were excluded.

Results: 81 subjects [average age 78 yrs, 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. Radiological and clinical diagnoses agreed in only 38 cases (Pneumonia agreed present in 11, absent in 27. Kappa 0.041, very poor agreement).

Core clinical diagnostic features 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 guidance 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.

Procedures in respiratory medicine

BTS GUIDELINES FOR BRONCHOSCOPY: PHYSICIAN 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 [2]. 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...
physicians (2%) measured blood gases in all patients, 70 (21%) did so depending upon spirometry, 48 (15%) upon the patient’s clinical status, and 35 (11%) when the SpO2 was 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 endoscopy 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, those gloved (98%), with 290 (88%) gowns (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.

### PROSPECTIVE RANDOMISED TRIAL OF ABRAM’S BLIND BIOPSIES VERSUS CT GUIDED CUTTING NEEDLE BIOPSIES IN UNDIAGNOSED PLEURAL EFFUSIONS

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**Introduction:** Approximately 180,000 people in the U.K., develop a pleural effusion each year, of which 40,000 will turn out to be due to malignancy. Unfortunately, cytological examination alone has a sensitivity for malignancy of only 60%, necessitating further more invasive investigations in many cytology negative pleural effusions. With the rising incidence of mesothelioma (where track invasion by tumour is common), the minimum number of invasive investigations to obtain a diagnosis is desirable. We have assessed whether CT guided pleural biopsy is more sensitive than blind Abram’s biopsy in these patients.

**Methods:** 30 consecutive patients with undiagnosed effusive exudate who required pleural fluid for cytology and admittance, were recruited. All received a contrast enhanced CT thorax, with the degree of pleural thickening recorded. Patients were randomised to blind Abram’s pleural biopsy or CT guided cutting needle biopsy. The Abram’s pleural biopsy was performed by NAM without knowledge of the CT findings. The CT guided biopsy was performed by FVG.

**Results:** Of the 50 patients, 3 did not have a biopsy [1 withdrew consent, 1 pleural effusion resolved and 1 had dranded blood clotting]. There was 1 chest wall haemotoma in the Abram’s group. The median age was 72 (range 25–88) in the CT group and 73 (41–85) in the Abram’s group. The maximal pleural thickening on CT was <5mm in 17/25 patients in the radiology group and in 17/25 of the Abram’s group. The final diagnosis was confirmed with a minimum follow up of 1 year. Abram’s blind biopsy gave the true positive (TP) rate for malignancy was higher at 13/15 (p = 0.02, 100% and Negative predicted value (NPV) 44%. In the CT group, TP followed up of 1 year. Abram’s blind biopsy gave the true positive (TP) rate for malignancy was higher at 13/15 (p = 0.02, 100% and Negative predicted value (NPV) 44%. In the CT group, TP (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:** In cytology negative pleural effusions CT guided pleural biopsy has a significantly higher sensitivity for malignancy and should be the biopsy method of choice in patients unable to tolerate thoracoscopy.

### THE COMPLICATION RATE OF PERCUтанEOUS IMAGE-GUIDED CHEST DRAIN INSERTION

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**Purpose:** The aim of this study was to assess prospectively the success and complication rate associated with image-guided percutaneous pleural drainage.

**Materials/Methods:** A prospective single institution study of all image-guided chest drains placed over a 36-month period was carried out. All drains were using the Seldinger technique. Data collected included, indication for drain insertion, size of drain, type of image-guidance used (CT or ultrasound), demographic data, nature and amount of fluid aspirated, success rate, duration of drainage and complications.

**Results:** 352 drains were inserted into 273 patients. 121 patients were male and 152 female. 149 were inserted on the left and 203 on the right. The majority of drains were 12 French, 258, other drain sizes were 8 French (90), 10 French (2) to 14 French (3) 16 French (1). 333 drains were placed under ultrasonic guidance and 19 under CT. Indications included 236 malignant effusions 94 empyemas and 22 benign non-infective effusions. 350 drains were successfully inserted. Two patients suffered significant immediate complications of hemothorax due to intercostal artery laceration. Both drains were inserted posteriorly. Both patients underwent percutaneous arterial embolisation. One procedure was successful; unfortunately one procedure was unsuccessful and the patient died within 24 hours of drain insertion of intrathoracic haemorrhage. Both of these patients had drain insertion for a current empyema, had a history of chronic renal failure and a prior empyema.

**Conclusion:** Percutaneous image-guided drain placement is successful in the majority of patients (99%). Posteriorly inserted drains may have a higher and more significant complication rate compared to other drain position. Patients with renal impairment appear at greater risk.

### TALC BUT NOT TETRACYCLINE PLEURODESIS INDUCES HYPOXIA AND INCREASED DTPA CLEARANCE OF THE CONTRA-LATERAL LUNG

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**Introduction:** Talc slurry is the most commonly used and effective pleurodesis agent in the UK. There are concerns about its safety and it is associated with at least 34 reported cases of severe lung inflammation leading to Adult Respiratory Distress Syndrome (ARDS). It is not known if milder generalised lung inflammation is a consistent feature of talc pleurodesis. 99mTc-DTPA lung clearance is a very sensitive marker of lung inflammation. This study assesses whether DTPA clearance from the lung contra-lateral to a pleural effusion is pleural is more sensitive than blind Abram’s biopsy in these patients.

**Methods:** 30 patients with recurrent symptomatic effusion consented to the study. 11 were excluded (5 with trapped lung, 3 unable to perform baseline DPTA, 1 M.I. pre pleurodesis, 2 chest tube displacements). 20 were randomised to 4g talc slurry (10) or 20mg/Kg tetracycline (10) balanced by type of malignancy and pleural effusion. Oxygen saturation breathing air, serum C-Reactive Protein (CRP), limited HRCT and DTPA scan were performed before and 48 hours after pleurodesis. Pleural fluid IL-8 was measured at before and 24 hours after pleurodesis.

**Results:** DTPA t1/2 of the contra-lateral lung fell significantly after talc but rose after tetracycline. Talc 64.4 minutes (90% range 40–111.1) to 59.5 (35.3–84.8) difference 8.85 (t = 12.4, tetracycline 60.1 (26.1–119) to 83.6 (27.8–189.2) difference 2.85 (-16.3–75.1), p < 0.03 Mann-Whitney. No changes were detected on limited HRCT.

**Conclusion:** Talc rise was significantly higher in the talc than tetracycline group. Talc 95.5 (2.3) to 92.2 (2.6) difference 3.2 (SD 1.6) , tetracycline 94.0 (4.7) to 93.3 (4.9) diff 0.7 (SD 1.5) p = 0.003. There was also a trend towards a greater increase in pleural fluid IL-8 levels in the talc group. Talc 12618 (258–29911) vs Tetracycline 50 (-1657–29919) p = 0.13.

**Conclusion:** Talc pleurodesis induces a greater systemic inflammatory response than tetracycline quantified by CRP. Increased aerosol DTPA clearance from the contra-lateral lung and greater hypoxaemia are induced by talc but not by tetracycline. This suggests that occasional severe ARDS induced by talc is the severe end of a spectrum and not an idiosyncratic adverse reaction.

### TRANSPORTED NEEDLE ASPIRATION (TNA)—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
spreading with endobronchial biopsy, brush and wash (CS) remains relatively low (Dasgupta, et al. Chest 1999;115). TBNA is reported to increase the pick up rate in this group, and also in necrotic endobronchial tumours, but is not widely used (Mehta. Clin Chest Med 1999;20:39–51).

Methods: We prospectively recorded the results of TBNA in addition to appropriate conventional sampling in 23 patients over a 12 month period. All the sampling was done by a single operator, and during regular bronchoscopy lists. 22G Olympus and Millrose-Wang needles were used.

12 patients had submucosal/extrinsic disease and 7 had necrotic endobronchial lesions. Bronchoscopy was normal in 4 patients. CT scans were performed prior to the bronchoscopy in 13 patients.

Results: TBNA was positive in 21/23 patients (91%), whereas conventional samples were positive in 16/22 patients (73%). Biopsy was positive in 13/15, Brush in 12/15 and wash in 9/22 patients respectively. TBNA was the only positive diagnostic test in 5 patients (22%). The diagnosis was non-small cell malignancy in 15 and small cell carcinoma in 5 patients. One patient presented with isolated subcarinal adenopathy, and acid fast bacilli were demonstrated on the FNA sample. There were no significant complications during or after the procedure.

In short, with the addition of TBNA, the diagnostic yield of bronchoscopy went up from 73% to 91%.

Conclusions: TBNA is a cost-effective and safe technique to improve the diagnostic yield of bronchoscopy, particularly in patients with (a) extrinsic/submucosal disease (b) normal bronchoscopy but CT scan evidence of peribronchial disease or mediastinal abnormality and (c) necrotic, haemorrhagic endobronchial lesions. It can also be used to diagnose benign disease. TBNA can be performed during a standard flexible bronchoscopy list, and could potentially reduce the need for a surgical biopsy.

Abstract S101

<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>

S102 AUTOFLOW BRONCHOSCOPY IN CLINICAL PRACTICE

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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 toconventional 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

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

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.

Abstract S102

<table>
<thead>
<tr>
<th>Test (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>NS</td>
<td></td>
</tr>
<tr>
<td>SD=13.3</td>
<td>SD=10.8</td>
<td></td>
<td></td>
<td></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>
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<td>SD=24.2</td>
<td>SD=25.8</td>
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</tr>
<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>p=0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD=45.9</td>
<td>SD=30.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For definitive diagnosis from clinic review</td>
<td>n=155</td>
<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>p=0.06</td>
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<tr>
<td>SD=90.6</td>
<td>SD=59.7</td>
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</tr>
</tbody>
</table>

NS, not significant.
THERAPEUTIC DELAYS IN LUNG CANCER MANAGEMENT

A. Coote, K.R. Patel, J.S. Sarveswaran, 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.

<table>
<thead>
<tr>
<th>Abstract S103</th>
<th>Time taken in days from referral for treatment during Jan 1999–Dec 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC chemotherapy</td>
<td>n=88 median=6</td>
</tr>
<tr>
<td>NSCLC chemotherapy</td>
<td>n=47 median=23</td>
</tr>
<tr>
<td>NSCLC surgery</td>
<td>n=55 median=18</td>
</tr>
<tr>
<td>Oncology review</td>
<td>n=38 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. Erat, A. Hutchings, A.S. Haque, A. Lamont, C. Trask. Southend Associate University Teaching Hospital, Southend on Sea, Essex SS0 ORY, 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).

S105 LUNG CANCER: ARE THE NSF TARGETS FOR RESSECTION 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 set of guidelines suggests that the target resection rates of 25% were achievable (Laroche, et al. Thorax 1999;53:445–9). We set 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 MDT meeting. The MDTs, bronchoscopy, CT scanning, 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.

S106 SURGICAL REFERRAL AND RESECTION RATE FOR NSCLC AT QUEEN ELIZABETH HOSPITAL OVER A 5 YEAR PERIOD: WHY IS IT SO LOW?

J.I. Whitehouse, N. Jahan, J.R. Webb, T.C. Stokes. Department of Respiratory Medicine, Queen Elizabeth Hospital, Stadium Road, Woolwich, London SE18 4QH, UK

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...
The genetics of respiratory disease

J.C. Davies1,2, M. Johnson3, C. Booth3, K. Fidler1, A. Bush1, D.M. Geddes1, E.W.F.W. Alton1, M.W. Turner1, N. Klein1. 1Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, UK; 2Department of Gene Therapy, Imperial College, UK; 3Immmunobiology Unit, Institute of Child Health, University College, London, UK

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 MBL2 genotypes were reported in two studies of 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 O; wild-type A) and the low [X] or high [Y] expressing 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 (X/O or O/O; 13.1%). At the earliest time point available (7.0 [6.9–7.4] 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 of FEV1 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 is the age of year of birth, other studies having been reported 10 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.

ST09 POLYMORPHISMS IN THE HYDROPHILIC SURFACTANT PROTEINS A AND D ARE MODIFIERS OF LIVER INVELOVEMENT BUT NOT LUNG DISEASE IN CHILDREN WITH CYSTIC FIBROSIS

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The surfactant proteins A and D are members of the collectin family involved in the innate immune system. Polymorphisms within 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 SP-A1, SP-A2 and SP-D 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 SPA-I allele 6A−, and the SP-A2 allele, 1A−, were significantly overrepresented [6A−/6A− 68% vs 33%; 6A+/non-6A− 32% vs 47%; non-6A−/non-6A− 0% vs 19%; p<0.01; 1A−/1A− 63% vs 34%.
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 75, 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-HD5), 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 showed significantly different frequencies (p<0.05) on chromosomes 1A2/non1A2 32% v 47%, non1A2/non1A2 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 gastro-intestinal tract. Our data, until now, SP-D has been found in the bronchial mucosa. 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

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Background: 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.

Methods: We undertook a cross sectional study of 7,410 employees in contact, at work, with laboratory rats at 6 pharmaceutical sites across the UK. 109 cases (defined as having a skin prick test wheal ≥3mm to rat urine and/or a rat urine RAST ≥2% binding) and 379 non-sensitised referents were HLA typed for DR8 and DQ8 loci. Participants were 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 1.91–3.27), 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

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Background: Maternal factors including atopy and smoking during pregnancy are associated with the risk of developing asthma in children. HLA type and smoking are therefore likely candidates for controlling the immune response. In this study, we examined whether maternal factors and smoking were associated with HLA-DR and DQ types in a cohort of high-risk young adults.

Methods: 7,410 employees in contact, at work, with laboratory rats at 6 pharmaceutical sites across the UK.

Results: HLA-DR7 was found to be associated with sensitisation (OR 1.99 CI 1.91–3.27), 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.

**S113** MATERNAL BUT NOT PATERNAL GENETIC VARIATION IN GSTP1 IS ASSOCIATED WITH ASTHMA PHENOTYPES IN CHILDREN

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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 polymorphisms in glutathione S-transferase, GSTP1 is associated with asthma, airway hyper-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

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questionnaire, skin prick testing, total serum IgE, spirometry and methacholine challenge testing. Phenotypic data were analysed as continuous and categorical variables. Bronchial challenge data were corrected for age, gender, height and baseline lung function. GSTP1 genotyping was determined using PCR.

**Results:** GSTP1 Val<sup>105</sup>/Val<sup>105</sup> genotype in the child was weakly associated with a reduced risk of atopy (p=0.038) and AHR (p=0.069). In mothers (p=0.026) but not fathers (p=0.407), GSTP1 Val<sup>105</sup>/Val<sup>105</sup> was associated with a reduced risk of AHR in the child. This was independent of the child’s genotype, maternal and child atopic status, maternal smoking during pregnancy, and transmission of parental GSTP1 alleles.

**Conclusion:** For the first time, we have shown an association between maternal genotype and the child’s asthma phenotype that is not due to transmission of specific maternal alleles to the child. This suggests an in utero effect of maternal genetic genotype on the child and adds new insights into the mechanisms by which maternal factors may influence the development of asthma in childhood.

### Asbestos and the pleura

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

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There has been an assumption that diffuse pleural fibrosis (DPF) is an indicator of heavy dust exposure. This has considerable implications in the decision as to whether a given lung cancer has been caused by asbestos. The UK Industrial Injuries Advisory Council<sup>1</sup> 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 McG).

**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 had more exposure than those with unilateral (t=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.

1. International Expert Meeting on Asbestos, Asbestosis & Cancer: the London WC1E 6JJ, UK

### IMMUNOHISTOCHEMICAL PROGNOSTIC MARKERS IN MALIGNANT MESOTHELIOMA

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**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.

**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 67.7 years) diagnosed with malignant mesothelioma between 1997 and January 2001.

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

<table>
<thead>
<tr>
<th>Abstract S116</th>
<th>Survival ≥ 10 mths (Mean (SD))</th>
<th>Survival &lt; 10 mths (Mean (SD))</th>
<th>p Value</th>
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<td>Age (years)</td>
<td>66.1 (10.2)</td>
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<td>75.5 (14.4)</td>
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<td>BAX score</td>
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<td>4.7 (1.1)</td>
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<tr>
<td>Bcl2 score</td>
<td>0.9 (1.4)</td>
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<tr>
<td>PS1 score</td>
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<tr>
<td>PS1 stain</td>
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<table>
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<th>Histological subtype</th>
<th>Mean Survival (days)</th>
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<tr>
<td>Sarcomatous</td>
<td>127.8</td>
<td>113.2</td>
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</table>
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.

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. The 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 (from diagnosis) 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.

ACTIVATION OF PROTEASE ACTIVATED RECEPTOR-2 IN MESOTHELIAL CELLS: A NOVEL MECHANISM OF PLEURAL INFLAMMATION

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Pleural inflammation underlies a vast range of pleural diseases, but its mechanism remains poorly understood. Protease activated receptor (PAR)-2 is a novel seven-transmembrane G-protein-coupled receptor. We recently showed that PAR-2 are present in abundance on human pleural mesothelial cells, and stimulation of PAR-2 in vitro resulted in significant release of inflammatory cytokines (ARJCCM 2002;165:A66).

We now show that PAR-2 in mesothelial cells has a functional role in pleural inflammation in vivo.

C57BL/6 mice were given a single intrapleural injection of 10mg/kg of SUGRL-NH2 (a specific PAR-2 activating peptide), or 10mg/kg of LSIGRL-NH2 (control peptide), or the vehicle, phosphate-buffered saline (PBS). At 4 hours, the mice were sacrificed. Cytokines were measured with ELISA. Neutrophils were counted on cytospin slides (Giemsa stains).

Pleural fluid MIP-2 levels were significantly higher in mice injected with SUGRL-NH2 (27.1±15.6pg/ml) than in those given control peptide (BB81±15.5pg/ml) or PBS (BB8±40pg/ml, p<0.001). Similarly, pleural fluid TNFa was significantly higher in the SUGRL-NH2 group. In the SUGRL group, the neutrophil counts in the pleural fluid were significantly higher than the control peptide (by 40 fold) and the PBS groups (by 26 fold). The MIP-2 and TNFa levels were 15- and 4-fold higher in the pleural fluid than in serum, consistent of local pleural production. There were no differences in the serum levels of these cytokines among the three groups. The MIP-2 and TNFa levels were strongly correlated in the pleural fluids (r=0.92, p<0.00001) and in serum (r=0.76, p<0.01). There were no differences in the pleural fluid volume or in its VEGF concentrations among the three groups.

This study is the first to show a functional role for PAR-2 in the pleura. Our results confirmed that activation of PAR-2 in mesothelial cells in vivo resulted in significant production of pro-inflammatory cytokines with resultant neutrophil recruitment into the pleural cavity.

Asthma mechanisms II

INCREASED SUB-EPITHELIAL PROTEOGLYCANS IN THE AIRWAYS OF MICE FOLLOWING OVALBUMIN SENSITISATION AND CHALLENGE

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The sub-epithelial thickening of asthmatic airways is manifested by increased fibroblast/myofibroblast proliferation and deposition of extracellular matrix components including collagens 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 subepithelial 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 each airway was examined using separate colour thresholding 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 fibres, 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 S117

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<th>Hospital</th>
<th>Number of cases</th>
<th>Median survival (days)</th>
<th>Days to 25% dead</th>
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<td>162</td>
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</table>

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WNT SIGNAL TRANSDUCTION IN ADULT BRONCHIAL EPITHELIAL CELLS

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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-I Wnts induce the accumulation of cytoplasmic phospho-Ser/Thr-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, re-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 re-activation 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. Glenfield Hospital, Goby 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 and had paired measurements over the period of one year. We found a significant positive correlation between exhaled NO and sputum eosinophil count (r=0.461, p<0.001) and between change in the variables (r=0.262, p<0.001). There was no significant correlation between the two measurements in smokers. Within the non-smoking group the correlation was stronger in: males (r=0.637, p<0.0001) than females (r=0.387, p<0.001), in those not on inhaled steroids (r=0.497, p<0.001) compared to those who were (r=0.385, p<0.001) and in atopic (r=0.605, p<0.001) compared to non-atopic patients (r=0.366, p<0.01). The relationship between change in sputum eosinophil count and exhaled NO was also stronger in males (r=0.303, p<0.001) than females (r=0.183, p=0.016). Smoking, gender, atopy and inhaled steroid use have a significant impact on the relationship between exhaled NO and sputum eosinophil counts in cross sectional analysis. In both cross sectional and longitudinal analysis there is a marked difference in the relationship 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

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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 cellularity (mean ± SD: simvastatin 17.9 ± 5.53 × 10⁶/ml vehicle control 19.4 (15.2) × 10⁶/ml, p < 0.01) and eosinophilia (simvastatin 5.59 (3.17) × 10⁶/ml vehicle control 19.4 (9.92) × 10⁶/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.

ACIDS IN ASTHMA

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Rationale: As substrates for eicosanoid production, it is hypothesised that omega-6 polyunsaturated 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 asthma has increased levels of erythrocyte 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.

Methods: 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 erythrocyte 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 erythrocyte membrane levels of the omega-6 fatty acid linoleic acid and higher levels of the saturated fatty acid stearic acid. See table.
**Drug therapy in cystic fibrosis**

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

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**Introduction:** Linezolid is a new antibiotic with efficacy against methicillin resistant *Staphylococcus 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).

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

**Methods:** 10 (5 male & 5 female) adult CF patients were recruited over a 3 month period. The mean (range) age, BMI and % predicted FEV1 were 25.4 years (19–36), 20 (2.2) and 47.8% (22–90) respectively. Inclusion criteria included the absence of MRSA infection or significant liver disease. Treatment was administered under nursing supervision. Subjects received 600mg of Linezolid orally every 12 hours for 6 months. Serum and sputum drug levels were measured before and at 2 hours after the final dose of Linezolid. A further serum level was measured at 4 hours. Serum and sputum levels were measured by High Performance Liquid Chromatography.

**Results:** Mean (SD) serum Linezolid levels were 2.3mg/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 observed 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 serum levels within the studied population. However, even 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 controls.

**Conclusion:** The administration of 12 hourly, 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 PAEDIATRIC CYSTIC FIBROSIS


Following significant improvements in lung function in a pilot study of seven patients with cystic fibrosis who received azithromycin daily for over three months, we now report a prospective, double blind, placebo controlled, double blind, crossover trial of AZM in paediatric CF patients.

**Methods:** 41 CF children aged 8 to 18 years, median expired volume in one second (FEV1) 61% (range 33 to 80%) participated in a 15 month randomised double-blind placebo controlled crossover trial receiving either Azithromycin (body weight <40kg: 250mg daily, >40kg: 500mg daily) or placebo for 6 months. Following 2 months washout, the treatments were crossed over. Spirometry, sputum cultures, sputum interleukin 8 and neutrophil elastase, exercise testing, quality of life, antibiotic usage and pulmonary exacerbation rates were outcome measures. Side effects were assessed by pure tone audiometry and liver function tests.

**Results:** The median 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<0.05). In a median relative difference between azithromycin and placebo was +11.5% [5.3 to 16.7] when not receiving concurrent rhDNase (n=26) and −3.6% (−22 to +3.9) for the 15 receiving rhDNase (Mann Whitney p=0.003). There was no significant overall change 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 5/15 when on placebo (p<0.05). There were no changes in sputum bacterial densities, inflammatory markers exercise tolerance or subjective well-being. There were no significant side effects.

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


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**Abstract S123**

<table>
<thead>
<tr>
<th>% composition</th>
<th>Asthmatic</th>
<th>Controls</th>
<th>Mean difference</th>
<th>Standard error</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitic acid</td>
<td>38.2</td>
<td>37.5</td>
<td>0.678</td>
<td>1.003</td>
<td>0.50</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>20.1</td>
<td>18.0</td>
<td>2.090</td>
<td>0.478</td>
<td>0.00</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>13.1</td>
<td>13.0</td>
<td>0.060</td>
<td>0.443</td>
<td>0.89</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>7.4</td>
<td>8.6</td>
<td>−1.197</td>
<td>0.347</td>
<td>0.00</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>15.4</td>
<td>16.3</td>
<td>−0.936</td>
<td>0.533</td>
<td>0.08</td>
</tr>
<tr>
<td>Docosahexaenonic acid</td>
<td>5.8</td>
<td>6.3</td>
<td>−0.535</td>
<td>0.612</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Conclusion:** These findings are consistent with the hypothesis that dietary omega-3 PUFA 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.
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 (SLN) 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 (SLN 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.

**Abstract S127**

**INTERACTION BETWEEN AEROSOL DELIVERY SYSTEM AND BRONCHODILATORS IN CF PATIENTS TAKING COLISTIN**

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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 make 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) age9.97 years (3.89 to 16.75)] 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 mLs 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 (8.96, 4.98, 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 measure confirmed 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.

**Abstract 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 make 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) age9.97 years (3.89 to 16.75)] 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 mLs 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 (8.96, 4.98, 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 measure confirmed 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.

<table>
<thead>
<tr>
<th>Device combination</th>
<th>Baseline age (years)</th>
<th>Baseline FEV1 % predicted mean (CI)</th>
<th>% Change in FEV1, % predicted at 28 days (CI)</th>
<th>% Change in FEV1, % predicted at 182 days (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD SLN</td>
<td>19 (13 to 26)</td>
<td>50 (44 to 56)</td>
<td>6.6 (1.0 to 12.1)</td>
<td>0.5 (n=48)</td>
</tr>
<tr>
<td>NEB SLN</td>
<td>19 (14 to 28)</td>
<td>53 (47 to 60)</td>
<td>-3.9 (-8.6 to 0.8)</td>
<td>-3.7 (n=41)</td>
</tr>
<tr>
<td>AAD INHL</td>
<td>13 (10 to 18)</td>
<td>65 (59 to 70)</td>
<td>-7.3 (-12.5 to -2.1)</td>
<td>-7.0 (n=39)</td>
</tr>
<tr>
<td>NEB INHL</td>
<td>15 (13 to 18)</td>
<td>64 (57 to 72)</td>
<td>-0.8 (-4.7 to 3.2)</td>
<td>-5.1 (n=38)</td>
</tr>
</tbody>
</table>
Abstract S129

<table>
<thead>
<tr>
<th></th>
<th>Leg FFMI</th>
<th>Arm FFMI</th>
<th>Trunk FFMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>0.556</td>
<td>0.429</td>
<td>0.418</td>
</tr>
<tr>
<td>METS</td>
<td>0.652</td>
<td>0.555</td>
<td>0.507</td>
</tr>
</tbody>
</table>

Preferential loss of FFM occurs in adults with CF. Such loss is related to severity of lung disease and physical activity. It can occur in the presence of a normal weight/height ratio. A similar loss of BMC occurs with preservation of FM. A hierarchical pattern of FFM loss of legs > arms > trunk was demonstrated whilst bone mineral loss occurred generally.

Sponsored by the CF Trust, UK and The British Lung Foundation.

TNFα: Its role in respiratory disease

S130 GENETIC SUSCEPTIBILITY TO OZONE EXPOSURE


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. 1 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, SPSS 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 large 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


S131 POLYMORPHISMS IN THE PROMOTER OF TUMOR NECROSIS FACTOR (TNF) ALPHA GENE IN PATIENTS WITH SILICOSIS AND THE DEVELOPMENT OF PROGRESSIVE MASSIVE FIBROSIS

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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 roentgenological severity of silicosis in 124 sex, smoking, and exposure history - matched Japanese silicotic patients. Silicotic patients were divided into three groups: Pr (proliferation rate) 1 (0/1–0/1, n=47), Pr2 (0/2–2/2, n=36), and PMF (progressive massive fibrosis) (4c, n=43) according to the ILO classification. We also examined 122 healthy controls within the same age and 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.

S132 TNF PROMOTER REGION SINGLE NUCLEOTIDE POLYMORPHISM IN ARDS

A.L. Logan, E. Beddow, S. Mummy, G.J. Quinlan, P. Goldstraw, J.D. Christie, P.N. Lanken, A.B. Fisher, R.M. Du Bois, K.I. Welsh, T.W. Evans. Unit of Critical Care, Dept Thoracic Surgery & Clinical Genomics Group, ILDU Imperial College Faculty of Medicine, Division of Pulmonary Medicine, Department of Medicine, University of Pennsylvania Medical School, Philadelphia, USA

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 rarer −857 T allele 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.

S133 AUGMENTATION OF TNFα-INDUCED APOPTOSIS OF HUMAN NEUTROPHILS BY THE AMINOPEPTIDASE INHIBITORS BESTATIN AND ACTIONIN

A. Sobolewski, B.J. Reed, E.R. Chivers. Department of Respiratory Medicine, University of Cambridge, School of Clinical Medicine, Addenbrookes’ and Papworth Hospitals, Hills Road, Cambridge, CB2 2QG, UK

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 novel mode of action for drugs. TNF is unique in its ability to induce both neutrophil apoptosis and priming. Aminopeptidase 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 aminopeptidase inhibition on TNFα-induced apoptosis in human neutrophils. Neutrophils were isolated from human blood using...
EFFECT OF ETHNICITY ON ASTHMA PREVALENCE

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

Methods: Children were seen in primary schools for measurements of FVC, FEV1, PEF, PEF/FVC, FEV1/FVC and FEV1, using a spirorometer. Circumference, chest height, transverse diameter and AP diameter were measured using an anthropometric tape measure and anthropometer. Relationships between standing height, lung function, airway 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 values). 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 without atopic disease in 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 10Lmin−1 (95% CI −0.2 to 0.6). The influence of chest dimensions (both singly and in combinations) to represent the chest volume as 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.

Epidemiology and ethnicity in respiratory disease

DO VARIATIONS IN CHEST WALL DIMENSIONS EXPLAIN ETHNIC-RELATED DIFFERENCES IN LUNG FUNCTION?

A.L. Whittaker1, A.J. Sutton1, C.S. Beardmore1. Departments of Child Health2 and Epidemiology and Public Health, University of Leicester, UK

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 African Caribbean children and Africans in the UK following immigration

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, PEF/FVC, FEV1/FVC, and FEV1, using a spiroimeter. Circumference, chest height, transverse diameter and AP diameter were measured using an anthropometric tape measure and anthropometer. Relationships between standing height, lung function, airway dimensions, gender, and ethnicity were assessed using multiple linear regression analysis.

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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.

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 atopic disease, normative data must be made 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, Bangladeshis, and white British; with no personal history of atopic 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 Bangladeshis, 58 Afro-Caribbeans, and 72 white British children. Log10 total IgE increased with age (Log10 IgE = 1.29 + 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 those with atopic illnesses.


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

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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 con-
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 (5 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.

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

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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 identified 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 became 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?

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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 one year 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

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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 I (EARS I) in Norfolk and Norwich. 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 EARS 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 asthlm in EARS 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 EARS 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.

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Drug therapy in COPD

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

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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 for each group were 1.4, 1.6, 1.8, and 1.9 exacerbations/patient/year 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=0.76) in the B, F, and Pl groups, respectively. Statistically significant reductions in severe exacerbations were in the B/F and B groups (1% and 0.99 L [61% predicted]) compared to Pl, and B/F (p=0.003) and F (p=0.002) compared to Pl. These improvements were early and sustained.

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

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COPD patients (n=812, median 5 y since diagnosis, mean age 64 years, mean baseline FEV1 0.99 L [36% predicted]) received two 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, PEF, and SGRQ. Daytime symptom scores of breathlessness, morning and evening PEF (mean change from run-in) were compared. At 12 months, B/F increased both morning and evening PEF by 15.6 L/min and 9.0 L/min (B 7.3 L/min, F 8.6 L/min; B/F v Pl, p<0.001). B/F also reduced mean exacerbation rates by 23% (p=0.043) and increased awakening-free nights by 15% (p=0.001).

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

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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, nighttime 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 vs Pl, B and F by 1.12, 0.83 (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 vs 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.

**S144** THE EFFECT OF 3 MONTHS ORAL CLARITHROMYCIN ON SPIROMETRY, SHUTTLE WALK DISTANCE AND HEALTH STATUS SCORES IN PATIENTS WITH MODERATE TO SEVERE STABLE COPD

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Introduction and aims: Macrolides antibiotics are commonly used in the treatment of acute exacerbations of COPD. This study looked at the possible effects of long-term oral clarithromycin on spirometry, shuttle walk distance and health status scores in patients with COPD during the stable clinical state.

Methods: Randomised, double-blind controlled trial of oral clarithromycin 500mg o.d. (Cl) vs Placebo (Pl) o.d. for 3 months in stable patients with moderate to severe COPD who have not had an exacerbation for 6 weeks. The St George respiratory questionnaire (SGRQ) and short form—36 (SF-36) were measured. The mean changes in parameter for each group were compared using either a 2 test or a Mann-Whitney U test where appropriate.

Results: 67 patients were randomised to receive Cl (n=31) or Pl (n=36). 46 (69%) were male, mean age (SD) was 66.7 (7.9) years and 27 (40%) were current smokers. Mean (SD) FEV1 and FEF1 % predicted were 1.12 (0.41) L and 43.2 (11.4) % respectively. All patients were taking inhaled corticosteroids. Data for 7 patients were unavailable and intention to treat analyses were performed on the Cl group compared to the Pl group. Differences in the other health status parameters were not statistically significant.

Conclusion: In this study, long term oral clarithromycin improved improvement in physical functioning scores in moderate to severe stable COPD patients.
EFFECT OF BUDERONIDE/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 years; median 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, F, and PL. The time to the first oral steroid course was increased and 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 β AGONIST AND ANTICHOLINERGIC BRONCHODILATORS DELIVERED BY NEBULISER OR BY INHALER AND SPACER IN MODERATE TO SEVERE STABLE COPD PATIENTS

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Introduction: This abstract reports a comparison of high dose salbutamol + ipratropium bromide delivered by inhaler+spacer 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 +200mcg ipratropium bromide) 6 puffs via Volumatic 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.

Analysis: where possible analysis was undertaken on an intention to treat basis. Treatment order effect (whether treatment effect differed depending on the order of treatment) was assessed using a graphical test was used to detect any between treatment 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 revealed a treatment order effect for cycle 1 i.e. those randomised first to active nebuliser had a lower average SOBQ and higher average PEF for the cycle. This was not seen in cycle 2. As a consequence, further analyses were confined to cycle 2, n=36 (32 male). Missing data due to hospital admission (n=2) and consent withdrawal (n=1), all during the active nebuliser phase, caused exclusion from the analysis. The differences were not significant between nebuliser v inhaler. They were: SOBQ (n=33) 2.5 (95%CI -1.3 to 6.4) t = 1.3 p =0.19; PEF (n=32) 2.8l/min (95%CI -3.8 to 9.3) t =0.9 p=0.40; VAS (n=32) -0.1cm (95%CI -4.2 to 0.2) t =-0.7 p=0.48.

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

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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) and FEV₁% of 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 LGIT, 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 non. 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 ANOVAR 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, IV, or NIV. These issues should be discussed with vulnerable patients preferably before hospital admission.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE—ALIGNING PATIENT AND PHYSICIAN VIEWS

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COPD patients suffer many debilitating symptoms which ultimately impair their quality of life. A Respiratory Disease-Specific Programme was conducted in respiratory and primary care clinics in 5 European countries. Primary care physicians (PCPs) and Respiratory Specialists (RNs) (n=769) completed patient record forms (PRFs) prospectively, on the type and severity of COPD symptoms and impact of these on patients’ lifestyle in terms of ability to undertake activities of daily living (ADL). Similarly, patients returned a self-completion form (SCF), detailing the severity, frequency, and impact of their respiratory symptoms on ADL. A total of 2446 patients were diagnosed with COPD (diagnosis recorded as COPD, emphysema or chronic bronchitis) and 72% (n=1768) of these returned a SCF.

PRF data showed that the most commonly reported symptoms of patients diagnosed with COPD were breathlessness on exertion (86%), daytime cough (82%), sputum (75%), and nocturnal cough (67%). SCF data showed that patients also identified these as key symptoms, recorded as either a moderate or major problem in the previous 6 months for 71%, 70%, 64%, and 61% of patients reporting severity respectively. For these 4 key symptoms and others [wheezing, breathlessness at rest, tightening of chest, and nocturnal wakening] COPD patients regarded these to be more severe than PCPs and RSs. Patients suggested that COPD restricts their ability to undertake ADLs (work/housework, leisure activities and ability to exercise) to a greater degree than that perceived by PCPs (p<0.01) and RSs (p<0.001).
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.

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<th>Prevalence of Symptoms in COPD Patients</th>
<th>Overall</th>
<th>Smokers</th>
<th>Non-smokers</th>
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<tr>
<td>Breathlessness on mild exertion</td>
<td>29%</td>
<td>34%</td>
<td>25%</td>
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<tr>
<td>Frequent winter colds</td>
<td>22%</td>
<td>29%</td>
<td>20%</td>
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<tr>
<td>Persistent cough</td>
<td>13%</td>
<td>19%</td>
<td>9%</td>
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<tr>
<td>Persistent sputum production</td>
<td>9%</td>
<td>13%</td>
<td>7%</td>
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<tr>
<td>Any</td>
<td>49%</td>
<td>61%</td>
<td>41%</td>
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Abstract S150

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Risk factors in allergic disease

Abstract S152

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<tr>
<th>The Effect of Mite Allergen Control by the Use of Allergen-Impermeable Covers in Adult Asthma: The SMAC Trial</th>
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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 has been 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 428.9 l/min, p<0.0001; placebo 419.3 to 428.9 l/min, p<0.0001).

In 6 months. PEFR improved significantly in both groups (active 409.7 to 428.9 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 in means (95% CI), active v placebo: all subjects −2.11 (−6.55 to 2.32), p=0.35; mite sensitive subjects −1.71 (−7.28 to 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

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A prospective cohort study of childhood asthma and allergic disease based in Ashford, Kent has been underway since 1993. A consecutive series of newly pregnant women 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 aeroallergens (Der p 1, house dust mite, and Fel d 1, cat fur) were measured.

Each child was visited annually, and at age 5–6 sensitivity to Der p 1, Fel d 1 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 this age. Rates of sensitisation and atopic, current wheezing by quartiles of exposure categories using measurements from the living room carpet were as shown in the table.

The patterns above suggest that the association between levels of Der p 1 and Fel d 1 experienced in early-life and subsequent sensitisation/wheeze has an “inverted U” shape. The reductions in risk at the highest exposure levels may be explained by an immunotolerance or by confounding determinants of sensitisation. Further investigations into these are underway.

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

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Subclinical infection with environmental mycobacteria (eMB) may exert a strong immuno-regulatory 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 aeroallergens; 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 DISEASES?: A BIRTH COHORT STUDY

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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 consulted 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.
REGULAR OILY FISH CONSUMPTION IS PROTECTIVE AGAINST SYMPTOMATIC ASTHMA

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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 PGD$_2$ 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=0.08).

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.

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

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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.
Respiratory muscles

**P1** MULTIDISCIPLINARY MOTOR NEURONE DISEASE CLINICS: DO THEY IMPROVE PATIENT CARE?

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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 four 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 FVC 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 alleviated.

**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

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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, 7.4% 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 PaO2 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

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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-Meier 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 completed a randomised 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 (Vd), expired tidal volume (Vex), expired minute volume (MVe) and respiratory rate (RR) were measured throughout the night. Minute leak was calculated by (Vex–Vd) x RR.

Results: See figure.

Ventilation was slightly greater in the volume group. There was significantly more leak during PSV than compared to VCV (16 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.

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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 suggests that some more severe patients were inadequately treated with PCV (Schonhofer B, et al. Eur Respir J 1997; 10:184–91). The second study found no differences between the modes but suggested that patient fatigue was reduced using PCV (Ferris G, et al. Am J Phys Med Rehabil 2000; 79:24–9).

Patients & methods: Twelve patients (nine male, mean age 59 [8.9] years) 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 the cause remains controversial. Better understanding of the distribution of muscle weakness may reveal the underlying causes.

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 ventilator use was greater during PCV compared with VCV (8.22 v 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 v 38.5; p<0.04). This was supported by the subjects reported sleep quality during PCV (2.17 v 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: 12 patients with KS (nine male, 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. Subjects completed the St George’s Respiratory Questionnaire (SGRQ), the SF-36 health questionnaire, and the Beck depression score pre-treatment and after four weeks on the trial ventilator at each setting.

Results: One subject was excluded due to intercurrent illness, three due to obstructive sleep apnoea, and one subject could not tolerate VC. 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 scores were within the normal range.

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

ADDCUTOR 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
Pathological process; chronic inactivity and disuse atrophy should lead to preferential involvement of the muscles with the greatest decrease in utilisation—that is, the lower limbs—whereas the loss of muscle function should be equally distributed if the underlying pathology is a more generalised process such as inflammation or malnutrition. To address this question, we used the non-volitional technique of supramaximal magnetic nerve stimulation to assess the strength of the adductor pollicis and quadriceps muscles.

Methods: 14 patients with stable COPD (not on oral corticosteroids) and 14 age matched healthy controls were recruited. Twitch adductor pollicis tension (Twap) and twitch quadriceps tension (TwQ) were determined following supramaximal magnetic stimulation of the ulnar and femoral nerves respectively.

Results: Patients and controls were well matched for age, weight, height, and BMI. Mean FEV1 was 1.77 (1.42) L. Mean FVC was 2.63 (1.95) L. FEV1/FVC was 0.66 (0.37). TwAP was significantly lower in the COPD group (68.2 (30.4) cmH2O; p<0.001).

Discussion: The threshold and 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 MIP 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.

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In subjects with acute and chronic type 2 respiratory failure (due to kyphoscoliosis, sleep hypventilation, and chronic obstructive pulmonary disease) application of nasal intermittent positive pressure ventilation (NIPPV) helps to restore arterial blood gases to normal levels, and aids breathing by unloading inspiratory muscles.10 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 (MIP) and expiratory maneuvers (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 IMe testing procedure.

Results: Group one patients (dNIPPV <1 month) had significantly (p<0.05) lower PaO2 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 (Group1 32 (4) vs Group2 47 (9) cmH2O) as well as sustainable MIP, a measure of IMe (Group1 102 (50) vs Group2 158 (50) time/pressure units). 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.

COPD exacerbations: ITU to discharge

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 a specialist respiratory physician and if the benefits spread, NIV became the treatment of choice for patients admitted in hypercapnic respiratory failure secondary to COPD. The number of patients requiring NIV grew steadily and a business case was prepared. The rHDU has significantly contributed to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability.

P12 VARIATION IN CONSULTANT’S PROGNOSTIC ESTIMATES FOR IDENTICAL PATIENTS MAY EXPLAIN VARIATIONS 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 the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability. This study exploits the fact that consultants on the Heart of England Critical Care Network were invited to the management of identical patients and the causes for the variability.

Methods: One hundred and twenty consultant cardiologists were surveyed with a questionnaire asking for their opinion on whether a COPD patient requiring ICU admission would be admitted to ICU. The questionnaire included four scenarios of identical patients with COPD presenting in acute respiratory failure secondary to an exacerbation of COPD. The decision to institute mechanical ventilation in a patient presenting in acute respiratory failure secondary to an exacerbation of COPD can be difficult and controversial. This study aimed to determine whether there is a real difference in the views held between respiratory physicians, general physicians, and intensivists, whether there are significant differences in practice between individual clinicians and which clinical factors most influence decision making.

Method: A questionnaire was circulated by post to 600 consultants (200 in each specialty) selected randomly and at meetings to 125 GPs. It included 25 different demographic, chest and comorbidity variables that were each scored 0 to 3 according to the perceived relevance of the variable in the decision to embark on a trial of ventilation (where 0 was irrelevant and three contraindicated ventilation). The total score for all the variables was calculated for each clinician (0 to 75).

Results: 356 questionnaires were returned; 321 were completed and analysed (120 respiratory, 109 general medicine, 92 intensive care). The total scores for the clinicians in each specialty were: respiratory: mean 37.5, 95% CI 35.8 to 39.3, range 15 to 68; general medicine: mean 39.5, 95% CI 37.7 to 41.4, range 12 to 65; intensive care: mean 38.8, 95% CI 36.9 to 40.8, range 16 to 64. The importance placed on the different variables was ordered similarly across specialties. The most influential factors in deciding not to ventilate a patient were documented permanent cognitive dysfunction resulting constant supervision, nursing home resident failing all activities of daily living, lung cancer deemed inoperable due to COPD, previous CVA such that patient chair bound or aphasic, and previous difficulty weaning from ventilation. The factors regarded as being least important were documented depression requiring treatment, osteoporosis with vertebral body collapse, continued smoking >20 cigarettes/day, plasma albumin <30g/l, and an above knee amputation for peripheral vascular disease.

Conclusions: There were no significant differences in clinical decision making between the specialties but there was wide variation between individual clinicians. Few of the factors investigated would contraindicate ventilation alone.

P13 CLINICAL DECISION MAKING: VENTILATING PATIENTS WITH EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Introduction: Previous research has shown that doctors considering patients with exacerbations of chronic obstructive pulmonary disease (COPD) are less likely to ventilate patients who present in acute respiratory failure secondary to COPD than those who present with acute coronary syndromes. This study sought to understand why this might be and elicit the factors influencing clinical decision making in a multi-centre, multi-specialty sample of doctors.

Methods: A paper or electronic questionnaire (2006-2007) was distributed to 600 consultant cardiologists, respiratory physicians and general physicians in the UK. The questionnaire included four scenarios of identical patients with COPD presenting in acute respiratory failure secondary to an exacerbation of COPD. The decision to institute mechanical ventilation in a patient presenting in acute respiratory failure secondary to an exacerbation of COPD can be difficult and controversial. This study aimed to determine whether there is a real difference in the views held between respiratory physicians, general physicians, and intensivists, whether there are significant differences in practice between individual clinicians and which clinical factors most influence decision making.

Method: A questionnaire was circulated by post to 600 consultants (200 in each specialty) selected randomly and at meetings to 125 GPs. It included 25 different demographic, chest and comorbidity variables that were each scored 0 to 3 according to the perceived relevance of the variable in the decision to embark on a trial of ventilation (where 0 was irrelevant and three contraindicated ventilation). The total score for all the variables was calculated for each clinician (0 to 75).

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Conclusions: There were no significant differences in clinical decision making between the specialties but there was wide variation between individual clinicians. Few of the factors investigated would contraindicate ventilation alone.

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 suggest that patients who have cardiovascular disease (CVD) are at higher risk of death.
have highlighted the difficulty of predicting mortality in this patient group from standard clinical and other scoring systems.10 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 St Thomas's 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. In five of 14 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 54% (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.

**Abstract**

**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 the 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) FEV1 was 1.28 (0.55) l, FEV1 predicted 50.0 (18.0%), mean FEV1/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 with a range of 7.7 to 93.3. The AQ20 was strongly correlated to the SGRQ (Spearman rank correlation); SGRQ symptom (0.548), activities (0.681), impacts (0.742), and total (0.749) p<0.001. Other statistically significant findings with AQ20 were predicted FEV1 (−0.271) and pack years smoked (0.242) p<0.005. Patients were divided into those who had less than three COPD exacerbations per year (infrequent exacerbators) and those who had three or more exacerbations per year (frequent exacerbators).

The AQ20 shows a strong relationship to yearly exacerbation rate. The AQ20 is simple to implement and can be used to assess health status for patients with COPD in primary care where time and resources are limited.

**P19 USING A PRIVATE SECTOR PARTNERSHIP TO PROVIDE SUPPORTED EARLY DISCHARGE FOR ACUTE EXACERBATIONS OF COPD IN A DISTRICT GENERAL HOSPITAL**


Home care is successful in about 25% patients hospitalised with an exacerbation of COPD, though nursing resources are not always available to provide it. Encouraged by the government’s endorsement of partnerships between the NHS and the private sector, a six month home care service was commissioned from Nestor Primecare, for nurse led 24hr care for selected patients following early hospital discharge. The Torbay Hospital Outreach Respiratory Team (THORT) has been providing regular maintenance visits to patients with exacerbations of chronic obstructive pulmonary disease (COPD) since December 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 had 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 completed sets of admission data for 12 months prior to the visits, and had been receiving maintenance visits for at least two months. Total bed days and THORT days were averaged over the previous 12 month period, and for the period since the onset of maintenance visits to give an indication of whether admissions had subsequently reduced.

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. The average number of maintenance visits undertaken per month was 12.8.

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.

**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 December 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.

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**P21 PRIMARY CARE EXPERIENCE OF PATIENTS ADMITTED TO HOSPITAL WITH AN EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

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Although ‘Hospital at Home’ schemes for early facilitated discharge of patients with exacerbations of chronic obstructive pulmonary disease (COPD) have become more prevalent, schemes to prevent admission are less widespread. AC was awarded a Health Action Zone fellowship to investigate the role of a respiratory therapist in assessing and triaging potential admissions with exacerbations of COPD into those who require admission, early facilitated discharge (by referral to our Hospital at Home Scheme) or conventional discharge. This survey was done to inform the design of the potential new service.

Fifty three patients (mean age 71) admitted to hospital with exacerbations of COPD were questioned about their contact with primary care prior to admission. There were 26 men and 27 women. Symptoms which prompted admission included increased breathlessness (92%), wheeze (72%), cough (55%), increased sputum volume (49%), sputum colour change (45%), fever (38%). Three patients denied any change in symptoms. Prior to admission, 25% of the patients had had no contact with primary care services, 25% had telephone contact only, 34% were seen at home, and 17% were seen in the GP surgery. Of the 40 patients who had some contact with primary care, 40% had contact in the morning, 40% in the afternoon to July 2002 there were 276 admissions to the Trust coded J44.1 (exacerbation of COPD). The average hospital stay for this condition locally is eight days. Of these patients, 124 (44%) (50% male) received supported discharge within 1–2 days of admission. Fifty four calls for support came from 34 patients but none needed referral to their GP. There were 18 readmissions during the period of home care (11%). Seven patients died during readmission, but none of those remaining at home. Patient satisfaction was high, and only one person refused home care.

Conclusion: This 10 day service was successful in a higher proportion of patients than in previous studies, and at a total cost of £85 000.

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 training may be able to deal with some patients with exacerbations and prevent unnecessary admission to hospital.

## 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 SPUTUM CYTOTOLOGY

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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 premalignant 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 66.5yrs (range 51 to 79yrs). 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.

<table>
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<td>Disease free 42 mths</td>
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<tr>
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<td>Abnormal fluorescence</td>
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<tr>
<td>1 Sputum SQC</td>
<td>Abnormal fluorescence</td>
<td>CIS in area of abnormal fluorescence (12 mths follow up)</td>
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<td>Normal histology (false +ve)</td>
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### P24 ENDOBRONCHIAL MIMICS OF LUNG CANCER: A CASE REPORT AND REVIEW OF BRONCHOSCOPY DATA BASE

S. Lohani, P.R. Chadwick, G.R. Armstrong, B.R. O'Driscoll, S.C.O. Taggart. Respiratory Medicine Department, Hope Hospital, Salford M6 8HD, UK

**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 effusion. CXR examination confirmed the clinical findings. ESR was 122 mm/hour. CT scanning revealed a loculated effusion and loss of volume in right lower lobe (RLL) with associated distal consolidation. Initial and subsequent bronchoscopies demonstrated an endobronchial RLL “tumour” but biopsies were negative for cancer. The patient was informed that cancer seemed the most likely cause of his symptoms. However, ultrasound guided aspiration of the fluid revealed an empyema which grew Actinomyces israeli. This was subsequently demonstrated to be present in both previous biopsy specimens. The patient made a full clinical and bronchoscopic recovery after six weeks of penicillin treatment.

**Review of bronchoscopy data base:** 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).

**Conclusions:** 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.
P25 BRONCHOALVEOLAR LAVAGE, NON-INVASIVE INVESTIGATIONS AND RADIOLOGY: IMPACT ON TREATMENT IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES AND PULMONARY INFILTRATES

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Pulmonary infiltrates are a frequent complication in immunosuppressed 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 periperostrum. Post FOB, 1/21 patient required admission to the intensive care unit.

Blood cultures, sputum cultures, and nasopharyngeal aspirates were positive 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 with treatment modification in 8/13 cases. In 7/25 cases, CXR was normal of which 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.

P26 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 postprocedure 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.

P27 GENERAL PRACTICE OPEN ACCESS SPIROMETRY: WHO WAS REFERRED IN 2001?

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We provide an Open Access spirometry service to primary care. Patients attend from 09:30 to 11:30 Mon to Fri. A technologist obtains a history, spirometry pre and post β2-agonist and pulse oximetry. A report and recommendations are sent to the GP.

Aim: To review the throughput of this service in 2001.

Methods: The records of all patients attending the service were reviewed. Data are given as median (range).

Results: 706 patients attended, with 55 having further studies after a trial of steroids. Age was 54.7 yr (10 to 91), 366 were female and body mass index [BMI] was 27.4 kg.m-2 (14.9 to 32.6). 198 had a BMI > 30 kg.m-2. 36% were smokers, 43% had cough, 20% had wheeze, and 397 had sputum production. MRC dyspnoea grade (n = 696) was Grade 1–110, Grade 2–230, Grade 3–223, Grade 4–116, and Grade 5 – 17. One hundred and ninety six patients had no medication, 49 were on antibiotics, 261 on a β2-agonist, 24 on an anti-muscarinic, 177 on oral/inhaled steroids, 32 on a β2 blocker, 57 on a blood pressure tablet, and 203 patients were on other therapies.

Lung Function: FEV1%predicted was 84.7 (1 to 143), FVC%predicted was 89.1 (14.7 to 144) and FEV1/FVC was 74.9 (23.9 to 100). Sixty one studies showed submaximal/variable efforts. One hundred and fifteen patients had treatment modification, 68 reversible airflow obstruction, 438 irreversible airflow obstruction, and 24 a restrictive defect. For reversibility, absolute change in FEV1 was 0.41 (0.2 to 1.45) and % change was 29.8% (15.4 to 27.1). Nine out of 55 steroid trials showed a positive response with the absolute change in FEV1 (post β2 agonist) of 0.45 J (0.2 to 0.8) and % change of 29.8% (15.1 to 64.0). Pulse oximetry (n = 676) showed 34 patients had an O2 saturation ≤92%. Recommendations: 25 patients with airflow obstruction to change from β blockers, 145 patients for a trial of inhaled steroids with repeat spirometry, 40 to be prescribed a β2 agonist, 184 to be referred for further investigations—LTOT (n = 34), occupational lung disease (n = 36), ?EIA (n = 27), excessive dyspnoea for spirometry (n = 63), and restrictive defect (n = 24).

Conclusion: This service (1) accurately assesses simple lung function, (2) identifies groups of patients requiring further investigation or a change in therapy, and (3) provides recommendations to assist the primary care physicians to manage their patients.

P28 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 quantity 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.

Abstract P24

<table>
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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 ADVANCED ASTHMA AND 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 and healthy workers exposed to irritant agents, and which index of PEF variability is best at doing so.

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. (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 for change was 2.8% (95% CI: 1.5% to 4.1%). The within period (eight weeks) range of change was ±0.17% (p=0.05). Sensitivity for diagnosing occupational asthma using this index of PEF variability is best at doing so.

Conclusion: The variability of measured levels is similar for within test (paired estimates of the same sample), within day and between visits, for both normals and children with asthma and CF. Thus our data suggest 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 by 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 day. On each of the three days, 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)(0.35) 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

J. B. McCafferty1, P. K. Kew1, A. Haston2, J. A. Innes1. 1Respiratory Unit, Western General Hospital, Edinburgh; 2Department of Mechanical and Chemical Engineering, Heriot-Watt University, Edinburgh

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 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 increased 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—base line FEV1 1.59 (SD 0.45), FEV1 % predicted 55 (16%), FVC/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 conductance (Z5Hz 0.77 – predicted 2.531) in response to baseline. Median PC20 was 0.54 (range 0.1 to >16) and all but one subject achieved a PC20 at <2 mg/ml.

After challenge mean FEV1 fell by 34 to 1.051 (p<0.01), mean FVC fell by 38% to 2.081 (p<0.01), mean SVC from 3.741 to 2.611 (p<0.04), and IC by 38% to 1.601 (p<0.01). TCL, when measured, was constant therefore these changes represent significant increases in RV. Airway resistance by body plethysmography (Raw) increased overall (3.04 v 12.16) but showed minimal change in three subjects while measurement in five other subjects was technically difficult.

IOS measurements showed an overall modest increase in impedance (0.77 v 1.01; p<0.01) which was due to a fall in reactance (-0.35 v -0.55; p=0.04). There was no significant change in resistance (0.67 v 0.83; p=0.12).

In individuals with COPD who are subject to bronchial challenge assessment of changes in FEV1, does not give a true measure of change in respiratory system resistance. BHR is likely to be determined less by ASM contraction and more by increases in hyperinflation, which in turn alter the ability of the lung to overcome airway narrowing.
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).

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 grades 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 grades 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% felt they were not doing well compared with 43% with grade 4 and 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 (KCADE, 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 increased 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 ~910H.U., the 15% 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.

P38 CT SCANNING IN SUBJECTS WITH COPD AND THEIR RELATIVES

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Participants in a prospective COPD genetics study underwent thoracic HRCT 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 radiological 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 impressive in identifying mild-moderate emphysema but severe obstruction correlated well with CT findings. In subjects without a recent infection bronchiectasis is frequently present without symptoms.
**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.

### Table 1

<table>
<thead>
<tr>
<th>IDS criteria</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ &gt; 50%, mild/mod dyspnoea, no</td>
<td>FEV₁ &gt; 50%, mild/mod dyspnoea, no nutritional</td>
<td>FEV₁ &lt; 35%, severe dyspnoea, nutritional</td>
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</tr>
<tr>
<td>nutritional depletion</td>
<td>nutritional depletion</td>
<td>depletion</td>
<td></td>
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**P40** A COMPARISON OF INTENSIVE, MDI-DELIVERED AND NEBULISED BRONCHODILATOR THERAPY IN SEVERE COPD

T.K. Rogers, A. Venners, H. Drayton, P. Camplin, G. Segust, R. McCook. Chest Clinic, Doncaster Royal Infirmary, Arthington Road, Doncaster, S. Yorks, DN2 3LT, UK

**Background:** We have investigated whether nebulised therapy provides superior bronchodilation to a combination of high-dose anti-inflammatory 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 out-

**Results:** Seventy three patients were enrolled, until the required number of 42 subjects with adequate data was obtained. Each of the three nebulised regimes 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 Ipr/ Salbutamol</th>
<th>Nebulised Salbutamol</th>
<th>Nebulised Ipratropium</th>
<th>Nebulised CombiVent</th>
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</thead>
<tbody>
<tr>
<td>am</td>
<td>189 (10)</td>
<td>223 (13)</td>
<td>224 (12)</td>
<td>227 (12)</td>
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<tr>
<td>pm</td>
<td>201 (11)</td>
<td>227 (13)</td>
<td>229 (12)</td>
<td>234 (13)</td>
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<tr>
<td>noite</td>
<td>204 (11)</td>
<td>229 (13)</td>
<td>226 (12)</td>
<td>231 (13)</td>
</tr>
</tbody>
</table>

**P41** ECONOMIC IMPLICATIONS OF REDUCTIONS IN COPD REHOSPITALISATION DUE TO TREATMENT WITH INHALED CORTICOSTEROIDS (ICS)

M.D. Spencer. GlaxoSmithKline, Greenfield, 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, Greenfield, 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. Am J Respir Crit Care Med 2001;164:580–4). 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 1995, 96, and 97 (96 only for health status) forms the population for this study. Respondents with

### Table 2

<table>
<thead>
<tr>
<th>IDS</th>
<th>GOLD</th>
<th>ATS</th>
<th>BTS</th>
<th>ERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre %</td>
<td>Pst %</td>
<td>Pre %</td>
<td>Pst %</td>
<td>Pre %</td>
</tr>
<tr>
<td>Normal</td>
<td>37</td>
<td>70</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Mild stage I</td>
<td>37</td>
<td>70</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Moderate stage II</td>
<td>51</td>
<td>74</td>
<td>5823</td>
<td>518</td>
</tr>
<tr>
<td>Severe stage III</td>
<td>57</td>
<td>77</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
Abstract P42

Mean (Median) by ICS prescription group

<table>
<thead>
<tr>
<th>FEV₁, % predBMI</th>
<th>EQ-SD</th>
<th>SF-6D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS 47 (47)</td>
<td>26 (25)</td>
<td>0.66 (0.69)</td>
</tr>
<tr>
<td>No ICS 55 (57)</td>
<td>26 (25)</td>
<td>0.78 (0.79)</td>
</tr>
</tbody>
</table>

on FEV₁/FVC ratio <70% and an FEV₁ % predicted of <70% were selected for analysis. Mean age = 65.9 and 42.2% were women. The relationship between disease severity and ICS prescription in COPD was investigated and the statistical significance tested using the independent t-test.

Results: No statistically significant relationship was found between ICS prescription and BMI (p=0.518), whilst in the case of FEV₁ % predicted and of health status measured by both the EQ-5D and by the SF-6D patients taking ICS had an average worse scores than those not taking ICS (all p<0.001). See table.

Conclusions: The majority of patients who are prescribed LTOT are likely to be explained by these differences between those taking and not taking ICS.

P43 AUDIT OF LTOT PRESCRIPTIONS IN BLAENAU GWENT

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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 concentrators 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 concentrators 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.

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. Twenty hundred and seventy six consecutive patients with COPD (143 male; 133 female) were reviewed by the dietician 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 underweight, 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 change 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 no non-significant trend for increasing BMI to be associated with shorter length of hospital stay (5.9 (12.7) days for underweight to 2.9 (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.

P45 BRONCHOSCOPIC LUNG VOLUME REDUCTION (BLVR) WITH ENDOBRONCHIAL VALVE IMPLANTS


Background: Surgical lung volume reduction (LVRS) 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 Emphasys® valve implant and delivery system, in patients unsuitable for surgical LVRS.

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 emphysematous 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 drainage, 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. Ghiassi, 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 medication 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 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 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. Correlations 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).

Machine on-time was correlated to Urinary Obstructive Scores with rho –0.221 (p=0.301) to Urinary Irritative Scores with rho –0.030 (p=0.798) and Total Urinary Scores rho 0.032 (p=0.790).

Conclusion: Patients with OSA have Urinary Scores similar to the normal population as measured by standard urology tools, and any increased urinary disturbance, prior to CPAP is not significantly correlated 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 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) vs 60 (10)) nor did BMI (27 (2) vs 28 (4)). AHI was significantly higher for cases (41 (IQR 27–52) vs 13 (IQR 10–20). There was no significant difference in the distribution of either alleles or genotypes of Apo E between cases and controls (genotypes shown). See table.

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<tbody>
<tr>
<td>Cases</td>
<td>16</td>
<td>7</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Controls</td>
<td>22</td>
<td>5</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Discussion: There is no difference in distribution of Apo E alleles and genotypes between subjects with SDB and their siblings. Our results are supported by two other studies looking at Apo E in relation to SDB. Further samples will be genotyped both for Apo E and other candidate genes in this ongoing study.

Acknowledgements: nursing staff & technicians of the Scottish National Sleep Laboratory; Dr N Mcardle; Genetics Core, Wellcome Trust Clinical Research Facility, Edinburgh.

Supported by: Helen Bearpark Scholarship; AFUW fund; ERS LITT fellowship.

Abstract P49

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. Data files were converted into European Data Format (EDF) (SleepLab 1000e, Jaeger). A single scorer manually scored the study in random order. Subject demographics are presented in the table.

Results: Subjects completed the 10 min tasks in the afternoon, in random order. Subject demographics are presented in the table. There were no significant differences between the untreated OSA and healthy volunteers as compared to R&K.

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.

Abstract P50

P50 ANALYSIS OF SLEEP STAGE USING A NEURAL NETWORK: COMPARISON TO MANUAL SCORING IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA (OSA)

F. Buchanan, N. Wiltschre, J.R. Catterall A.H. Kendrick. Papworth Hospital Sleep Centre, Cambridge, UK

Sleep is a continuum, often with short 2–3 s events. Traditional scoring methods are time consuming, expensive and relates poorly to symptoms. An attractive alternative based on neural net technology is the BioSleep system. It is a single channel method, which provides second by second measurements and classifies sleep as awake, light or deep using probability assessment rather than the traditional 6–7 point staging system. This may provide better analysis of microarousals and also shorten technician analysis time to less than five minutes.

We compared BioSleep to R&K analysis using the same data set from 28 patients with moderate or severe OSA (Mean AHl = 52.4 [SD 18.4]) during split night polysomnography in which therapeutic CPAP was administered for half the night. BioSleep (B) was as good as R&K (R) at detecting differences between CPAP and air in terms of arousals (B: 44 v 80; p<0.001, R: 51 v 79; p<0.02), arousal index (B: 12 v 22; p<0.001, R: 18 v 29; p<0.005), deep sleep % time (B: 30% v 8%; p<0.0001, R: 24% v 7%; p<0.0001) and light sleep % time (B: 70% v 92%; p<0.02) and number of awakenings (B: 24 v 36; p<0.002, R: 2.8 v 3.2; p=0.53) and total time awake (B: 0.9 hrs v 1.27hrs; p<0.05, R: 0.46hrs v 0.35hrs; p=0.15) but was inferior at detecting differences in sleep onset latency (B: 0.1 v 0.14; p=0.80, R: 0.26 v 0.10; p<0.001). BioSleep gave a more detailed picture of sleep architecture that was clearly different with therapy. Direct comparison showed that BioSleep predictably scored more awakenings and less total sleep time and sleep maintenance efficiency but there were no significant differences in % light or deep sleep, number of arousals or arousal index.

BioSleep is a method of sleep analysis comparable to R&K for several important parameters. While not replacing R&K for investigation of REM related and complex sleep disorders BioSleep provides additional information compared to R&K while shortening analysis time and this makes it an attractive analysis method for more widespread use.

Abstract P51

P51 COMPARISON OF R&K AND BIOSLEEP SYSTEMS FOR ANALYSIS OF OBSTRUCTIVE SLEEP APNOEA

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At present the gold standard in the objective assessment of sleep apnoea is still polysomnography with data analysis using the Rechtschaffen & Kales (R&K) guidelines for 20–30 second sleep epochs. This is time consuming, expensive and relates poorly to symptoms. An attractive alternative based on neural net technology is the BioSleep system. It is a single channel method, which provides second by second measurements and classifies sleep as awake, light or deep using probability assessment rather than the traditional 6–7 point staging system. This may provide better analysis of microarousals and also shorten technician analysis time to less than five minutes.

We compared BioSleep to R&K analysis using the same data set from 28 patients with moderate or severe OSA (Mean AHl = 52.4 [SD 18.4]) during split night polysomnography in which therapeutic CPAP was administered for half the night. BioSleep (B) was as good as R&K (R) at detecting differences between CPAP and air in terms of arousals (B: 44 v 80; p<0.001, R: 51 v 79; p<0.02), arousal index (B: 12 v 22; p<0.001, R: 18 v 29; p<0.005), deep sleep % time (B: 30% v 8%; p<0.0001, R: 24% v 7%; p<0.0001) and light sleep % time (B: 70% v 92%; p<0.02) and number of awakenings (B: 24 v 36; p<0.002, R: 2.8 v 3.2; p=0.53) and total time awake (B: 0.9 hrs v 1.27hrs; p<0.05, R: 0.46hrs v 0.35hrs; p=0.15) but was inferior at detecting differences in sleep onset latency (B: 0.1 v 0.14; p=0.80, R: 0.26 v 0.10; p<0.001). BioSleep gave a more detailed picture of sleep architecture that was clearly different with therapy. Direct comparison showed that BioSleep predictably scored more awakenings and less total sleep time and sleep maintenance efficiency but there were no significant differences in % light or deep sleep, number of arousals or arousal index.

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Abstract P52

P52 THE EFFECT OF RECORDING SITE IN ACOUSTIC ANALYSIS OF SNORING

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Introduction: Several groups have investigated acoustic analysis of snoring, in order to investigate the mechanism of snoring, to distinguish obstructive sleep apnoea from non-apnoeic snorers and to predict the outcome of surgical intervention. However, the recording site has varied, and it is not known how this affects the acoustic parameters measured.

Methods: We studied 47 subjects prior to laser-assisted palatoplasty for severe snoring. All underwent preoperative polysomnography and patients with AHl > 25/h were excluded.
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 dB A 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 1999;24:119–23], and peak factor ratio (the ratio of peak to RMS sound energy) [Clin Otolaryngol 1999;24:130–3]. 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.

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 mm Hg), (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<0.05) but the curve was not displaced. Asphyxia alone increased blood pressure (+7.0 (1.1) mm Hg, p<0.0005) and displaced the curve higher pressures by +16.8 (2.1) mm Hg (p<0.0003) 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 baroreceptor reflex 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 oximeters 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 disturbances.

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?

E. Morrish, S.N. Pilsworth, M.A. King, J.M. Sheenerson, I.E. Smith. Papworth Hospital, Cambridge, UK

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.11 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 in1 (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 τb coefficient.

Results: One hundred and three subjects (82 male) met the study criteria (table). Hours of CPAP use per night and change in ESS were not significantly correlated (τ = −0.094; p=0.170).

Discussion: In a month long trial setting only 4% of subjects withdrew from using CPAP.11 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.

Abstract P55 Study group baseline demography and outcome measures

<table>
<thead>
<tr>
<th>Baseline demography</th>
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<th>Outcome measures</th>
<th>Median (5th, 95th percentiles)</th>
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<tr>
<td>Age (years)</td>
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<td>CPAP use (hrs/night)</td>
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<tr>
<td>Weight (kg)</td>
<td>111 (76, 158.1)</td>
<td>Length of use (days)</td>
<td>523 (231.6, 802)</td>
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<tr>
<td>BMI</td>
<td>36.2 (27.5, 53.5)</td>
<td>ESS</td>
<td>6 (0, 16)</td>
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<td>DI (dips/hr)</td>
<td>40 (10, 60)</td>
<td>Change in ESS</td>
<td>−10 (−20.8, −1)</td>
</tr>
<tr>
<td>ESS</td>
<td>17 (10, 23)</td>
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</tr>
</tbody>
</table>

Abstract P56

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>SC 3 months</th>
<th>HV 3 months</th>
<th>P for diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>Base 3 months</td>
<td>Base 3 months</td>
<td>HV</td>
</tr>
<tr>
<td>Symptoms</td>
<td>28.4</td>
<td>12.8*</td>
<td>27.4</td>
</tr>
<tr>
<td>Epworth</td>
<td>15.3</td>
<td>7.8*</td>
<td>13.8</td>
</tr>
<tr>
<td>HAD Anx</td>
<td>8.2</td>
<td>5.9*</td>
<td>8.4</td>
</tr>
<tr>
<td>HAD Dep</td>
<td>7.2</td>
<td>3.9*</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Data are mean values; *Differs from baseline (p<0.01).

Conclusion: CPAP led to marked improvement in patients with SAHS treated in the DGH setting. There was no difference between our two groups, both obtaining a similar magnitude of improvement to that reported in the enhanced care group from the National Sleep Laboratory.

Funded by the William Sutherland Trust.

P57 CONTINUOUS POSITIVE AIRWAYS PRESSURE (CPAP) TREATMENT CAN REDUCE ANXIETY AND DEPRESSION IN OBSTRUCTIVE SLEEP APNOEA

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Introduction: We tested the hypothesis that CPAP treatment will improve anxiety and depression scores and if effects are correlated to machine use.

Methods: Eighty consecutive patients (74 male), age 51.2 (9.7) (mean (SD)) years, mean BMI 35.5 (5.7), mean Epworth Sleepiness Score 14.4 (5.2), mean AHI 25.1 (22.8), and mean % dip-rate of 31 (21.7) per hour, were prospectively studied. They completed the Hospital Anxiety and Depression Score at autotitration and after approximately one month of treatment with CPAP. Clock timers were hidden and machine “on time” was recorded at one month as a surrogate marker for machine use.

One sample t tests assessed if change in anxiety and depression were statistically significantly different from zero. Pearson’s correlation assessed the relationship between “on time” and changes in HAD scores.

Results: Patients were followed for a mean of 33.7 (13.4) days. Data was available on 70 patients. No patients reported life events or medication changes over this period. The mean anxiety score fell from 7.8 (3.7) to 6.3 (4.2) and the mean value for depression fell from 6.0 (3.7) to 4.9 (3.4) post treatment. Test statistics are −4.03 and −4.11 for hypotheses of zero change in anxiety and depression, respectively, p<0.001 in both cases. Pearson’s correlations between change in anxiety and depression with machine use were r = −0.297 (p=0.012) and r = −0.382 (p=0.001), respectively.

Conclusion: OSA patients have similar anxiety and depression scores to the normal population but there were statistically significant improvements in both scores after only a short period of treatment. We conclude that CPAP has a graded effect, with the greatest benefits observed in those using their machines the most.

Lung cancer

P58 OUTCOME OF A CODED X RAY SYSTEM TO FACILITATE REFERRAL OF CASES OF SUSPECTED LUNG CANCER

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Chest radiography is an important investigation in patients with persistent chest symptoms, and can be an early indication of malignant disease. This is of particular importance when the x-ray abnormality is an incidental finding, for example on a preoperative routine film. In order to ensure the rapid investigation of patients with suspected lung cancer, we have introduced a coded x-ray reporting system for chest x-ray taken in Liverpool, including those performed in the community. When lung cancer is suspected, the reporting radiologist codes the report accordingly and the result is faxed to the relevant clinician, with a suggestion that the patient is referred to the rapid access service. In addition, all reports are electronically sent to the lung cancer specialist nurse, who monitors the referrals and ensures that the clinician acts on the report. We have audited the outcome of the first 477 patients in whom the radiologist flagged as suspected lung cancer using this coding system. Two hundred and fifty six were GP requests; nine of these were subsequently admitted to hospital, 215 were referred to the rapid access outpatient service, 24 were referred to a chest outpatient clinic, and eight refused further investigation. Within the secondary care sector, 206 were taken; 41 were admitted from the A&E department, one was a clinic attendee, and 164 were inpatients of whom 74 were discharged to attend the rapid access outpatient service. Eight of the latter group were surgical patients in whom the finding of a suspicious x-ray lesion was incidental. In the remaining 15 cases, further investigation was not deemed necessary by the supervising clinician. Mean time from chest x-ray to attendance at the rapid access outpatient clinic was 14 days, and mean time from referral to first appointment was 8.5 days. Overall 268 patients (56%) were subsequently diagnosed with lung cancer. Thus, we have shown that this x-ray coding system allows the rapid access of patients with suspected lung cancer to the relevant service. Furthermore, processing the reports through the dedicated lung cancer nurse acts as a safety net and ensures that cases are not missed by busy clinicians. We recommend the use of such coding systems to clinicians charged with providing rapid access lung cancer services.

P59 AVOIDING LATE PRESENTATION OF LUNG CANCER: A PROACTIVE APPROACH TO MANAGEMENT OF ABNORMAL CHEST RADIOGRAPH REPORTS

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Late presentation with lung cancer may preclude radical treatment. System breakdowns may result in abnormal chest radiograph (CXR)
reports not reaching the necessary clinician or being acted upon. In January 2000 we introduced a more pro-active approach to the handling of CXR reports that raise the possibility of lung cancer via a “failsafe” system. In partnership with our radiologists a coding system was used for CXR’s requested both from primary and secondary care. CXR’s with features strongly suggestive of a bronchial neoplasm were coded “TCXX” by the radiologist. Where neoplasia could not be excluded, a repeat film after 4–6 weeks was advised and a “TPXX” coding was given. All abnormal reports were immediately forwarded to the lung cancer team. Typically we would contact the patients’ GP by telephone to discuss the report and requested an urgent referral from the GP. We later audited all new patients attending our rapid access lung clinic confirm the presence of a primary cancer over a one year period to assess the impact of this system.

**Results:** The codes were initially not applied to all abnormal CXRs, especially by trainee and locum radiologists. Of 228 new patients seen, 102 (45%) had CXRs coded TCXX/TPXX and 126 (55%) had abnormal CXRs with no coding. The percentage of patients later confirmed to have lung cancer were: TCXX (71%), TPXX (23%), and no code (63%). The mean (range) time from day of CXR to clinic attendance was 8.5 (1 to 21) days in the TCXX group and 16 (1 to 162) days in the no code group (P<0.001). A survey of 66 local GPs found that 86% felt that the failsafe system was helpful and should be continued. A recent re-audit has found that 69% of abnormal CXR’s now receive the appropriate code.

**Conclusions:** A “failsafe” chest radiograph system is an effective tool that helps to ensure that patients with lung cancer are seen promptly and do not “slip through the net”.

**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 56:633 1991; 51:81–8). Some Units have such patients directly from the chest X ray department while others (including ours) rely on the patients’ GPs 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 was repeatedly died without being seen. The time patients were 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 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 of 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).

The 378 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 increase 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**
R.A. Heinink, H. Moudgil. Princess Royal Hospital NHS Trust, Apley Castle, Telford, UK

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; 124 of these patients 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 respiratory 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 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 elected 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**
N. McAndrew, J. Woolley, D.R. Baldwin, A.L. Burton. Wrexham Maelor Hospital, Wrexham, LL13 7TD; Nottingham City Hospital, Nottingham NG5 1PB; Royal Preston Hospital, Preston PR2 9HT, UK

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 with bronchoscopy, computerised tomographic scan of the thorax (CT) or both? We sent a postal questionnaire to 610 UK chest physicians.
Abstract P63

<table>
<thead>
<tr>
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<th>lx</th>
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<th>CT alone</th>
<th>Br alone</th>
<th>CT &amp; Br</th>
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<td>35NS</td>
<td>72%</td>
<td>28%</td>
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</tbody>
</table>

CXR, chest x-ray; CT, computed tomography; Br, bronchoscopy.

Physicians posing five clinical scenarios. The scenarios described patients with isolated haemoptysis and a normal CXR: a 35 year old never smoker [35NS]; a 59 year old smoker with acute bronchitis [59S]; a 70 year old smoker who had a violent coughing fit [70S]; a 65 year old smoker with haemoptysis “out of the blue” [65S]; a 70 year old never smoked [70NS]. We received 291 replies (48%) (table).

Older patients and smokers are more likely to be investigated (p<0.0001, 35NS v 70NS; p<0.01, 70S v 70NS; x²). A minority would not investigate minor haemoptysis occurring during acute bronchitis. CXR surveillance is more popular than CT alone (p<0.001; x²). For smokers nearly 1/3 of respondents would rely on bronchoscopy alone. The most popular strategy employs both bronchoscopy and CT, (p<0.025, Br alone v CT & Br). The reliance on bronchoscopy alone is interesting as there is some evidence to suggest CT has greater sensitivity for picking up lesions not visible on CXR (p<0.025, Br alone v CT & Br). CXR surveillance may have little benefit to the patient because it is less sensitive than either CT or bronchoscopy and because it will inevitably delay diagnosis. This survey has illustrated a lack of consensus in a difficult area of respiratory medicine.

P64 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 Hiné 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.

P65 ANALYSIS OF HISTOLOGY RESULTS TO IMPROVE PROTOCOLS FOR THE DIAGNOSIS OF LUNG CANCER

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There is still considerable variation in schematics for the management of pulmonary malignancies. This is particularly true for pleural disease where evidence is lacking. We looked at all 1012 cytological or histological assessments performed, in 654 patients referred between January 2000 and January 2001 with suspected pulmonary malignancy to produce local recommendations.

Pleural fluid cytology was analysed for diagnosis in 202 patients, of whom 48 had 2–4 samples taken. Twenty of 264 (9%) samples showed bronchoscopy. This was unhelpful in 18/21 irrespective of whether initial pleural cytology was reported as suspicious (7) or not (11). The 3/21 patients with diagnostic bronchoscopic abnormalities all had central abnormalities on CT.

At bronchoscopy where no lesion was visible 154 patients had a blind wash, brush biopsy or both. Eight of 154 (5%) had positive cytology and the addition of a brush biopsy increased the yield from 2% (2/92) to 11% (6/62). In 104 patients where a visible lesion was biopsied, an additional wash, brush biopsy or both increased the diagnostic yield by 2%–positive biopsy in 44 (42%), wash only in two (2%), brush only in three (3%) and wash and brush only in one (1%). Seventeen patients with a visible lesion and negative histology had a second bronchoscopy and 4/13 (31%) produced positive histology.

We recommend (1) Diagnostic rate for blind pleural procedures is small but significant. If initial pleural cytology is not "suspicious" further aspiration without biopsy is unhelpful. (2) Bronchoscopy should not be performed for undiagnosed effusions in the absence of central CT abnormalities. (3) If blind samples are taken at bronchoscopy they should be washed and brushed. (4) Wash, brush biopsy, and bronchial biopsy should be performed for all visible endobronchial lesions. (5) Repeat bronchoscopy is a reasonable option in some patients although histology is obtained in <50%.

P66 RADICAL TREATMENT FOR NSCLC IN NORTHERN AND YORKSHIRE REGION

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The casenotes of 400 consecutive patients with histologically confirmed non-small cell lung cancer (NSCLC) diagnosed in 1998 and registered with Northern and Yorkshire Cancer Registry Information Service (NYCRIS) database, were reviewed. The aim of the study was to determine the proportion of NSCLC patients receiving radical treatment (surgery or radiotherapy – dose >50Gy) and how they were assessed.

Data is presented on 368 patients (92%) in the table. In patients not receiving radical treatment, the commonest reasons for those decisions were: advanced lung cancer (54%), died (18%), refused (13%), other disease (12%). The open and close rate was 8%.

We conclude that staging and performance status are not well documented, although the majority of patients have significant comorbid illness, the main determinant of suitability for radical treatment is the extent of the disease.
LUNG CANCER IN WOMEN THROUGH THE 1990s
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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 F 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, adenoc, 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 v 41% F; adenocarcinoma 23% M v 28% F; small cell carcinoma 23% M v 31% F (chi2 p<0.001). Never smoking F were more likely to have adenocarcinoma than F who smoked (chi2 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%) (chi2 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 15 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 unresectable (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 point out 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.
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 FEV1/FVC (T = −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 allogeneic bone marrow transplantation (BMT) for haematological malignancy. Most of these patients are now managed with allogeneic and autologous 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 leukaemia (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 recipient mice 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 chromosome paint (Star-FISH, Cambia, Cambridge, UK) 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 lycopersicum esculentum, 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.

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**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 monocytosis (MO), 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 (Thickett DR, et al. Am J Resp Crit Care Med 2001;164:1601–5). However, VEGF is compartmentalised in normal human lung (Kaner RJ, et al. Mal Med 2001;7:240–6). More recently, VEGF 

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 disease with cytokine or other mediator effects on the bone marrow responsible for these changes.

P74  PULMONARY VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) RECEPTOR EXPRESSION IN ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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Previous work in our laboratory suggested a role for VEGF (an angiogenic and permeability factor) in the pathogenesis of ARDS (Thickett DR, et al. Am J Resp Crit Care Med 2001;164:1601–5). VEGF receptors (VEGFR1, VEGFR2) are thought to be predominantly expressed in vascular endothelium and monocytes. Modulatory VEGF neuropilin co-receptors (NP1 and NP2) expression occurs in a variety of human tissues. The expression of these receptors in human normal and ARDS lung has not been extensively investigated. We hypothesised that there would be expression of these receptors on both sides of the alveolar-capillary membrane with significant upregulation in ARDS lung consistent with VEGF having a significant role. Immunohistochemistry was performed on post-mortem human lung sections from normal subjects and patients with late ARDS (n=4) using semiquantitative densitometric analysis via Histometrix software. RT-PCR was performed on cultured human type II alveolar cells (AE2), alveolar macrophages (AMs) and peripheral blood monocytes (PBMs) from normal subjects and ARDS patients. In normal lung, VEGF, VEGFR1 and VEGFR2 protein were expressed in vascular endothelium, alveolar epithelium, and AMs. NP1 and two were confined to the alveolar side. In late ARDS lung, there was significant upregulation of VEGF, VEGFR1, VEGFR2, NP1 but not NP2. NP1 and 2 expression was also evident on the vascular side of the alveolar-capillary membrane. RT-PCR confirmed VEGFR1, VEGFR2, and NP1 mRNA expression in AMs and AE2 cells. PBMs expressed only VEGFR1 mRNA. These data confirm the presence of VEGF receptors and co-receptors on the alveolar side of human lung in addition to the known vascular endothelial expression of VEGFR1 and 2. There is significant upregulation of these receptors in late ARDS consistent with VEGF having a significant role in ARDS on both sides of the alveolar-capillary membrane. The type 2 alveolar epithelial cell and alveolar macrophage appear to be additional targets for VEGF in human lung.

P75 VASCULAR ENDOTHELIAL GROWTH FACTOR ISOFORM (VEGF165, b, VEGF165 AND VEGF189) EXPRESSION IN HUMAN AND MURINE INJURED LUNG

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Results: See table.

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 (Thickett DR, et al. Am J Resp Crit Care Med 2001;164:1601–5). However, VEGF is compartmentalised in normal human lung (Kaner RJ, et al. Mal Med 2001;7:240–6). More recently, VEGF 

Table: Table P74

<table>
<thead>
<tr>
<th>Parameter (normal range units)</th>
<th>Control mean</th>
<th>CFA mean</th>
<th>p Value unpaired T test</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV (84–98) FL</td>
<td>89 (4.20)</td>
<td>94 (6.1)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>n=160</td>
<td>n=91</td>
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</tr>
<tr>
<td>MØ (&lt;6.0) 10³/l</td>
<td>0.35 (1.1)</td>
<td>0.68 (0.24)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>n=160</td>
<td>n=91</td>
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<td></td>
</tr>
<tr>
<td>GGT (7–40) u/l</td>
<td>29 (22)</td>
<td>40.2 (31.7)</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>n=150</td>
<td>n=61</td>
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</tr>
</tbody>
</table>

CFA, Cryptogenic fibrosing alveolitis; MØ, peripheral blood monocytes; MCV, mean red cell volume; GGT, serum gamma glutamyl transferase.

Introduction: The publication of the British Thoracic Society (BTS) guidelines into community acquired pneumonia [CAP] (Thorax 2001;56(Suppl IV):iv1–iv64) prompted a review of clinical practices at Southampton General Hospital (SGH). The aim was to assess the present use of the core prognostic features outlined in the guidelines (confusion, urea, respiratory rate, and blood pressure) and their relation to management decisions.

Method: The patient groups was all those admitted to SGH between September and November 2001 (inclusive) given the diagnosis of pneumonia on their discharge summary. Patients were then excluded according to the BTS exclusion criteria. The data was collected from the patients’ notes; specifically initial investigations, core prognostic features, severity of the pneumonia, antibiotic prescription, and patient outcome. The results were then compared with the guidelines and national statistics.

Results: Seventy three notes were obtained from 113 requested, of which 38 met the inclusion criteria. The main reason for exclusion was a recent hospital stay. The average age was 70 years and the length of stay nine days. Only seven patients had any documented assessment of severity, three of which were said to be severe. Subsequent use of information within the notes indicated that 45% could be classified as severe, 42% non-severe, and 13% mild. Measurement of core prognostic features varied, with blood pressure measured in 97% of cases, urea 82%, respiratory rate 74%, and mental test score 50%. Other problems with note keeping included minimal inclusion of radiographic results in the notes. The majority of antibiotic choices were appropriate in type but with 70% of first line antibiotics given intravenously despite only 45% classifiable as severe. The overall death rate was 23.6% with three unrelated deaths. Two patients were subsequently changed to palliative management and four deaths were attributed directly to CAP. Thus the death rate from CAP was 10.5% with 89% of these initially graded as severe. 53% of all those graded as severe died.

References:

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.

P77 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 of 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-TYPICAL HAEMOPHILUS INFLuenZAE CLEAVES TWO SITES IN HUMAN IgA1 HINGE REGION

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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 partially 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 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 using 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 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.

P79 ELEVATED NASAL NITRIC OXIDE CORRELATES WITH REDUCED NASAL MUCOCILIARY CLEARANCE IN BRONCHIECTASIS

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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 inflammation.

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 subjects without nasal corticosteroids, nasal NO was significantly p<0.05) elevated in patients (n=6) with nasal MCC >60 minutes, mean 658ppb (SD 186) compared to patients (n=13) with nasal MCC =60 minutes, mean 402ppb (180), and controls, mean 416ppb (136). There was a correlation between nasal MCC and NO in patients with clear MCC >60 minutes and NO p<0.05. Although no significant difference in NO was found between subjects with no nasal corticosteroids and patients regularly taking nasal corticosteroids, in subjects regularly taking nasal corticosteroids there was no correlation between nasal MCC and NO.

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

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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 NO (r = 0.42, p<0.05); average walking distance (p<0.05); walking distance and CRP (r = 0.45); gas transfer (% predicted) and Total SGRQ (r = 0.5); walking distance and Total SGRQ and also the Activities component (r = 0.48). 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. Deprivation 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. Deprivation 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

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**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 structured self management education from a liaison nurse. Control practices received a liaison nurse visit to discuss standard asthma guidelines. Participants from control practices received a practice nurse technique check.

**Main outcome measures:** Participants free of unscheduled care; time to first unscheduled contact.

**Results:** Fifty per cent of participants were south Asian, 34% white, and 16% other ethnicities. Primary outcome data was available for 319/324 (98%) participants. Intervention by specialist nurse increased time to readmittance with an exacerbation (hazard ratio 1.17 (1.01–1.36) p=0.05) and percentage of participants not attending with exacerbations (p=0.056). Time to re-attendance was increased for white participants (1.33 (1.08–1.56) p=0.006) but not south Asians (1.18 (0.96–1.45) p=0.12).

**Conclusions:** 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.

**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.

**Aim:** 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. 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 repeat asthma prescriptions for each patient. The review, taking approximately 45–60 minutes, included asthma education, medication advice, and self management plans. Following review and telephone call a summary liaison form was sent to the GP.

**Results:** Telephone assessment rate was 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.

**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 (r= 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). Median dose of inhaled corticosteroid dose was 400 µg BDP upon admission and 800 µg equivalent upon discharge (p=0.009). There was no difference in the median steroid dose of patients admitted subsequently (805 µg) compared to those who were not admitted (800 µg, p=0.9). The time to first readmission after the index admission in 2000 was significantly longer in patients treated with long acting β agonists (105 days) compared to the group untreated.
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/or ICD10 diagnosis to response to the Hospital Anxiety Depression Questionnaire (HAD), a commonly used screening tool, with defined normal values.

**Methods:** Sequential new 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 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 poor self-management and reduced QoL (all p<0.001). Being overweight, use of coping strategies which involve focussing on asthma, and, interestingly, high compliance (both p<0.001) were also associated with poorer asthma control 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 would appear to be worthwhile.

**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, 63% not working, 63% receiving free prescriptions) with reduced QoL. (mean 1.7, 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 poor self-management 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 control and QoL.

**Conclusion:** 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 sensitivity and negative predictive value (NPV) for abnormal HADS scores for all psychiatric diagnoses. Anxiety and depression are atypical making diagnosis of underlying condition difficult.

**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 difficult 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 ACCSs (2.7 v 2.8, p=0.9). Best FEV1% was significantly less in this latter group (62 (21) v 96% (16%), p<0.0001). 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: One hundred and eleven (73 female) patients mean (SD) age 56 yr (12.8) were recruited. Main initial diagnoses were gastro-oesophageal reflux disease (GER) 52 (46.9%), asthma 23 (20.7%), and rhinitis 19 (17.1%). Thirty six patients have 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 the 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=0.05) and breathlessness (0.03).

Conclusion: In patients in whom we have made a diagnosis and are satisfied with 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.

P97 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 potent 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 independent 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 air-flow 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 radioallergosorbent 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%. 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=0.05, 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 do 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.

P98 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 effect 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 enquiring about 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 (sd 7.15, 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.

P99 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 ACE 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 and 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 prescriptions 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. Female: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. This did not always correlate with the reporting of other symptoms.

Conclusion and discussion: Amongst the HARIG questionnaire respondents there is considerable unmet need for asthma symptom control. The results broadly mirror those of the ACE survey with around one third of respondents suffering continuing symptoms. There may however 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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Introduction: Many subjects with severe asthma describe a worsening of symptoms on lying flat. This is felt to be due to an increase in vagal tone.

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.

To determine whether IOS could identify subjects who clinically had vocal cord dysfunction.

Poster presentations

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Methods: Forty one subjects with severe asthma attending a tertiary referral centre underwent spirometry and IOS whilst sitting using an MS-IOS digital instrument (Jaeger AG). IOS was repeated on lying flat. Subjects were clinically assessed (by JGA) as to whether they had a significant component of vocal cord dysfunction.

Results: Eighty per cent were female, mean age 43.6 years with an FEV1 69.5% predicted. Mean total airway resistance (RS) was increased at 203% predicted with 73% of subjects having abnormally high values (>150% predicted). Proximal airway resistance (R20) was a mean of 141% predicted being >150% predicted in 32%. An increase in R20 occurred on lying down (p=0.03) with a fall in distal capacitive reactance (X5) (p=0.05) for the group as a whole. Although total airway resistance (R5) did not increase significantly (p=0.18), increases in R5 on lying down did correlate with body mass index (r=0.47, p=0.003). R5 was inversely correlated with FEV1, and peak expiratory flow (r=-0.42) but R20 did not. X5 also correlated with FEV1 (r=0.52). IOS parameters or change in IOS parameters could not identify subjects who clinically had vocal cord dysfunction.

Conclusion: Increased airway resistance using IOS was demonstrated in some patients with severe asthma and increased significantly on lying down, possibly due to an increase in vocal tone. It was not helpful for identifying subjects thought to have vocal cord dysfunction.

Pulmonary vascular biology/pulmonary hypertension

P93 THE EFFECTS OF ACUTE HYPOXIA ON PROLIFERATION AND p38 MAP KINASE 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 phosphorylation in pulmonary artery 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 racic surgery and utilised between passages 3–10. Cells were

Results: [H]Thymidine uptake and p38 MAP kinase activity was measured by Western Blotting analysis.

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 a species and may be important in man.

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 3.74 ± 1.5 µg/Hb (range 1.11 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 HYPOTHIOXIC VSOCATION

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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 cells 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 pulmonary vasocsontriction 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. U44619 give preconstriction before a 10min hypoxic challenge (5%CO2, 95% N2). The lungs were then returned to normoxia for 10mins before changing the perfusate to one containing either 1mM 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 (1.7x10−10 – 1.7x10−6 moles) 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 vasocsontriction (3.5 (1.0) mmHg, n=7), and attenuated the SNAP induced vasodilation. These results suggest that superoxide can support or enhance hypoxic vasocsontriction, perhaps by consuming endogenous NO. However, there was a significant reduction of hypoxic vasocsontriction in the presence of DETCA (1.0 (0.3) mmHg, n=7) and SNAP (0.05). Overall, these results suggest that hypoxic vasocsontrction can be modified by endogenous superoxide, however this interaction may be dependent upon 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.

PH Milliken is funded by the British Heart Foundation (FS/ 2001056).

**P96** 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 hypertrophy and pulmonary hypertension has been reported in mice over expressing the 5HTT gene and there is 5HTT overexpression in patients with PAH (Eddahibi et al. J Clin Invest 2000;105:1555–62; Eddahibi 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×CBA hybrid (WT) mice (WT) (female 1 year old) exposed to two wks chronic hypoxia. Right ventricular (RV):total ventricular (TV) ratio was used as an index of pulmonary hypertension. In WT mice, RV/TV ratio was not altered after two wks hypoxia (0.205 (0.005) cf. 0.238 (0.012), n=6–7). In 5HTT+ mice, however, RV:TV ratio was increased (p<0.01, n=7) from 0.194 (0.009) to 0.297 (0.018). The number of remoulded small (~80 μm i.d.) vessels (assessed histologically) increased (p<0.001, n=6) from 2.61 (0.7%) to 7.8 (0.5%) [5HTT+ hypoxic]. ET-1, NA, and 5HT induced contraction was measured using wire myography in isolated pulmonary arteries (~200 μm i.d.) and were, in WT mice (n=8) compared to WT mice exposed to sham surgery (n=8). In 5HTT+ mice exposed to hypoxia however, there was a marked restoration of the relaxant response to NA (maxEC50: 9.8 (0.3) > 9.0 (0.2) respectively). NA contraction was markedly reduced in the 5HTT+ mice and the tonus of ET-1 and 5HT were reduced (p<0.05). In the 5HTT+ mice exposed to hypoxia however, there was a marked restoration of the relaxant response to NO (maxEC50: 8.6 (0.1)) and an increase in the response to ET-1 and 5HT (maxEC50: 8.6 (0.3) and 6.9 (0.4) respectively). The maximum response to ET-1 was increased by ~40%. In WT mice lung membranes, the 5HTT ligand and [H]5-HT-CIT bound with a Bmax of 1.0 (0.2) fmol/mg and a Kd of 0.6 (0.54) nM (n=3). Non-specific binding was assessed using cold fluoxetine. Binding was markedly increased in the 5HTT+ mice, with a Bmax of 13.32 (0.25) fmol/mg and a Kd value of 3.74 (0.033) nM (n=3). The results indicate that PAH is accelerated in 5HTT+ mice and in the presence of the NOS inhibitor L-NAME in a previously described in vivo rabbit model of PHT secondary to LVD (Deuchar, 38:201–4). Here we investigated the pulmonary and systemic effects of 5HTT alone and in combination with the NOS inhibitor, L-NAME, in a previously described in vivo rabbit model of PHT secondary to LVD (Deuchar, et al. Cardiovasc Res 1998;38:500–7). Briefly, eight weeks following coronary artery ligation or sham operation, ejection fraction (EF) was assessed using echocardiography and experiments were carried out in closed chest anaesthetised rabbits. Pulmonary arterial pressure (PAP) and systemic arterial pressure (SAP) were measured directly before and after cumulative administration of 5HTT (0.001–5.0 nmol/kg) either alone or after the infusion of L-NAME (30 pmol/mg per min). Coronary ligated rabbits had reduced EF (45.2 (1.0%) vs 73.0 (0.9%), p<0.001), elevated basal PAP (16.8 (0.4) mmHg vs 13.6 (0.2) mmHg, p<0.001) and evidence of right ventricular hypertrophy measured as right ventricular/final body weight ratio (0.69 (0.03) g/kg vs 0.48 (0.01) g/kg final body weight, p<0.001). A small significant pulmonary pressure effect was demonstrated to 5HTT alone, with the maximum response being greater in rabbits with PHT (2.6 (0.5) mmHg, n=8, v 1.0 (0.3) mmHg in controls, n=8, p<0.05). Following NOS inhibition, there was a trend towards the maximum pulmonary pressure effect being increased in both groups (8.5 (2.6) mmHg, n=12, and 4.8 (1.5) mmHg, n=13, in rabbits with PHT and controls respectively). In contrast, it was shown that U-II had no effect on systemic AOP in any of the experimental groups. In conclusion, U-II appears to act as a selective pulmonary vasodilator with no effect on AOP.

**P97** HUMAN UROTENSIN-II ACTS AS A PULMONARY VASOCONSTRICTOR IN AN IN VIVO RABBIT MODEL OF PULMONARY HYPERTENSION SECONDARY TO LEFT VENTRICULAR DYSFUNCTION

G.A. Deuchar, M.R. Maclean, M.N. Hicks. 'Department of Medical Cardiology, Glasgow Royal Infirmary; 'Institute of Biomedical and Life Sciences, University of Glasgow , Glasgow G12 8QQ, UK

The recently cloned peptide, human Urotensin-II (hU-II) has been described in vivo rabbit model of PHT secondary to LVD (Deuchar, et al. Br J Pharmacol 1998;130:201–4). Coronary ligated rabbits had reduced EF (45.2 (1.0%) vs 73.0 (0.9%), p<0.001), elevated basal PAP (16.8 (0.4) mmHg vs 13.6 (0.2) mmHg, p<0.001) and evidence of right ventricular hypertrophy measured as right ventricular/final body weight ratio (0.69 (0.03) g/kg vs 0.48 (0.01) g/kg final body weight, p<0.001). A small significant pulmonary pressure effect was demonstrated to U-II alone, with the maximum response being greater in rabbits with PHT (2.6 (0.5) mmHg, n=8, v 1.0 (0.3) mmHg in controls, n=8, p<0.05). Following NOS inhibition, there was a trend towards the maximum pulmonary pressure effect being increased in both groups (8.5 (2.6) mmHg, n=12, and 4.8 (1.5) mmHg, n=13, in rabbits with PHT and controls respectively). In contrast, it was shown that U-II had no effect on systemic AOP in any of the experimental groups. In conclusion, U-II appears to act as a selective pulmonary vasodilator with no effect on AOP.

**P98** THE PROSTACYCLIN ANALOGUE CICAPROST, INDUCES HETEROLOGOUS DESSENSITISATION IN PULMONARY ARTERY SMOOTH MUSCLE CELLS VIA PROTEIN KINASE A DEPENDENT INHIBITION OF ADENYLYL CYCLASE

A. Sobolewski, K.B. Jourdian, P.D. Upton, N.W. Morrell. Department of Respiratory Medicine, University of Cambridge, Addenbrooke's and Papworth Hospitals, Cambridge, CB2 0QG, UK

Prostacyclin is the major arachidonic metabolite produced in vascular cells and is a powerful vasodilator of the pulmonary vasculature. Long term infursion of prostacyclin analogues is an effective treatment for primary and secondary pulmonary hypertension, but due to desensitisation of the agonist response, increased doses are required to maintain efficacy. The aim of this study was to investigate the mechanisms of prostacyclin desensitisation using the prostacyclin analogue cicaprost in a primary cell culture system. Three cell lines were used: human pulmonary artery smooth muscle cells (HPASMC), pulmonary arterial smooth muscle cells (PASMC), and human atrial smooth muscle cells (HASMC). In preliminary studies it was shown that cicaprost desensitised HPASMC in a dose-dependent manner (EC50: 1.068 (0.022) fmol/mg protein), with a half-time of 13.32 (0.25) fmol/mg protein, and 8.5 (2.6) mmHg, n=12, and 4.8 (1.5) mmHg, n=13, in rabbits with PHT and controls respectively). In contrast, it was shown that U-II had no effect on systemic AOP in any of the experimental groups. In conclusion, U-II appears to act as a selective pulmonary vasodilator with no effect on AOP.

**P99** BONE MORPHOGENETIC PROTEIN-4 INHIBITS HUMAN LUNG FIBROBLAST PROLIFERATION VIA EFFECTS ON CELL CYCLE REGULATORS

T.K. Jeffery, P.D. Upton, R.C. Trembath, N.W. Morrell. Respiratory Medicine Unit, Department of Medicine, University of Cambridge, School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK; Division of Medical Genetics, University of Leicester, Leicester, UK

Introduction: Mutations in the bone morphogenetic protein type II receptor (BMPR2) have been identified in patients with primary pulmonary hypertension. Given that BMPR2 mutations may inhibit BMP effects on cell proliferation we examined the effect of BMP-4 on the cell cycle and signal transduction via Smad-1 and p38 MAPK pathways in human lung fibroblasts. Since this is the first time that pulmonary fibroblasts have been used to examine BMP-4 responses we also characterised BMPR2 receptor expression, ligand binding, and the effect of BMP-4 on fibroblast growth.

Methods: Human fetal lung fibroblasts (HFL-1) were used. BMP2 expression was determined using RT-PCR. Ligand binding studies were carried out by coated binding competition curves for [125I]BMP-4 against BMPs 2, 4, and 7, and TGFβ1. To determine the effect of BMP-4 on the cell cycle, propidium iodide stained cells were analysed utilising a fluorescence activated cell sorter (FACS). Western analysis using antibodies directed towards phospho-p38MAPK, phospho-Smad-1 and the cell cycle proteins, p21, p27, cyclin D, and cyclin dependent kinase-2 (cdk2) was performed.
Results: BMP-2 mRNA was expressed in HFLs and binding experiments demonstrated that BMP-2 and BMP-4 competed equivalently for BMPR2 mRNA expression. BMP-4 dose-dependently (1–100 ng/ml) inhibited proliferation of HFLs, with a corresponding down regulation in expression of the positive regulators, cyclin D and cdk2. Furthermore, BMP-4 induced cell cycle arrest in HFL-1 cells via induction of p21/cdk2 and inhibition of cyclin D/cdk2. The relative contribution of p21/cdk2 and Smad-1 on BMP-4 induced cell cycle arrest remains to be determined.

Background: It is now accepted that patients with non-fibrotic SSC-pulmonary hypertension (SSCPH) respond to epoprostenol therapy in a similar fashion to patients with primary pulmonary hypertension (PPH). We have observed that PHT in SSC-pulmonary hypertension is not predominantly hypoxia-driven and postulated that the mechanisms underlying fibrosis/non-fibrosis associated PHT in SSC may be similar and thus responsive to the same therapeutic strategy.

Methods: Forty seven SSC 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 mPAP=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 SMWT=175m fibrotics/215m non-fibrotics with a mean gain of 28 metres in both groups. Six month survival was 81%, with 23 (49%) patients surviving fibrotics/321m in non-fibrotics) with a mean gain of 28 metres in both groups. At 24 weeks this benefit was maintained (272m in non-fibrotics (n=27). Initial mean SMWT=175m fibrotics/215m non-fibrotics (n=20).

Conclusion: BMP-4 leads to cell cycle arrest in HFL-1 cells via induction of p21/cdk2 and inhibition of cyclin D/cdk2. The relative contribution of p21/cdk2 and Smad-1 on BMP-4 induced cell cycle arrest remains to be determined.

Funded by: British Heart Foundation and NHMRC of Australia (TK Jeffery).

**P101 THE RESPONSE OF FIBROTIC AND NON-FIBROTIC PATIENTS WITH SCLERODERMA ASSOCIATED PULMONARY ARTERIAL HYPERTENSION (SSCPH) TO CONTINUOUS AMBULATORY ILOPROST THERAPY: IS A SIMILAR THERAPEUTIC APPROACH JUSTIFIED?**

D. Mukerjee, B. Coleiro, C. Elliott, C. Knight, C.M. Black, J.G. Coghlan, Departments of Rheumatology and Cardiology, Royal Free Hospital, Pond Street, London NW3 2QG, UK

**Background:** It is now accepted that patients with non-fibrotic SSC-pulmonary hypertension (SSCPH) respond to epoprostenol therapy in a similar fashion to primary pulmonary hypertension (PPH). We have observed that PHT in SSC-pulmonary hypertension is not predominantly hypoxia-driven and postulated that the mechanisms underlying fibrosis/non-fibrosis associated PHT in SSC may be similar and thus responsive to the same therapeutic strategy.

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**Conclusion:** In a SSC patient cohort similar in structure in terms of underlying SSc-associated fibrosis is not predominantly hypoxia-driven and postulated that the mechanisms underlying fibrosis/non-fibrosis associated PHT in SSC may be similar and thus responsive to the same therapeutic strategy.

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=35), 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 10^5 parts per million (ppm) of inhaled nitric oxide during right heart catheterisation. The iNO was delivered in pulses via nasal cannulae using a breath activated device for five minutes. Pulsed iNO significantly reduced mean pulmonary artery pressure by 8.8 (14.5) mmHg (p <0.05) in all patients and was well tolerated in all cases. There was no significant change in mean arterial pressure (MAP; 92 (16) mmHg to 91 (14) mmHg) but a significant (p=0.05) fall in systemic vascular resistance (SVR; 1696 (560) dyne.s.cm^-5 to 1784 (508) dyne.s.cm^-5).

**Abstract P102**

<table>
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<th>Response type</th>
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<th>CO (L/min)</th>
<th>PVR (dyne.s.cm^-5)</th>
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<tbody>
<tr>
<td>Base</td>
<td>During iNO</td>
<td></td>
<td>Base During iNO</td>
</tr>
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<td>36 Non-responder</td>
<td>48.4</td>
<td>48.5</td>
<td>4.3</td>
</tr>
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<td>33.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Flow</td>
<td>49.5</td>
<td>47.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Resistance</td>
<td>42.8</td>
<td>37.2</td>
<td>3.9</td>
</tr>
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</table>

**P103 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, Dept of Radiology and Dept of Rheumatology, 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:aortic (P:A) 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.

**P104 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=35), 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 10^5 parts per million (ppm) of inhaled nitric oxide during right heart catheterisation. The iNO was delivered in pulses via nasal cannulae using a breath activated device for five minutes. Pulsed iNO significantly reduced mean pulmonary artery pressure by 8.8 (14.5) mmHg (p <0.05) in all patients and was well tolerated in all cases. There was no significant change in mean arterial pressure (MAP; 92 (16) mmHg to 91 (14) mmHg) but a significant (p=0.05) fall in systemic vascular resistance (SVR; 1696 (560) dyne.s.cm^-5 to 1784 (508) dyne.s.cm^-5).

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<thead>
<tr>
<th>Response type</th>
<th>MPAp (mmHg)</th>
<th>CO (L/min)</th>
<th>PVR (dyne.s.cm^-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>During iNO</td>
<td></td>
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</tr>
<tr>
<td>36 Non-responder</td>
<td>48.4</td>
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<tr>
<td>Pressure</td>
<td>43.3</td>
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<tr>
<td>Flow</td>
<td>49.5</td>
<td>47.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Resistance</td>
<td>42.8</td>
<td>37.2</td>
<td>3.9</td>
</tr>
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</table>

**P105 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.
Sildenafil at doses of 25 to 50 mg three times per day resulted in a significant improvement in shuttle walking test (274 (189) m vs 201 (116) 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.

**Abstract 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 the 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 four, showing peaking with exercise.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>MPAP (mmHg)</th>
<th>CO (l/min)</th>
<th>PVR (mHg/l/m)</th>
<th>6mwt (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PPH</td>
<td>59</td>
<td>3.7</td>
<td>12.7</td>
<td>438</td>
<td></td>
</tr>
<tr>
<td>2 PPH</td>
<td>66</td>
<td>2.6</td>
<td>15.4</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>3 PPH</td>
<td>31</td>
<td>6.3</td>
<td>6.5</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>4 Normal</td>
<td>48</td>
<td>3.4</td>
<td>4.7</td>
<td>550</td>
<td></td>
</tr>
</tbody>
</table>

**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.

**Abstract P105**

**HAEMODYNAMICS DURING EXERCISE ARE A BETTER MEASURE OF VASODILATOR RESPONSE IN HUMAN SUBJECTS WITH PULMONARY HYPERTENSION**

R. Syed, 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 micromonometer 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 measured 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 cardiology. 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 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.

**Abstract P106**

**FUNCTIONAL AND HAEMODYNAMIC RESPONSE AFTER PULMONARY THROMBENDARTERECTOMY FOR THROMBOEMBOLIC PULMONARY HYPERTENSION**

F. Reichenberger, J. Parameshwar, D. Hodgkins, J. Dunning, J. Pepke-Zaba. Papworth Hospital, Papworth Everard, Cambridge, UK

Pulmonary Thrombo-Endarterectomy (PTE) is the treatment of choice in pulmonary hypertension due to proximal chronic thromboembolism. We evaluated the mid-term 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 at 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...
Abstract P106

<table>
<thead>
<tr>
<th></th>
<th>6MW (metres)</th>
<th>RAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>Cardiac index (l/min/m²)</th>
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<tr>
<td>preop (88)</td>
<td>238 ± 110</td>
<td>10 ± 6</td>
<td>48 ± 11</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>3 mo postop (58)</td>
<td>386 ± 124</td>
<td>3 ± 4</td>
<td>24 ± 9</td>
<td>2.5 ± 0.7</td>
</tr>
<tr>
<td>1 year postop (35)</td>
<td>382 ± 123</td>
<td>3 ± 3</td>
<td>22 ± 10</td>
<td>2.4 ± 0.5</td>
</tr>
</tbody>
</table>

*p<0.0001.

increased right atrial pressure (RAP) and mean pulmonary artery pressure (mPAP). Three months after surgery there was a significant increase in 6MW and cardiac index, and a decrease in RAP and mPAP. These changes were statistically significant (*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 and 4 (3M) with other bacterial infections (B cepacia, 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), 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 (77.6 (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.

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 chronically infecting outbreaks of cystic fibrosis (CF) centres. The clinical significance of acquisition of an epidemic strain for patients who already harbour P aeruginosa is unclear. If epidemic strains are more virulent they may be more likely to provoke an enhanced host inflammatory response. We compared levels of inflammatory markers in clinically stable CF patients who harbour epidemic and unique strains of P aeruginosa.

Methods: Patients at the Manchester Adult CF Centre were invited to participate if they were clinically stable and had received a course of intravenous antibiotics 4–6 weeks earlier. Patients were grouped upon the basis of bacterial fingerprinting results into those who harbour epidemic and unique P aeruginosa strains; patients co-infected with Burkholderia cepacia complex were excluded. The following were measured: total white cell (WCC) and neutrophil blood counts; sputum neutrophil elastase (NE), interleukin (IL)-8, tumour necrosis factor (TNF) α, plasma IL-6, NE/α-antitrypsin complex serum Creactive protein (CRP); and urine TNF1. The groups were compared using t tests and Mann Whitney U tests.

Results: The two groups [unique v epidemic] (n=20 patients both groups) were well matched for mean age (28.5 ± 28.0 years), BMI (20.8 ± 20.4). The two groups had similar mean (SD) WCC (10.3 (2.8) ± 11.5 (3.3)) and neutrophil (7.4 (2.8) ± 7.6 (3.1) counts. There were no significant group differences in median [range] levels of sputum NE (22.0 (10.5 to 38.6) ± 17.3 (7.1 to 173.5) pg/ml), IL-6 (13.449 (5521 to 56514) ± 9989 (3782 to 155 500) pg/ml), and TNFα (11 (0 to 169) ± 9 (0 to 278) pg/ml), plasma IL-8 (5.8 (1.3 to 25.7) ± 6.4 (1.2 to 38.8) pg/ml) and NE/α-antitrypsin complexes (246 (109 to 2115) ± 229 (118 to 533) ng/ml), serum CRP (8 (1 to 29) ± 8 (1 to 21) mg/l) and urine TNF1 (1167 (286 to 5351) ± 988 (286 to 5082) pg/ml).

Conclusions: There are no differences in levels of inflammatory markers between clinically stable adult CF patients who harbour epidemic and unique strains of P aeruginosa.

P109 A PSEUDOMONAS AERUGINOSA EXOTOXIN, PYOCYANIN, IMPAIRS PHAGOCYTOSIS AND CLEARANCE OF APOPTOTIC CELLS

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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 of 1 hour (0%) 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 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
Poster presentations

**P110 BURKHOLDERIA CEPACIA COMPLEX: A MULTIFACET SEQUENCE TYPING (MLST) SCHEME BASED APPROACH**

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The accurate identification of Burkholderia cepacia complex in cystic fibrosis (CF) is challenging. A polytaxonomic approach is often employed in the study of B cepacia complex, including total protein electrophoresis, fatty acid analysis, biochemical tests, PCR amplification of rDNA, random PCR amplification (RAPD), pulse-field gel electrophoresis, and ribotype analysis. However, molecular diagnostic probes based upon the polymerase chain reaction (PCR) provide a rapid and frequently highly discriminatory means of identifying microbial infection. Recently recA sequence analysis has helped to unravel the phylogenetic relationships within the B cepacia complex and has facilitated typing for a rapid PCR based identification of B cepacia complex genomovars. 1. Multi locus sequencing type (MLST) is a powerful, portable and rapid means of undertaking identification, typing and population genetic analysis and enables population based analyses not possible by pulse field gel electrophoresis (PFGE) or other macrorestriction profiling and ribotype analysis. However, molecular diagnostic probes based upon the polymerase chain reaction (PCR) provide a rapid and frequently highly discriminatory means of identifying microbial infection. Recently recA sequence analysis has helped to unravel the phylogenetic relationships within the B cepacia complex and has facilitated typing for a rapid PCR based identification of B cepacia complex genomovars.

**P112 VARIABILITY IN PRO-INFLAMMATORY ACTIVITY OF PURIFIED LIPOPOLYSACCHARIDE (LPS) FROM SELECTED BURKHOLDERIA CEPACIA GENOMOVARS: THE ROLE OF LPS STRUCTURAL DIFFERENCES AND CHEMOTYPE**

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Gram negative bacterial infections are a major cause of morbidity in adult cystic fibrosis patient. As compared to those infected with Pseudomonas 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 Crit Care Med 1999). The role of variation in LPS is a focus of many studies. Necrotising Soft Tissue Syndrome is a fatal pneumonic-sepsis syndrome. 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 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 8 different LPS from Burkholderia cepacia genomovars.

**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 the LPS extracted. The LPS (0.2); p<0.05 compared with other infected groups). BAL neutrophil infiltration was measured both in BAL and serum. Although the GII strains were more invasive than the GIV, this was not reflected by differences in cytokines. This model confirmed a differential host response to various B cepacia organisms, which appear to be related both to genomovar and strain. Strains from GII and GIII, those associated with cepacia syndrome in patients, were highly invasive. Further, the GII organism elicited the greatest inflammatory response, both locally and systemically, suggesting a mechanism for the reported poor outcome after lung transplantation. Further studies, both in animal models and in the clinical setting are warranted, to improve attempts to identify patients most at risk of disease.

**P111 STRAIN DEPENDENT SYSTEMIC INVASION AND INFLAMMATION IN A MURINE MODEL OF ACUTE PULMONARY BURKHOLDERIA CEPACIA INFECTION**

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Burkholderia cepacia infection in CF may be asymptomatic, adversely affect lung function or invade systemically leading to the potentially fatal "cepacia syndrome". Certain genomovars appear more detrimental than others, possibly related to invasiveness and pro-inflammatory activity: cepacia syndrome has been reported with GII and GIII organisms, and GII infected lung transplant recipients have increased mortality. To explore this further, we tested a variety of B cepacia strains in a murine model of acute pulmonary infection. C57Bl/6 mice (6/group) were infected by nasal snifling with 106 CF organisms including: 18822 & 13010 (GIIa&b), 16870 & 14294 (GIVa&b) (BCCM/LMG, Belgium). Forty eight hours later blood was obtained by abdominal venesection, the spleen was removed, and a BAL performed. Homogenised spleens were cultured in a semi-quantitative fashion on cepacia-specific medium. Growth was scored as 0 (negative), 1 (scanty colonies), 2 (multiple colonies), or 3 (confluent growth) and the bacterial levels of systemic invasion were seen in animals infected with GII and GIII strains (scores of 3 in every animal). In contrast, the GIV strains produced less frequent and lower levels of invasion (meanSEM score GIVa & GIVb: 0.8 ± 0.4, GIVc 1.7 ± 0.2; p<0.05 compared with other infected groups). BAL neutrophil counts were higher in all infected groups than in PBS controls (p<0.05 or less), the highest levels being in groups GII and GIII. ET12 was significantly more pro-inflammatory than all the other strains, when the cytokines TNFa, IL-6, and IL-1b were measured both in BAL and serum. Although the GII strains were more invasive than the GIV, this was not reflected by differences in these cytokines. This animal model confirms a differential host response to various B cepacia organisms, which appear to be related both to genomovar and strain. Strains from GII and GIII, those associated with cepacia syndrome in patients, were highly invasive. Further, the GII organism elicited the greatest inflammatory response, both locally and systemically, suggesting a mechanism for the reported poor outcome after lung transplantation. Further studies, both in animal models and in the clinical setting are warranted, to improve attempts to identify patients most at risk of disease.

**P113 LIPOPOLYSACCHARIDE STRUCTURAL PROFILES ARE NOT ALTERED IN GENOMOVAR III BURKHOLDERIA CEPACIA QUORUM SENSING KNOCKOUTS**

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**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
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 migA a lipopolysaccharide 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, H1114 and H111-R have been created that are defective in the acylhomoserine lactone (AHL) synthase cepR and the AHL receptor cepP respectively. The effect of these mutations is 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 chomotype with multiple bands suggesting variable O side chain lengths. There were however no differences between the bands 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 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

Comparison of the HaloLite* Adaptive Aerosol Delivery (AAD™) System with a High Output Nebuliser System in Cystic Fibrosis Patients

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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 intravenous 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 days following an exacerbation requiring oral or IV antibiotics.

Methods: Nebuliser use was 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

Conclusion: AAD and NEB did not show a difference in efficacy over 12 months. Patients taking AAD had a 25% improvement in adherence compared to NEB: Of 382 patients, 101 (26%) of AAD patients and 40 (15%) of NEB patients took all doses of aerosol prescribed (p=0.006). AAD patients had a trend to better lung function as measured by FEV1: 43% for AAD and 34% for NEB, p=0.07. AAD patients had significantly fewer oral or IV antibiotic courses (78% for AAD and 81% for NEB, p=0.03). The AAD had an adherence improvement of 30% in patients who did not need oral or IV antibiotics for an exacerbation (n=14). AAD patients reported no correlation between true compliance and % change in FEV1, after 28 days, neither was there a correlation between true compliance and % of doses prescribed) and “compliance” (the % of doses taken correctly) were recorded. AAD accurately taken doses was defined as delivery of >90% of the pre-programmed dose, and for the NEB when the Aero-Neb® Puls 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=0.005). 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, whereas there was a correlation between true compliance and % of doses prescribed. For AAD there was no correlation between true compliance and FEV1, however for the subgroup of patients who did not need oral or IV antibiotics for an exacerbation there was a 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.

Inhalation Duty Cycle in-vitro Predicted Inhaled Dose during Domiciliary Nebuliser Use? Drug delivery to the lungs VIII

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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 whilst sitting or lying, 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 and incorporates an anti-backflow valve.

Methods: Nebuliser use was 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

Conclusion: AAD and NEB did not show a difference in efficacy over 12 months. Patients taking AAD had a 25% improvement in adherence compared to NEB: Of 382 patients, 101 (26%) of AAD patients and 40 (15%) of NEB patients took all doses of aerosol prescribed (p=0.006). AAD patients had a trend to better lung function as measured by FEV1: 43% for AAD and 34% for NEB, p=0.07. AAD patients had significantly fewer oral or IV antibiotic courses (78% for AAD and 81% for NEB, p=0.03). The AAD had an adherence improvement of 30% in patients who did not need oral or IV antibiotics for an exacerbation (n=14). AAD patients reported no correlation between true compliance and % change in FEV1, after 28 days, whereas there was a correlation between true compliance and % of doses prescribed. For AAD there was no correlation between true compliance and FEV1, however for the subgroup of patients who did not need oral or IV antibiotics for an exacerbation there was a 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.


Portacath Complications in Cystic Fibrosis Patients

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Introduction: Cystic fibrosis (CF) patients requiring repeated intravenous antibiotic courses eventually benefit from insertion of peripherally inserted central 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 ANTI-BIOTIC RELATED RENAL IMPAIRMENT IN ADULT CF PATIENTS
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Colonisation with multiresistant Pseudomonas aeruginosa (Pa) in CF patients 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 multiresistant strain colonising many CF patients that is only sensitive to aminoglycosides and polymyxins, antibiotics that are known to cause renal damage that may be associated with excess levels and also cumulative lifetime dose. To assess the impact of repeated dosing with these antibiotics, we have compared renal function in those colonised with multiresistant Pa with a group of CF patients with similar clinical parameters but who are colonised by sensitive Pa strains. Overall, 52 patients (32 multiresistant) were studied (mean age (range): multiresistant 23.6 years (15 to 42) v 29.4 (18 to 37); FEV₁ % predicted: 61.3 (16 to 95) v 61.8 (17 to 115); BMI: 21.6 (18 to 28) v 20.6 (14 to 27); CF related diabetes: 9 v 4 (all P=NS)). During exacerbations, all patients had aminoglycoside levels measured and adjusted after the 4th dose as per protocol. 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, demonstrated 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 multiresistant strains had a lower creatinine clearance (mean 75 ml/min (range 11 to 115) 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 colymycin courses (22 (0 to 80) v 7.4 (0 to 50)), (p<0.006)). Also, the total number of IV courses correlated with a reduced 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 multiresistant Pa strains, and in some patients we can now no longer use these important antibiotics. This study illustrates the need to prevent colonisation by such strains if possible in CF patients. This is best achieved by measures designed to prevent cross infection, including 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) allows patients with cystic fibrosis (CF) who have problems absorbing fat-soluble nutrients to consume a regular diet, as opposed to an elemental diet. This study aimed to investigate the variation in reported intake of PERT, the number of enzymes taken with food, in CF patients attending an annual review at the CF Centre between July 1995 and May 2002.

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 each day. 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 diaries 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 slightly 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/Δ, 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=4; Staphylococcus aureus, n=1 (one had coliforms and one had Stenotrophomonas maltophilia in addition); no growth, n=2. Median (range) length of treatment was 8.5 (6–15) 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 (5.5) 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 suggest 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.
FACTORS DETERMINING DIAPHRAGM STRENGTH IN CHILDREN AND YOUNG ADULTS WITH CYSTIC FIBROSIS

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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 mass (FM), 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 AC (r = +0.134 * biceps SK / 2 + triceps SK / 2). FM, FFM, and AMC were expressed as percent predicted for stature (% 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 159.8 (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 FEV1 (p=0.001; r = +0.68); % Pred FRC (p=0.005; r = -0.65); PaO2 (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.; BMI (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 an effect of diaphragm strength.

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) in comparison with 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; mean (95% CI) 28.0 (24.7 to 31.3) and 21.5 (18.6 to 24.3), respectively, p<0.01.

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 pre-transplantation 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 Bronchiectatics (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 67% 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/m) 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.
postinfection in murine mammary epithelial cells (C127 −/−) using a radioactive iodide efflux assay after challenge with forskolin/IBMX (F/I). Cells infected with a SeV vector carrying a mutated CFTR sequence (SeV-mCFTR) were used as controls whilst T84 were used as positive controls and results expressed as ∆Amin min−1 (n.m.e.) T84 cells exhibited an efflux rate 2 min after F/I addition (0.24 ± 0.10, n=30) compared to C127 −/− values (0.004 ± 0.004, n=11), p<0.001. All three SeV-mCFTR clones tested showed a characteristic delayed peak three minutes after F/I addition (SeV-mCFTR 23–3/23–4 (0.34 ± 0.04), SeV-CTF 23–4 (0.26 ± 0.03), n=6); SeV-mCFTR 23–3 (0.16 ± 0.05, n=12). As for untreated C127 −/− cells, treatment with SeV-mCFTR did not lead to any change in efflux (−0.01 ± 0.02, n=12).

In vivo experiments were carried out in G551D CF transgenic mice by administration of SeV-CTF 23–3 and 23–4 (5 × 105 pfu per mouse) through nasal perfusion and CFTR activity analysed at day 2, 7, 14, and 28. Se-mCFTR (n=9) was used as control. Two days post-infection, NPD− values in animals treated with SeV-CTF 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). NPD− values in animals treated with SeV-CTF 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-CTF 23–3/23–4 they were not different from those observed in wild type mice [12.1 (1.5) mV] with p<0.01 compared to controls. The baseline and low chloride values had approached to typical G551D CF mouse values. In conclusion we have shown that SeV can mediate CFTR gene transfer both in vitro and in vivo.

**P214** 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 lungs in vivo. Balb/C mice (female 6–8 weeks) were simultaneously transfected with pcDNA3CAT (80µg/mouse) and 22 nts siRNA corresponding to CAT (40µg/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, while compared to controls (control siRNA: 736.9 (437) pg CAT/mg protein, CAT siRNA: 80.1 (31.4) pg CAT/mg protein, p<0.001). 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 with either eGFP plasmid co-transfected with eGFP plasmid or eGFP 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 RNA 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 gene silencing strategies that have been proposed for obstructive lung 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.

**P215** INFECTION OF THE MURINE LUNG WITH NON-TRANSMISSIBLE RECOMBINANT SENDAI VIRUS EXPRESSING THE SECRDED PROTEIN INTERLEUKIN 10

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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 Virol 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 transblasted by placing SeV-IL10/ΔF or a SeV-ΔF control virus (7×104 and 7×104 CFU/mouse) as a single 100 µl bolus into the nasal cavity and the solution was sniffl 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 not significantly increased two days after infection and was 2.2 and 4 logs above control levels for 7×104 and 7×104 CFU/mouse, respectively. At day seven expression in mice transblasted 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 7×104 CFU/mouse, but not in animals infected with 7×104 CFU/mouse, and were still significantly increased seven days after infection (SeV-IL10/ΔF: 3500 ± (492) and 75 (18) pg/ml at day two and seven respectively, SeV-ΔF: 5.2 ± (5.4) and 0 pg/ml at day two and seven respectively, n=6, p<0.05). When compared to the previously used transmission-competent, first generation SeV virus (historical data), there was no difference in IL10 expression in lung homogenate or serum. We also transblasted fresh and mucus depleted segments of primate trachea with SeV-IL10/ΔF or a SeV-LacZΔF control virus (1010 and 1010 CFU) ex vivo (n=1) and preliminary results indicated efficient transfection of fresh and mucus-depleted tissue (Fres: SeV-IL10/ΔF = 405048 pg/mg, ΔFSeV-LacZΔF: 3294 pg/mg, Mucus depleted: SeV-IL10/ΔF = 4708/4708 pg/mg, SeV-LacZΔF: 2096 pg/mg). In conclusion, the non-transmissible second generation SeV-IL10/ΔF infects airway epithelium as efficiently as the first generation virus. Preliminary results indicate that the virus titre at least in part determines the decline of transgene expression and that SeV-IL10/ΔF infects primate trachea efficiently.

**P216** 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 data on an seven week, x2 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 FEV1.42 (0.4), FVC 1.8 (0.5) l . Sixty seven patients completed the course. Of these patients, 57 had baseline spirometry from which 48 were classified as obstructive; mean FEV1.42 (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=0.00003), 91.1 (64.1) m at p=0.002) respectively. However, the difference between the groups (43.3) m was not significant (p=0.05). 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 (step 3), and long acting β2 trial (step 4), 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 20 severe using BTS criteria for severity) were used to examine 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 and mean improvement (MI) after stage 2 and 3 is shown in the table.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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</thead>
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<tr>
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<td>3.68</td>
</tr>
<tr>
<td>MI</td>
<td>4.5</td>
<td>4.2</td>
<td>3.83</td>
</tr>
<tr>
<td>Stage 3</td>
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<td>0.7</td>
<td>0.83</td>
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<tr>
<td>MI</td>
<td>4.5</td>
<td>5.35</td>
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</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 comorbid 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 hrs 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 consists of resting pulse and respiratory rate, 6MWD (with final and post 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, FEV1 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 ox.

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 to3.1, 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) score of the 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 HYPERVENTILATION

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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 are 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)bpm/min) in the chronic group compared to the those demonstrating acute hyperventilation in addition to their chronic hyperventilation (mean (SD) 27.7 (8.3) (p<0.02). There was a significant correlation between anxiety, resting PETCO2 and BHTs and between PETCO2 at rest and at maximal work rate achieved in the chronic group (p<0.05). Resting RR was significantly correlated with resting VE and resting PETCO2 also in the chronic group. These relationships were not evident in the two groups which demonstrated acute and chronic hyperventilation. There was a significant correlation in these groups between anxiety and resting heart rate, which may be explained by anticipatory anxiety.

These data demonstrate that within this population of seemingly homogeneous 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 (LTOT)

M. Logue, J.G. Daly, R. Sharkey. Allnaglevin Hospital, Derry, N Ireland

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 living with LTOT.
and how they coped. Unstructured audio-taped interviews lasting approx 60 minutes were conducted in the patients’ homes. Interviews were directed by the patients. Tapes were transcribed verbatim, checked for accuracy, and analysed using Colazzi’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.

**Abstract P132**

<table>
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<tr>
<th>Activity level</th>
<th>Before rehab</th>
<th>Mean (SD)</th>
<th>After rehab</th>
<th>Mean (SD)</th>
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**Dyspnoea score**

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<th>Activity level</th>
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<th>Mean (SD)</th>
<th>After rehab</th>
<th>Mean (SD)</th>
<th>Significance</th>
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<td>Mean score per activity</td>
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<td>4.9 (6.8)</td>
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<td>Number of episodes of severe dyspnoea per month</td>
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<tr>
<td>Score “today”</td>
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<td>4.2 (2.2)</td>
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<tr>
<td>Score in “day to day activity”</td>
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<td>4.6 (2.1)</td>
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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<0.001). 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 (p<0.03) 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 evolution linked to our prospective HIV database. Over a six week survey period, 394 ambulant subjects were enrolled (85% male, median age 34 - IQ97: 29–39), with 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 increase of 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.

**THE EFFECT OF SCHOOL TUTOR GROUP SMOKING PREVALENCE ON THE RISK OF INCIDENT SMOKING IN SECONDARY SCHOOL CHILDREN: A LONGITUDINAL STUDY**

A.W.P. Molyneux, S.A. Lewis, M. Antoniak, W. Browne, A. McNellie, R.J. Madeley, C.A. Godfrey, R. Britton. 1 City Hospital; 2 University Hospital Nottingham; 3 Institute of Education; 4 St George's Hospital, London; 5 Centre for Health Economics, University of York, UK

**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 an independent risk factor for incident smoking after adjusting for females, 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.

**SMOKING CESSATION SERVICES FOR TEENAGE SMOKERS: QUALITATIVE AND PILOT INTERVENTION STUDIES**

A.W.P. Molyneux, S.A. Lewis, T.J. Coleman, A. McNellie, R.J. Madeley, C.A. Godfrey, R.J. Britton. 1 City Hospital; 2 University Hospital Nottingham; 3 St George's Hospital, London; 4 Centre for Health Economics, University of York, UK

**Rationale:** Most adult smokers started smoking as adolescents. Half of adolescent smokers would like to quit and who have previously tried and failed is higher than expected. Views expressed will guide the design of specific smoking cessation services in this group.

**Methods:** 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 is higher than expected. Views expressed will guide the design of specific smoking cessation services in this group.

Funded by Cancer Research UK.
AN ASSESSMENT OF SMOKING IN ACUTE MEDICAL INPATIENTS
E. Poon, C.W. Lau, L.Y.C. Yam, C.W. Lam. Pamela Youde Nethersole Eastern Hospital, Ruttonjee Hospital, HK

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 to all patients on admission to all four 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) vs 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, age at which smoking commenced, or 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% acknowledged a willingness to quit, and 26 (45.6%) accepted help towards quitting. Neither current age, age at which smoking commenced, or 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.

DO SELECTIVE TOPICAL β ANTAGONISTS FOR GLAUCOMA HAVE LESS RESPIRATORY SIDE EFFECTS?
J.A. Nightingale1, J.F. Kirwan1. 1Royal Brompton and Harefield NHS Trust; 2Institute of Ophthalmology

Topical β antagonists are prescribed for glaucoma in approximately 500 000 people in the UK. We have previously shown that prescription of these drugs is associated with an excess incidence of airways obstruction. Selective topical β antagonists are marketed as being less likely to induce airways obstruction than non-selective topical β antagonists. The aim of our study was to determine whether selective topical β antagonists are associated with a smaller risk of developing airways obstruction than non-selective topical β antagonists.

Data obtained from the Mediplus® UK primary care database were used to perform a historical cohort study to determine one-year incidence of airways obstruction in subjects following treatment with topical β antagonists for glaucoma for the period 1993–1998. Cases were defined as having received a first prescription of a drug specifically used in the management of airways obstruction. Only subjects with no history of airways obstruction were included. Analysis was performed using proportional hazard modeling to minimize potential confounding.

For selective topical β antagonists 12 of 324 treated subjects developed airways obstruction, compared with 112 of 9094 controls (adjusted hazard rate 3.0 (95% confidence interval 1.6 to 5.4)). For non-selective topical β antagonists the corresponding figures were 69 of 2321 subjects compared with the same control group (adjusted hazard rate 2.2 (95% confidence interval 1.6 to 3.0)). There was no significant difference between groups (p=0.5), both being associated with a significantly increased risk of airways obstruction.

We conclude that selective topical beta antagonists do not appear to have less respiratory side effects than non-selective topical β antagonists in the treatment of glaucoma.

Poster presentations iii87

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)
C. Ward1, A. De Soysa, A. Fisher, G. Pritchard, P. Corris. Lung biology and transplantation group, university of Newcastle Upon Tyne; 1The Freeman Hospital, NE7 7DN, UK

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.


The therapy of asthma

P138 BODIPY-TMR-CGP 12177: AN IRREVERSIBLE FLUORESCENT PROBE FOR THE HUMAN β2-ADRENOCEPTOR WITH AGONIST PROPERTIES
J.G. Baker, J.P. Hall, S.J. Hill. Institute of Cell Signalling, Medical School, Queen’s Medical Centre, Nottingham NG7 2UH, UK

Current methods to study native receptors in cells from patients are thwarted by the need for large numbers of cells. Fluorescent 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 (EC50 = 28.2 (4.0) nM, n=3) and gene transcription (EC50 = 25.3 (3.6) nM, E, isoprenaline response) in CHO-K1 cells expressing 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.

Poster presentations iii87

JGB is a Wellcome Trust Clinical Training Fellow.
Methods: Thirty one SLT >3 months post transplantation, randomised to three months 400µg CFC BDP bd or a formulation designed to yield at least an equivalent small airway dose (200µg HFS BDP bd 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 SLT, 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.

[P141] RAPID EFFECTS OF SINGLE DOSE FLUTICASONE PROPIONATE ON ALLERGEN-INDUCED EARLY ASTHMATIC RESPONSES IN MAN

Department of Respiratory Medicine and Allergy, GKT School of Medicine, King’s College, Bessemer Road, London, SE5 9P, UK

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) between two hours (Ketchell, et al Allergy Clin Immunol 2002:(in press)).

Objective: 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 at each time interval, although differences were not significant until the 90 minute time point (p=0.01).

Results: 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 to 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.


Abstract P142

<table>
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<th>Symptom severity</th>
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<td>F**</td>
<td>A**</td>
</tr>
<tr>
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</tr>
<tr>
<td>Mild intermittent</td>
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</table>

A=adjustable; **F=fixed.

[P142] FOUR MONTH ADJUSTABLE OR FIXED BD DOING WITH BUDENOSIDE/FORMOTEROL IN A SINGLE INHALER REDUCES SYMPTOM SEVERITY

P. Indo, J. Haughney, D. Price, J.P. Rosen, J. Kennelly. 1Hammersmith Hospital, UK; 2University of Aberdeen, UK; 3AstraZeneca UK, Luton, UK

Objective: The efficacy of budesonide/formoterol combination (B/F; Symbicort Turbuhaler) administered as either adjustable or fixed bd dosing.

Methods: Patients (mean age 48 years) were randomised to two groups, n=772; B/F two inhalations bd for 4 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.

Inhaled corticosteroids (GCS) affect the EAR to inhaled allergen, underwent two constant-dose allergen challenges. The baseline and demographic characteristics of the two groups were well matched. 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.

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 Index (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 to 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.


Abstract P143

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. 1University of Aberdeen, UK; 2AstraZeneca 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.

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**P144** AIRWAY DRUG DELIVERY: SIZE MATTERS—BIGGER IS INDEED BETTER

O.S. Usmani, M.F. Biddiscombe, P.J. Barnes. Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK

Current inhaler devices are inefficient as the dose delivered is a polydisperse 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 compared to the CFC product. Beclomethasone (Qvar) is more potent compared to the CFC product. At the same time it has been observed that the HFA formulation of significantly more potent bronchodilators in asthmatics—6µm 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 were better matched to their target site of action. We aimed to investigate the effects of inspiratory flow and respiratory distribution of MDIs in patients 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 cells 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 (bm), [range 0–32], three month; 2/mm bm (p<0.01 v baseline), 12 month median 2/mm bm (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 airflow 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.

**P145** THE MEASUREMENT OF THE SUBMICROMETER SIZE DISTRIBUTION OF METERED DOSE INHALERS (MDI)

M. Crampton, R.P. Kinnersley, J.G. Ayres. Division of Environmental Health & Risk Management, University of Birmingham, Birmingham, B15 2TT; Department of Respiratory Medicine, Birmingham Heartlands Hospital, Birmingham, B9 5SS, UK

Recent studies indicate that toxicity of materials in ultrafine aerosol may be correlated with particle size, in that larger particles were better matched to their target site of action. 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.

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Conclusion: Ebb and BAL are complimentary, and further support the view that PD20 to methacholine reflects airflow 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.

**P146** 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. Poai2, B. Orsida3, B. Feltis1, R. Bush4, D. Johns1, E. Haydn Walters4. 1Lung 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 (ebb) 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 cells 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 (bm), [range 0–32], three month; 2/mm bm (p<0.01 v baseline), 12 month median 2/mm bm (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 airflow 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.

**P147** RELATIONSHIP BETWEEN ADHERENCE TO PRESCRIBED REGIMENS AND ASTHMA CONTROL IN PATIENTS WITH DIFFICULT ASTHMA

S. Aburuz1, J. McElney1, J. Millership1, J. Gamble1, L. Hearney1, School 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 (T)) and PD20. We used high dose inhaled steroids (HDIS) in a population of difficult asthmatics (persisting asthma symptoms/frequent exacerbations requiring systemic steroids despite maintenance high dose inhaled cortico-steroids and 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
P148 EARLY ANTIBIOTIC PRESCRIPTION AND ALLERGIC DISEASE IN UK ADULTS

P. Cullinan, J.M. Harris, P. Mills, S. Moffatt, 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 aerollergens. Prescription information for antibiotics was 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.

Sixty three percent of adults were atopic; 14% reported a history of asthma and 29% hay fever, 564 (76%) had at least one antibiotic prescription by the age of five years (adjusted OR 1.08 (1.03 to 1.13) per prescription) per prescription), a pattern which did not alter at any age or by antibiotic class. Asthmatics—with or without atopy—were more likely to have received 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; 1.14 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 sensitization. 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?

C. Lex, D.N.R. Payne, N.M. Wilson, A.M. Li, A. Zacharaiswicz, A. Bush. Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

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 >1600µg/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 13/25 (52%) 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 (5 ± 5) 28% of 25 patients taking P were non-adherent. Of 43 patients taking T and 11 (26%) had suppressed UCC ratio. ASCS, wheezeing 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 inhaled therapy. Failure to suppress urinary cortisol can be used as a marker of possible non-adherence to HDIS in this population.


P150 TUBERCULOSIS INCIDENT AND OUTBREAK SURVEILLANCE IN ENGLAND AND WALES: REPORTS FROM JANUARY 1999 TO JUNE 2002

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We are currently developing a central information resource on tuberculosis incidents and outbreaks that can be used to inform future management. The aims of this surveillance initiative are to gain insight into the occurrence and distribution of tuberculosis incidents and outbreaks; monitor and evaluate the effectiveness of control measures and inform policy; network relevant parties as an accessible information resource for one another; and provide a means of recording examples of best practice and lessons learned.

In order to more fully understand the terms and specification required for this new aspect of tuberculosis surveillance we have retrospectively collated tuberculosis related incidents and outbreaks reported to CDSC from January 1999 to June 2002.

A total of 47 reports associated with actual and potential tuberculosis transmission involving health workers and institutions have been received, 33 of which relate to health and allied professionals posing an infection risk. Similarly, 29 reports relating to education workers and educational institutions, including one outbreak, which involved extensive contact investigation have been received. There are four reported instances of tuberculosis among prisoners and one incident involving a prison guard. A total of 22 instances of tuberculosis among passengers have been reported, 18 involving passengers and four airline employees.

Incidents and outbreaks reported to CDSC to date represent only a sample of the total episodes. It is planned that the development of a more formal system to capture, collate, and report on tuberculosis incidents and outbreaks will enable a more accurate assessment of their frequency, distribution and public health impact to be made.

P151 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, 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.

**P152 ERRORS IN THE NOTIFICATION OF TUBERCULOSIS**

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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 LSHA. 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 database for cases with microbiologically confirmed MTB 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.

Results: In 1996 to 2000, 279 cases were notified as tuberculosis, 229 (82%) being MTB culture positive. Forty one 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 infection, giving an over-notification rate of 4/45 or 8.8% (CI 2 to 17). 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 prisons 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 IV drug users and sex workers along with documented compliance problems in 38% of cases has made control of the outbreak difficult.

**P153 UPDATE ON AN OUTBREAK OF ISONIAZID MONO-RESISTANT TUBERCULOSIS IN NORTH LONDON**

M. Ruddy1, A.P. Davies2, M.D. Yates3, S. Yates1, S. Balasegaram1, B. Patel1, S. Lozewicz1, S. Sen4, M. Bahia5, E. James1, M. Lipman6, Y. Drabu1, J. Watson1, M. Piper1, F. Dronniewski1, H Maguire7, 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 eight 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 prisons 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 IV drug users 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 patient information cards were traced: 143 (84%) were for TB related episodes, 12 (7%) were episodes unrelated to TB, and 16 (9%) did not want 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 only 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.

**LONDON ACCIDENT AND EMERGENCY (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 have 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.

**PERFORMANCE STATUS ON ADMISSION TO HOSPITAL: A SIMPLE PREDICTOR OF DEATH IN PATIENTS WITH PULMONARY TUBERCULOSIS IN SOUTH AFRICA**

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**Background:** Simple measures are required to identify patients most at risk of dying from tuberculosis. Performance status has been used in studies of cancer patients but we are not aware that it has been tested as a predictor of mortality among patients with tuberculosis.

**Methods:** During a period of three months all adults (age >15 years) admitted to one of six South African hospitals and put on anti-tuberculous treatment for suspected or confirmed pulmonary tuberculosis were eligible. At the time treatment was initiated 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.

**OUTCOME OF HIV ASSOCIATED TUBERCULOSIS IN THE ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)**

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**Background:** The benefit of HAART on outcome in TB/HIV co-infected patients is unclear due to concerns about drug adherence, absorption,
overlapping toxicities, drug interactions, and paradoxical reactions. We therefore investigated the effect of HAART on survival in co-infected patients.

Methods: Ninety two HIV/TB co-infected patients treated at a London HIV clinic were retrospectively identified. Patients starting TB treatment prior to 1 January 1996 (n=36) were compared to those starting TB treatment after 1 January 1996 (n=56), when HAART was introduced. HAART was included as a time-updated covariate in a Cox regression model with adjustment for other prognostic factors.

Results: Compared to patients treated for TB prior to 1996, those treated during or after 1996 were older (median age 35 v 30), and were more likely to be women (43% v 17%), Black African (63% v 44%), and in the heterosexual risk group (68% v 47%). Baseline CD4 count tended to be lower for patients in the post-1996 compared to the pre-1996 group (73% versus 61% <200 /mm³). TB treatment with Rifabutin was much more common in the post-1996 group (34% v 6%). During a median of 2.6 years of follow up there were 29 deaths. Three years after initiation of TB treatment, survival was 63% in the pre-1996 group compared to 79% in the post-1996 group (p=0.19). This difference in survival was significant after adjustment for baseline CD4 count [HR for post-1996 versus pre-1996: 0.42; 95% CI 0.18 to 0.96, p=0.039]. In a Cox model that included HAART use as time-updated variable, and adjusted for baseline CD4 count, extrapulmonary TB, previous AIDS and calendar period (pre or post 1996), the use of HAART resulted in a marked reduction in risk of death [HR: 0.26, 95% CI 0.10 to 0.72, p=0.009] and explained the effect of calendar period. Initial CD4 count < 200 /mm³ [HR: 3.4; 95% CI 1.3 to 9.3, p=0.015] and a prior history of AIDS [HR: 2.3; 95% CI 1.1 to 5.1, p=0.032] were also independently associated with risk of death.

Conclusion: Use of HAART in patients with TB/HIV co-infection results in a substantial reduction in risk of death.

Abstract P159  A summary of the cost analysis

<table>
<thead>
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<th>Cost category</th>
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<td>Inpatient</td>
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<tr>
<td>Respiratory outpatient</td>
<td>24 322</td>
</tr>
<tr>
<td>Other outpatient</td>
<td>7 362</td>
</tr>
<tr>
<td>Surgical procedures</td>
<td>13 862</td>
</tr>
<tr>
<td>Radiology</td>
<td>72 605</td>
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<tr>
<td>Medication</td>
<td>20 710</td>
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<tr>
<td>TB Nurse service</td>
<td>75 000</td>
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<tr>
<td>Other</td>
<td>6 438</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>353 231</td>
</tr>
<tr>
<td><strong>Cost per patient treated</strong></td>
<td>3 592</td>
</tr>
</tbody>
</table>

Abstract P160 TUBERCULOSIS AND HEALTH BELIEFS IN THE BANGLADESHI COMMUNITY OF EAST LONDON

V. White, S. Hillier, J. Moore-Gillon. 1 Deps of Respiratory Medicine; 2Human Science and Medical Ethics, Bart’s and the London School of Medicine & Dentistry, EC1A 7BE, UK

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 used 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 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 have been significantly different had we studied UK born white TB patients.

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P161 NO BOOSTER EFFECT IN BCG IMMUNISED TUBERCULOSIS CONTACTS UNDERGOING REPEAT HEAF TESTING

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Individuals who undergo repeat tuberculin testing may exhibit increasing reaction size in the absence of new infection. This phenomenon is known as boosting. Boosting is thought to be commoner in BCG vaccinated individuals compared to non-vaccinated individuals. 1 BTS guidelines only advise repeat tuberculin testing in non-BCG vaccinated TB contacts whose initial tuberculin (Heaf) test is negative. 2

We performed a retrospective analysis of TB contacts to establish if there was an excess of increased Heaf reaction on repeat Heaf testing in BCG vaccinated individuals. One hundred and forty one TB contacts, with an initially negative Heaf test (grade 0–1), had repeat tuberculin testing at our clinic [74 female; age range 18 days to 60 years]. Sixteen had neither history of BCG nor BCG scar; 119 had either (n=19) or both (n=100); six had no recorded details of BCG vaccination.

<table>
<thead>
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<th>No Heaf grade</th>
<th>Heaf grade increase increase</th>
</tr>
</thead>
<tbody>
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<td>Previous BCG</td>
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</tr>
<tr>
<td>No previous BCG</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>
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.