Epidemiology of tuberculosis

**SO01** SUBSTANTIAL INCREASE IN TUBERCULOSIS INCIDENCE IN ENGLAND AND WALES IN 2005


**Background/Aim:** The epidemiology of tuberculosis in England and Wales has changed over the last two decades with a gradual increase in overall incidence. The majority of cases are now reported in the foreign-bom while cases among the UK born are more likely to be from certain risk groups. Using national surveillance data, this study examines recent trends in tuberculosis epidemiology, including clinical and demographic characteristics of cases.

**Methods:** The Enhanced Tuberculosis Surveillance (ETS) system collects information on tuberculosis cases, including demographic, clinical and microbiological data. Cases occurring in England and Wales have been reported to this system since 1999. Population figures used for calculating national rates were calculated using mid year estimates provided by the Office for National Statistics (ONS).

**Results:** Provisional ETS data show that 8136 tuberculosis cases were reported in 2005 in England and Wales, a rate of 15.3 per 100 000. This compares with 7086 cases (13.4 per 100,000) reported in 2004. The rate increased by 14%, significantly more than in previous years (4% average annual increase between 1999 and 2004). This large increase is seen in both adults and children, and in those born in the UK (6% increase between 2004 and 2005 vs no increase from 1999–2004). The trend differs considerably by region and is mainly comprised of non-pulmonary cases (27% increase versus 7% for pulmonary).

**Discussion:** Preliminary surveillance data indicate an increase in the incidence of tuberculosis in England and Wales in 2005 that is considerably larger than in previous years. Differential reporting by clinicians is an unlikely explanation, as we found a similar increase in the number of isolates reported from mycobacterial reference laboratories. While the final corrected figure for 2005 will be lower than the preliminary estimate, the increase is likely to remain substantial. The factors driving the increase need to be determined.

**SO02** CLINICAL PRESENTATION OF PULMONARY TUBERCULOSIS WITH AND WITHOUT HIV CO-INFECTION


As part of a study of the effects of adding micronutrients to the treatment of pulmonary tuberculosis, a total of 1186 patients presenting with symptoms consistent with a diagnosis of pulmonary tuberculosis to one of eight Chest Clinics in Abuja, Nigeria had sputum tested for smear and culture for M tuberculosis. Of these 731 (62%) were culture positive and of these 353 (48%) smear positive. 1002 patients were tested for HIV and 546 (54%) were positive. Of the 625 patients who were culture positive and tested for HIV 329 (53%) were HIV positive. A total of 217 (58%) of 377 culture negative patients were HIV positive.

Of the 329 culture and HIV positive patients 158 (48%) were sputum smear positive but those who were HIV negative were statistically significantly more likely to be sputum smear positive than those who were HIV positive.

Spoken sessions

**SO03** TUBERCULOSIS IN HEALTHCARE WORKERS IN NORTH EAST LONDON

T. Sanghera1, W. G. Roberts1, J. Moore-Gillon2, G. H. Bothamley1. 1NE London TB Network, Hamerton University Hospital, UK; 2Barts and the London Trust, UK

**Introduction:** We have investigated the occurrence of tuberculosis (TB) in healthcare workers in North East London.

**Methods:** The TB Network receives notification data from all boroughs within the sector. Those identified as healthcare workers were analysed by site of disease, place of birth, GP registration and place of work for the period 2003–05.

**Results:** We identified 105 healthcare workers with tuberculosis (TB), 4% of all cases of TB seen in North East London in this period. Most (79/105) were born outside the UK and were predominantly Black African (46/105) or from India (29/105). 12% of healthcare workers with TB were not registered with a GP. 20% had developed TB within 1 year of entry to the UK. 33/105 were sputum smear positive and thus potentially infectious. Recorded workplace contact tracing was only available for 21 of these 33; 6 of the 33 cases had clear reasons why screening was not performed and for 6, records of screening were not available. Doctors represent 9% of the NHS workforce (Government Statistical Service: Staff in the NHS 2004), but account for 26% of the healthcare workers notified with TB.

**Comment:** TB is common in our healthcare workers with doctors appearing to be over represented. The large number of smear positive cases create a substantial workload in terms of risk assessment for spread to patients and colleagues. We were struck by the numbers of healthcare staff who were not registered with a GP. While firm conclusions cannot be drawn from this study, the very high proportion of newborns born cases suggests that most TB was probably not contracted from patients in these healthcare workers. This reinforces the need for effective occupational screening.

**Study funded by the NHS Culver allocation and the NE London TB Network.**

<table>
<thead>
<tr>
<th>Abstract SO03</th>
<th>Sputum smear positive TB (n = 33)</th>
<th>All cases with TB (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not registered with GP</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Non-UK born</td>
<td>85%</td>
<td>79%</td>
</tr>
<tr>
<td>Workplace screening completed and recorded</td>
<td>64%</td>
<td>21%</td>
</tr>
<tr>
<td>Doctor</td>
<td>18%</td>
<td>25%</td>
</tr>
<tr>
<td>Nurse</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Healthcare assistant</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>GP</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Midwife</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>Developed TB within 1 year of entry to the UK</td>
<td>21%</td>
<td>19%</td>
</tr>
</tbody>
</table>
The incidence of tuberculosis in relation to distance from a diagnostic and treatment centre: a study in rural Zimbabwe

R. D. Barker, F. J. C. Millard, V. A. L. Graham, R. M. Smith, E. Manonano, M. Glenshaw. Department of Respiratory Medicine, Kings College Hospital, Bessemer Road, London SE5 9PJ, UK; "Murumbinda Hospital, PO Box 16 Murumbinda, Buhera, Manicaland, Zimbabwe

Background: The millennium development goals (MDG) target a 70% detection rate and 85% treatment completion rate for patients with tuberculosis (TB) (Dye, et al. JAMA 2005). Progress towards these targets is satisfactory in many parts of the world but poor in Sub-Saharan Africa (World Health Organization 2006). Zimbabwe has one of the highest rates of TB in the world with an estimated incidence of 674 cases/100 000/year. We have been reviewing the TB programme in Buhera health district, Manicaland, Zimbabwe. The district is rural, has a population of 230,000 and is 120 km long and 50 km wide. TB diagnosis and initiation of treatment occurs from Murumbinda hospital which is at least 80 km from some of the primary health care clinics (PHC). We wanted to determine whether the distance patients have to travel for diagnosis acts as an obstacle to case detection.

Methods: The PHC catchment area of residence was established, for all patients with TB, identified in the district, between 1 January 2005 and 1 April 2006. The population of each PHC catchment area was identified from the 2002 census. PHC areas which could be sending their patients out of the district for treatment were excluded. The incidence of TB in each PHC catchment area was calculated and compared with the distance from the district hospital by simple regression.

Results: Seven hundred and five patients with TB were identified, 579 (82.1%) had pulmonary disease and 285 (40.4%) were documented to be smear positive (SS+). The overall incidence of TB was 282/100 000/year and appeared to vary between 20 and 1176/100 000/year in different PHC catchment areas. The overall incidence of SS+ was 114/100 000/year and varied between 0 and 410/100 000/year. The apparent incidence of TB was strongly, inversely related to the distance from the diagnosis and treatment centre. The incidence of TB appeared to fall by 66 (95% CI 14 to 39)/100 000/year for every 10 miles from the hospital.

Conclusion: These data suggest that many people with TB in this rural area have problems accessing diagnosis and treatment. There is a need to bring TB diagnostics closer to the patients' home. This should be a stimulus to further operational and laboratory research.

Supported by TB Alert.

Outcomes of new immigrant screening for tuberculosis: implications for implementation of NICE guidelines

B. Datta, J. P. Watson. Leeds Chest Clinic, Leeds, UK

Background: NICE guidelines for tuberculosis published in March 2006 have recommended changes in immigrant screening. Tuberculin skin test (TST) is recommended for selected groups only (<16 years and 16–35 years from Sub-Saharan Africa or from a country with incidence >500/100 000). Recommendations in the use of Interferon Gamma Testing (IGT) depends on the proportion of infection within a community: below a prevalence of 10%, none of the testing strategies are cost effective, between 10–40%, the two-stage TST/IGT strategy is cost effective and above 40%, IGT alone is the most cost effective. Screening immigrants from countries of lower prevalence close to the threshold reported by NICE at which IGT alone is more cost effective. Screening immigrants from countries of lower prevalence (although above WHO recommended prevalence of 40/100 000) may not be worthwhile.

Conclusions: Immigrant screening of patients from very high prevalence countries is worthwhile. Among Africans the frequency of positive TST is close to the threshold reported by NICE at which IGT alone is more cost effective. Screening immigrants from countries of lower prevalence (although above WHO recommended prevalence of 40/100 000) may not be worthwhile.


Lung transplantation: bench to bedside

Evidence of increased gastric aspiration in acute lung allograft rejection

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A major limitation to long term survival in lung transplantation is bronchiolitis obliterans syndrome (BOS), a chronic disease involving airway fibrosis. BOS is thought to be an overall response to epithelial injury resulting from multiple insults to the graft and acute rejection is a consistently documented risk factor. Increasing evidence links gastrooesophageal reflux to BOS, and we have therefore investigated pepsin as a marker of reflux in bronchoalveolar lavage (BAL) samples from lung allograft recipients.

3×60 ml BAL samples from 36 transplant patients were assayed using an ELISA based on a monospecific goat antibody for pepsin/pepsinogen and compared to 4 normal volunteer controls and 17 subjects with chronic cough (disease control). Allograft samples were assigned to a group depending on the patients status; stable patients showing no sign of either acute rejection or BOS, acute rejection-lung ISHLT biopsy grade A2 or higher and BOS. Data were analysed using a non-parametric analysis of variance.

Pepsin levels marking gastric aspiration were higher in transplant patients compared to volunteer controls and chronic cough ‘controls’. The highest levels were observed in subjects with acute rejection, which were significantly different to both control groups. This suggests a possible novel link between aspiration, acute rejection and eventual BOS.

Abstract S006.

<table>
<thead>
<tr>
<th>Pepsin (ng/ml)</th>
<th>Normal</th>
<th>C. cough</th>
<th>Stable</th>
<th>Acute</th>
<th>BOS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>C. cough</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Stable</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Acute</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>BOS</td>
<td>35</td>
<td>40</td>
<td>45</td>
<td>50</td>
<td>55</td>
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Abstract S005.

<table>
<thead>
<tr>
<th></th>
<th>Invited, n</th>
<th>Attended, n</th>
<th>TST Recorded</th>
<th>TST -ve</th>
<th>TB cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>109</td>
<td>92</td>
<td>84</td>
<td>27 (32%)</td>
<td>1</td>
</tr>
<tr>
<td>Asia</td>
<td>105</td>
<td>57</td>
<td>55</td>
<td>6 (10%)</td>
<td>1</td>
</tr>
<tr>
<td>W Pacific</td>
<td>70</td>
<td>39</td>
<td>35</td>
<td>3 (8.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Middle East</td>
<td>62</td>
<td>37</td>
<td>36</td>
<td>4 (10%)</td>
<td>0</td>
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</table>
**S007** THE EFFECT OF IMMUNOSUPPRESSANTS ON SECRETORY LEUCOPROTEINASE INHIBITOR PRODUCTION BY LUNG EPITHELIUM IN THE PRESENCE OF TRANSFORMING GROWTH FACTOR-BETA

R. Anderson¹, P. S. Hiemstra², R. Verhoosel², L. Borthwick¹, P. A. Corris¹, J. Lordan¹, A. J. Fisher¹. ¹Applied Immunobiology and Transplantation Research Group, Institute of Cellular Medicine, University of Newcastle, UK; ²Pulmonology Department, Leiden University Medical Centre, Leiden, the Netherlands.

Introduction: Secretory leucoproteinase inhibitor (SLPI) is the major inhibitor of human neutrophil elastase within the lung and can also act as an endogenous antibiotic. We have previously demonstrated that lung transplant recipients with bronchiolitis obliterans syndrome (BOS) have lower airway levels of SLPI than stable recipients. This may be because BOS is associated with increased levels of transforming growth factor-beta (TGF-β) which has been shown to be a potent inhibitor of SLPI production (Jaumann, et al. Eur Respir J 2000). Immunosuppressive drugs used post lung transplant may also contribute to the lower SLPI levels as their use is associated with an increased risk of infection.

Aims: We aimed to determine whether the two commonly used calcineurin inhibitors, Ciclosporin A and Tacrolimus can modify SLPI production in A549 cells, and whether exacerbation of TGF-β exposure causes an exaggerated loss of SLPI production in the presence of calcineurin inhibitors.

Methods: A549 cells were serum starved for 24 hours and pretreated with either Ciclosporin A 100, 10 and 1 ng/ml or Tacrolimus 10, 1 and 0.1 μg/ml for 1 hour. Cells were stimulated with IL1β 20 ng/ml and TNFα 20 ng/ml for 24 hours to induce SLPI production. These experiments were then repeated in the presence of TGF-β 10 ng/ml. Cytotoxicity was excluded by an MTT assay.

Results: Neither immunosuppressant altered the basal production of SLPI in unstimulated cells. Stimulation with IL1β and TNFα significantly increased SLPI production compared to basal levels. Ciclosporin increased SLPI production in stimulated cells in a dose dependent manner when compared with control. The mean increase in SLPI at 100 ng/ml of cyclosporin was 19.6 ng/ml (0.12 SD) p<0.001. Tacrolimus significantly reduced SLPI production in stimulated cells in a dose dependent manner compared to stimulated control cells. The mean decrease in SLPI at 10 μg/ml of tacrolimus was 25.8 ng/ml (0.5 SD) p<0.001. The addition of TGF-β 10 ng/ml to the experiments significantly reduced SLPI production upon stimulation in the presence of both immunosuppressants.

Conclusion: The elevated levels of TGF-β seen in BOS are likely to reduce levels of SLPI in the airway leading to increased susceptibility to damage from human neutrophil elastase. Changing immunosuppressant from Ciclosporin to Tacrolimus, which is commonly-done in BOS will further reduce SLPI production in response to inflammatory stimuli and increase susceptibility to airway damage.

RA is funded by ISHLT fellowship and AJF by a GSK Clinical Fellowship.

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**S008** COMPARISON OF GLUCOCORTICOID SENSITIVITY IN LUNG ALVEOLAR MACROPHAGES AND PERIPHERAL BLOOD MONOCYTES FROM CLINICALLY STABLE LUNG TRANSPLANT RECIPIENTS

L. G. Spencer, M. Al-Aloul, D. Singh, C. T. Leonard. Transplant Unit, Wythenshawe Hospital, Southmoor Road, Wythenshawe, Manchester M23 9LT, UK.

Introduction: Immune-mediated chronic rejection significantly limits survival following lung transplantation, and tends to be glucocorticoid resistant. The role of alveolar macrophages (AM) in this process is not well characterised. AM glucocorticoid resistance is noted to be an important feature of many respiratory diseases. Glucocorticoids (for example, Prednisolone) are a key part of the anti-rejection regime after lung transplantation. This study investigated glucocorticoid sensitivity in AM from clinically stable lung transplant (LTx) recipients and compared it to glucocorticoid sensitivity in their peripheral blood mononuclear cells (PBMC).

Objective: To compare glucocorticoid sensitivity in of AM and PBMC from “healthy” LTx recipients.

Methods: Nine LTx recipients were recruited (6M:3F). Five had a single LTx for a variety of interstitial lung diseases and 4 had a double LTx for COPD. At the time of bronchoscopy and blood collection all were clinically stable—that is, free of acute or chronic rejection and infection. AM and PBMC were isolated from bronchoalveolar lavage fluid and peripheral blood respectively. Cells were suppressed with dexamethasone (10, 100 and 1000 μM) for 2 hours (h) then stimulated with lipopolysaccharide (LPS) (1 μg/ml) for 4 h. Cell supernatant was collected and TNFα and IL-8 was measured using EUSA (R&D Systems). Data were analysed using paired t-tests.

Results: The inhibitory effect of dexamethasone on TNFα release in PBMC was significantly greater (p=0.044) than on AM. There was no significant difference in percent inhibition of IL-8 release between PBMC and AM (p=0.14).

Discussion: In clinically stable lung transplant recipients we have found that LPS induced TNFα release from AM is steroid resistant compared to PBMC from the same patients. No significant steroid resistance was demonstrated from the same samples when LPS induced IL-8 release was measured. This is the first report of differential glucocorticoid resistance in the lung compartment compared to peripheral blood compartment in lung transplantation. We are progressing with this model of lung AM and PBMC activation induced by LPS to investigate mechanisms of corticosteroid resistance in lung transplantation.

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**S009** IS THERE A ROLE FOR NATURAL KILLER CELLS FOLLOWING LUNG TRANSPLANTATION?

J. E. Fildes, A. H. Walker, K. Tunstall, N. Yonan, C. T. Leonard. The Transplant Centre, South Manchester University Hospital Trust, Wythenshawe Hospital, Manchester, UK.

Background: Natural killer cells are potential effectors and/or mediatory cells of allograft rejection, as they display receptors allowing them to recognise self from allogeneic tissue, and act as a critical bridge between the innate and adaptive response. In this study, we aimed to determine if NK cell activation in peripheral blood and broncho-alveolar lavage (BAL) fluid correlated with clinical outcome following lung transplantation.

Methods: Fifty patients were included in the study. Lysosomal associated membrane proteins (CD107a and CD107b) were used as markers of NK cell activation, and immunophenotyping was performed using CD3, CD16, and CD56. The activating receptor, NKR-P1A (CD161) was also included as a surrogate marker of cytotoxicity.

Results: We found significant associations between early onset allograft rejection and NK cell populations in the BAL fluid, and mean expression of CD107a+ and CD107b+ (p=0.001, co-eff 0.7370), CD107b+ (p=0.001, co-eff 0.8754) and CD107b+ CD56+ (p=0.051, co-eff 0.8900) NK cells in peripheral blood. Using Pearson’s correlation co-efficients, there was a significant negative correlation between BOS grade and the percentage of NKR-P1A+ NK cells in peripheral blood (p=0.006). Comparing NK cell populations in broncho-alveolar lavage fluid from patients (n=5) with or without acute rejection (grade A3 or A0 respectively), we found a substantial NK cell population in A3 patients, compared to no NK cells in A0 patients.

Discussion: We describe the potential migration of NK cells from peripheral blood to the lung during acute rejection. We also describe a systemic activation of NK cells in patients with bronchiolitis obliterans syndrome. The NK cell has largely been ignored in solid organ transplantation.

Abstract S008

<table>
<thead>
<tr>
<th>Dexamethasone μM</th>
<th>% Inhibition of TNFα release</th>
<th>% Inhibition of IL-8 release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM</td>
<td>PBMC</td>
</tr>
<tr>
<td>10</td>
<td>20.8</td>
<td>36.50</td>
</tr>
<tr>
<td>100</td>
<td>40.0</td>
<td>75.40</td>
</tr>
<tr>
<td>1000</td>
<td>54.8</td>
<td>84.50</td>
</tr>
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<table>
<thead>
<tr>
<th></th>
<th>AM</th>
<th>PBMC</th>
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<tr>
<td>55.80</td>
<td>60.5</td>
<td></td>
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<tr>
<td>22.50</td>
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</tr>
<tr>
<td>54.70</td>
<td>74.6</td>
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</table>
Our data implicates this cell type in the complex cellular orchestration of the rejection cascade.

S010 FACTORS AFFECTING SUITABILITY OF PATIENTS FOR LUNG TRANSPLANTATION ASSESSMENT IN A COHORT REFERRED TO A SINGLE CENTRE 2000–05

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Background: Lung transplantation (LT) provides a realistic therapeutic option for selected patients with end-stage respiratory disease. Many of the patients referred for consideration of this procedure are deemed unsuitable by international criteria and will never reach formal inpatient assessment. This may unnecessarily raise expectations among patients as well as stretch resources in the transplant centre.

Aims: Data on patients who were referred to our centre for lung transplant assessment over a 6 year period were reviewed. We aimed to identify which patients were deemed unsuitable on referral information and determine why they were not formally assessed.

Methods: A retrospective review of the referral database, prospectively collected, for demographic information, clinical information and any contraindication as measured against international referral guidelines for all patients referred to our centre from January 2000 to December 2005. Those patients who were deemed suitable on referral data and received a formal assessment were then compared with those who did not get formally assessed.

Results: 1249 patients were referred over this 6 year period, 749 (60%) underwent formal inpatient assessment, average 124 (range 78–151) per year, of these 193 (26%) have subsequently received a transplant. 500 (40%) did not get to assessment. Age spread is similar for all patients referred with a small peak at 21–30 years old and larger peak at 51–60 years old. Patients assessed are younger compared to those who did not receive assessment, mean values 41 years (standard deviation 15) and 50 years (13) respectively (p = 0.0005 unpaired t-test). Significantly more cystic fibrosis (CF) patients received assessment compared to not assessed, only 37 CF were not assessed compared to 192 assessed (z = 0.0005). Death very soon after referral was a major reason for no assessment, 22% of patients who were not assessed died within 3 months of referral. Of the remaining patients, 10% had absolute contra-indications (CI) for LT, 22% had a single relative CI and 68% had multiple CI. Common relative CI included age, severe osteoporosis, cardiovascular disease, low and high BMI or performance status. All these relative CI are increasing over the years from 2000 to 2006.

Conclusion: Significant numbers of patients referred to our transplant centre never reach formal assessment. This is due to a significant proportion of deaths early after referral suggesting that referral was too late. In addition increasing numbers of absolute and relative CI contributed, suggesting better awareness of referral criteria and better work up of patients ahead of referral may provide a better insight into a development of ablative branchitis, limiting 5 year survival to approximately 45%. Better understanding of the effects of infection on pulmonary allograft vasculature could aid in development of better diagnostic and therapeutic targets.

Methods: After single lung transplantation, dogs were immunosuppressed with methylprednisolone acetate, cyclosporine, and azathioprine. After 5 days, infection was induced in one group of dogs by endobronchial inoculation of antibiotic resistant Eschericia coli (infection group, n = 5); in the second group, the same amount of culture medium without bacteria was flushed into the bronchus (control group, n = 4). All animals were medicated under the same drug protocol. On post-operative day 8, all animals were sacrificed, the pulmonary arteries were recovered, cut into rings and suspended for pharmacological characterisation in organ chambers.

Results: Contractions to phenylephrine and angiotensin-1, but not endothelin-1 were reduced in rings with endothelium from pulmonary arteries from infected lungs (p < 0.05). Inhibition of nitric oxide synthase with L-NMMA, restored these contractions. Rings without endothelium did not demonstrate altered reactivity. Endothelium-dependent relaxations to adenosine diphosphate and calcium ionophore, which stimulate release of endothelium-derived nitric oxide by receptor and non-receptor mediated processes, respectively, were not different between groups. Relaxations to nitric oxide were also not different between groups.

Conclusions: These results suggest that infection selectively affects contractions of the allograft pulmonary vasculature and that these effects are mediated in part by endothelium-derived nitric oxide.

Can we improve respiratory healthcare provision?

S012 SURVEY OF RESPIRATORY UNITS IN THE UK: PLANNING FOR THE NATIONAL COPD RESOURCES AND OUTCOMES PROJECT


The 2003 RCP/BTS UK National COPD audit demonstrated wide variations in quality of care and outcomes between hospitals linked to resources and notably staffing. In 2005 the same units collected additional data on resources and organisation of care in preparation for a future audit programme. Data below are from 237 hospitals in 2003 and 163 in 2005. They suggest improved resources and best practice organisation of care. There remain significant deficiencies in some areas that should be addressed by clinicians and managers working together.

The 2006/07 NCROP interventional will pair hospitals with differing quality attainments in order to share good practice and develop bilateral improvements in COPD services. This group intends to report on the success of this strategy at next year’s BTS meeting.


Abstract S012 Table 1

<table>
<thead>
<tr>
<th>Staffing levels in UK Respiratory Units</th>
<th>Mean WTE 2003</th>
<th>Mean WTE 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Consultants</td>
<td>2.20</td>
<td>2.78</td>
</tr>
<tr>
<td>Number of Associate Specialists</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>Number of SpRs</td>
<td>1.18</td>
<td>1.95</td>
</tr>
<tr>
<td>Number of SHOs</td>
<td>1.68</td>
<td>2.41</td>
</tr>
<tr>
<td>Number of PRHOs</td>
<td>1.37</td>
<td>1.81</td>
</tr>
<tr>
<td>Number of COPD Nurses</td>
<td>1.09</td>
<td>1.43</td>
</tr>
<tr>
<td>Number of other Specialist Respiratory Nurses</td>
<td>1.80</td>
<td>1.69</td>
</tr>
<tr>
<td>Number of Specialist Respiratory Physiotherapist</td>
<td>1.01</td>
<td>1.61</td>
</tr>
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S013 PATIENT VIEWS ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE SERVICES: A FOCUS GROUP STUDY


Introduction: The RCP/BTS/BLF NCROP study aims to improve chronic obstructive pulmonary disease (COPD) services in the three key areas of NIV provision in acute respiratory failure, early discharge from hospital and pulmonary rehabilitation. In preparation the views of patients about these services were sought in order to inform future plans to develop optimum care for COPD patients.

Method: Four focus groups organised by the BLF were run in Scotland, England (2), and Wales involving a total of 36 COPD patients and each facilitated by two trained researchers. Each followed a set framework in which participants were asked their views on the patient perspective of the optimum service provision in the three areas identified above for improvement. The 2 hour long sessions were tape recorded with consent and transcribed later for analysis identifying emergent grouped themes.

Results: NIV: few patients understood the term, or the concept or had personal experience of this treatment. Those with experience reported insufficient information provision for them to make informed choices and this at a time when vulnerable and not physically or mentally supported to make such decisions themselves. Patients generally reported hospital admissions as times of severe fear and anxiety. There was a general suggestion that all hospitalised COPD patients should be told about this form of treatment at a time of relative stability and the options that may be offered at subsequent admissions. Pulmonary rehabilitation: In contrast to NIV, all participants were conversant with rehab. It was strongly advocated. Specifically it gave hope and support to patients and was felt a bridge between hospital and home. Suggestions were for ongoing programmes and not time limited ones. Separate COPD classes were preferred over general public gym sessions and the presence of nurses or physiotherapists were seen as important in providing reassurance. Early discharge: Just under a third of the group members had been through an EDS. Most rated them highly. Just over 50% of the remainder had not heard of the term at all. Of these some expressed concerns over discharge to free beds rather than to improve care and the psychological effects of COPD was requested and, again, more information about their condition and the treatments.

Conclusion: patients want more information about medical interventions before they are applied. These are best provided during periods of stable health.

S014 TREATMENT RECOMMENDATIONS FROM THE RESPIRATORY CLINIC: WHY ARE THEY NOT EFFECTED?

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A prospective audit, submitted also to this meeting, showed that changes or recommendations made by us in the chest clinic were not effected in 99 of 264 patients with airways disease (37.5%). We have further analysed the data from the 99 patients where changes were ineffective. 51 of the 99 events (54%) were patient initiated and 43 (46%) were due to other factors within primary care.

Abstract S014 Table 1 Reasons change/recommendation not effective in patients

| Reason                                      | Percentage
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Non-compliance with medication</td>
<td>35/51 (70%)</td>
</tr>
<tr>
<td>Side effects led to cessation</td>
<td>8/51 (16%)</td>
</tr>
<tr>
<td>Increased symptoms</td>
<td>4/51 (8%)</td>
</tr>
<tr>
<td>Exacerbated</td>
<td>2/51 (4%)</td>
</tr>
<tr>
<td>Letter not acted on</td>
<td>1/51 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/51 (2%)</td>
</tr>
</tbody>
</table>

Abstract S014 Table 2 Reasons change/recommendation not effective in primary care

| Reason                                      | Percentage
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter not acted upon</td>
<td>23/43 (53%)</td>
</tr>
<tr>
<td>Repeat script not changed</td>
<td>7/43 (16%)</td>
</tr>
<tr>
<td>Instruction to patient</td>
<td>4/43 (9%)</td>
</tr>
<tr>
<td>Increasing symptoms</td>
<td>4/43 (9%)</td>
</tr>
<tr>
<td>Side effects</td>
<td>3/43 (7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2/43 (5%)</td>
</tr>
</tbody>
</table>

Abstract S014 Table 3 Were specific medication changes ineffective

<table>
<thead>
<tr>
<th>Medication (top 7)</th>
<th>Total</th>
<th>Change not effective</th>
<th>Primary care event</th>
<th>Patient event</th>
<th>Main reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>41</td>
<td>10 (24%)</td>
<td>3 (33%)</td>
<td>7 (66%)</td>
<td>Stopped: 3</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>38</td>
<td>18 (47%)</td>
<td>14 (77%)</td>
<td>4 (23%)</td>
<td>Letter: 13</td>
</tr>
<tr>
<td>Symbicort</td>
<td>32</td>
<td>10 (31%)</td>
<td>2 (20%)</td>
<td>8 (80%)</td>
<td>Stopped: 8</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>28</td>
<td>14 (50%)</td>
<td>4 (29%)</td>
<td>10 (71%)</td>
<td>Stopped: 8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>27</td>
<td>9 (33%)</td>
<td>5 (55%)</td>
<td>4 (45%)</td>
<td>Stopped: 3</td>
</tr>
<tr>
<td>Serefixe</td>
<td>26</td>
<td>8 (31%)</td>
<td>4 (50%)</td>
<td>Nil clear</td>
<td></td>
</tr>
<tr>
<td>Combivent</td>
<td>24</td>
<td>7 (29%)</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
<td>Stopped: 13</td>
</tr>
<tr>
<td>Aminoph</td>
<td>3</td>
<td>3 (100%)</td>
<td>2</td>
<td>1</td>
<td>Intolerance</td>
</tr>
</tbody>
</table>

www.thoraxjnl.com
Thus, the commonest reasons for an ineffective change were non-compliance and clinic letters not being acted upon. It was notable that 13/18 letters recommending antibiotic therapy were not effected. Otherwise, no single drug was prescribed less effectively. We conclude there were significant problems over compliance and communication in this patient group. Personal COPD plans might improve matters.

**S015 ARE EVALUATED RESPIRATORY SERVICE DEVELOPMENTS IMPLEMENTED INTO CLINICAL PRACTICE?**

M. Glasser, N. J. Roberts, M. R. Partridge. Imperial College London, NHU Division at Charing Cross Hospital, UK

**Background:** In respiratory medicine there has recently been a growing interest in evaluating how best we deliver respiratory healthcare. This has led to a number of publications regarding service developments (or similar) which have been evaluated in key centres. However, it is not clear whether all such service developments subsequently become normal practice even in the originating institution.

**Methods:** Methodical search and review of potential service development studies in 4 respiratory journals over a 4 year period. A questionnaire was then sent to the corresponding authors regarding implementation of the study findings into clinical practice.

**Results:** 41 papers were identified in the four journals during the 4 year period, of which 121 had a title or key word which suggested the possibility that they were reports of a respiratory service development. Following review of the actual papers 85 of these were rejected because they contained negative results (n = 17), were not true service developments (n = 50) or were audits or systematic reviews (n = 13). The questionnaire was sent to the authors of the remaining 36 papers and 30/36 (83.3%) replied. 10 reports concerned evaluation of the sharing of care with nursing colleagues and 5 more concerned use of physiotherapists, pharmacists, peer group educators, practice assistants and smoking counsellors. The remainder of the studies involved new technologies, use of the telephone, patient information sheets, mailing patients, education and guideline implementation. 15/30 respondents have put the researched service development into practice; 11 of the 15 doing so immediately after the research ended. Delays in implementation of 12–40 months were due to staffing and organisational issues in 3 cases and the institution not being prepared to pick up costs in 1 case. For those 15/30 (50%) studies which have not been put into practice, 2 might be implemented and in 2 cases the benefits were perceived to have been rather marginal. 10 studies will not be put into practice. One study was completed 9 years ago and although initially implemented is no longer used. Out of the 10 studies not implemented the commonest single reason was due to the key person leaving (n = 5).

**Conclusions:** While it is encouraging that half of all reports of the evaluation of service developments are able to be continued, it is disappointing that many innovations were not implemented even in the reporting institution. These were equally distributed between studies of the use of different healthcare professionals and new technologies, but process changes were particularly unlikely to be continued. In a couple of cases reflection suggested the benefit of the reported intervention was not large, and in the remainder, costs or loss of key personnel were the explanation for non continuation of the service development.

**S016 ESTABLISHMENT OF A COMMUNITY RESPIRATORY ASSESSMENT UNIT**

R. Hassett1, K. Meade1, M. R. Partridge2. 1Hammersmith & Fulham Primary Care Trust; 2Imperial College London, NHU Division at Charing Cross Hospital, UK

Respiratory disease is common. There are many types and symptoms and are shared with disorders of other systems. Spirometry is one tool which can enhance diagnostic accuracy; previous studies have shown that without it use mistaken diagnoses occur in primary care. Hospitalisation rates for asthma and COPD within Hammersmith & Fulham PCT are among the highest in London. In 2004 the Hammersmith & Fulham PCT with the support of the North West Health Authority, Hammersmith Hospitals NHS Trust and Imperial College established a Community Respiratory Assessment Unit (CRAU) with three intentions: to improve the diagnosis of respiratory conditions, to empower patients, and to encourage implementation of national respiratory guidelines. The service was developed and run by two specialist nurses. Significant time was spent on the logistics of patient referral to the service, the development of a protocolised approach to patients, and to the development of a semi-standardised reporting system. Where a diagnosis was obvious, self-management advice and checking of inhaler techniques, SaO2 and breath CO measurements were also undertaken. Educational materials for different respiratory scenarios were included with the report to GPs and were designed to be of use for all patients not just those attending CRAU. Of the 33 primary care facilities in Hammersmith and Fulham PCT, 16 were given access to the service initially and the remaining 17 six months later. Prescribing data from GP practices were collected before and after implementation of CRAU. The service was based at Charing Cross Hospital and a peripatetic service was offered to practices furthest away. As part of the referral process GPs stated reasons for referral and what they would have done if the service had not been available. 364 patients were referred over the first 12 months and we provide full details on the 330 who attended (148M 182F, mean age 70 years (SD 14.9), 107 smokers 123 ex-smokers). 57% of all referrals related to definite/suspected COPD and definite/suspected asthma accounted for 28% of referrals. When asked what they would have done in the absence of the service, 57% of GPs would have referred patients to a hospital clinic and 54% would have instituted a trial of therapy (98/140 short acting beta-agonist; 74/140 inhaled cortico-steroid). Definite or suspected COPD, was the most common reason for referral (189/330) but airway narrowing was only demonstrated in 110/189 (58%) of these. GP satisfaction with the service was extremely high and 97% rated the education materials which accompanied the report as being helpful or very helpful. A community orientated respiratory diagnosis assessment service, offering more than spirometry alone, has the potential to improve the accuracy of respiratory diagnosis in primary care and potentially to lead to savings associated with delayed diagnosis and inappropriate trials of therapy.

**S017 PICTURE ARCHIVING AND COMMUNICATIONS SYSTEM: NATIONAL SURVEY OF ITS AVAILABILITY, IMPLEMENTATION, AND ACCEPTABILITY AMONG RESPIRATORY SPECIALISTS IN THE UK, 2006**

S. Singh, A. Gulati, B. D. W. Harrison, D. Seaton on behalf of the Joint Specialist Committee of the Royal College of Physicians, London and the British Thoracic Society (BTS). The Ipswich Hospital NHS Trust, Heath Road, Ipswich IP4 5PD, UK

As part of the "Connecting for Health" (CfH) project, it is the intention of the Department of Health to introduce the picture archiving and communications system (PACS) throughout NHS trust hospitals as a more efficient imaging process than film. A postal questionnaire on PACS was sent to 782 respiratory consultants (BTS database) in the first quarter of 2006 to make assessments of (1) current availability, (2) involvement of respiratory consultants in implementation, (3) clinical acceptability of the system, and (4) anticipated timing of introduction in hospitals which do not currently use PACS.

**Response rate:** The institutional response rate was 95% (276/290) with an individual response rate of 72% (561/782).

**Hospitals with PACS:** 45% of hospitals (124/276) had undergone either a complete (88/276) or a partial (36/276) transition to PACS, however 33% of these hospitals had not involved their respiratory consultants in discussions leading up to its implementation.

**Perceived benefits following introduction of PACS:** The majority (percentages in parentheses) of consultants were positive in response to questions concerning ability to manipulate images (83%), speed of access (77%), fewer lost images (71%), its use as a teaching or research tool (67%), its ability to reduce clerical time (64%) and to improve clinical interaction between colleagues within the same institution (61%).

**Perceived problems following introduction of PACS:** 33% of respondents had experienced difficulty transferring images to other hospitals and 68% recorded no benefit in clinical interaction nationwide. Further difficulties had been experienced: (1) in obtaining good quality images in the outpatient clinic (36%) or wards (48%), (2) with delay in displaying images on screen (52%), (3) in obtaining archived images (33%), (4) with IT training/backup (27%).

**Hospitals without PACS:** Of the 55% of hospitals with no PACS (152/276), 47% of these hospitals were expected by respondents to have PACS within the next year, 31% within 2 years, 8% in longer than this, the remaining respondents being uncertain.

We conclude that although the majority of respiratory specialists in hospitals with PACS respond positively about its use, too many clinicians complain of suboptimal image quality and other problems, particularly image transfer between hospitals, this being a stated aim of CfH. The responses suggest that there is a need for increased respiratory specialist involvement in local implementation and raise questions about the need for generic guidance for clinicians involved in this process.
**Cellular mechanisms in asthma**

**S018 PRIMARY AIRWAY FIBROBLASTS IN THE UNDERSTANDING OF ASTHMA: EXTRACELLULAR MATRIX GENE EXPRESSION**

P. N. Sanders, M. G. Buckley, L. C. K. Lau, P. H. Howarth. Southampton General Hospital, Inflammation, Infection and Repair (IIR) Department, UK.

**Introduction:** Asthma is a disease characterised by both chronic inflammation and structural airway changes associated with alterations in the extracellular matrix composition. The fibroblast is pivotal in maintaining the balance between production and breakdown of the ECM in the healthy lung. However fibroblasts in the asthmatic lung may deposit increased levels of ECM proteins, which contribute to the remodelling of the airways observed in asthma.

**Methods:** Primary cultures of fibroblasts were grown from endobronchial biopsies taken from healthy and asthmatic volunteers. Broncho-alveolar lavage (BAL) fluid from healthy or asthmatic donors, 10 ng/ml tumour necrosis factor (TNF)-α and 1 ng/ml transforming growth factor (TGF)-β1 were applied to the fibroblasts for 24 hours and TaqMan real-time PCR was used to quantify gene expression. Four genes were analysed: connective tissue growth factor (CTGF), interleukin-8 (IL-8), Collagen III and alpha smooth muscle actin (α-SMA). The RNA was extracted with TRI-reagent.

**Results:** Mild asthmatic BAL (n = 7) and moderate/severe asthmatic BAL (n = 7) was shown to significantly increase Collagen III, α-SMA, and CTGF mRNA expression from asthmatic fibroblasts compared to healthy fibroblasts (p < 0.0008). Asthmatic fibroblasts also exhibited a significant increase in CTGF and IL-8 (both p < 0.0001) mRNA expression compared to healthy fibroblasts after challenge with healthy BAL and healthy and moderate/severe asthmatic BAL respectively. 1 ng/ml TGF-β1 and 10 ng/ml TNF-α also caused a significant increase in Collagen III (p < 0.0001) mRNA expression in asthmatic fibroblasts compared to healthy cells. Healthy fibroblasts were shown to express significantly higher levels of CTGF mRNA than asthmatic fibroblasts after challenge with 1 ng/ml TGF-β1 and 10 ng/ml TNF-α (p < 0.0002), and also α-SMA (p < 0.001) mRNA after challenge with healthy BAL (n = 7).

**Discussion:** These data indicate that BAL fluids from asthmatic subjects contain factors that stimulate asthmatic fibroblasts to express genes for ECM production (Collagen III, α-SMA, CTGF, IL-8) compared to healthy fibroblasts. Factors from asthmatic donors may have increased potential to generate ECM. Identification of factors responsible for activating fibroblasts in asthma may help to generate new targets for therapeutic intervention to reduce the severity of lung remodelling in chronic asthma.

**S019 INTERLEUKIN-13 EXPRESSION BY MAST CELLS IN THE AIRWAY SMOOTH MUSCLE BUNDLE IN EOSINOPHILIC BUT NOT NON-EOSINOPHILIC ASThma**


**Background:** Mast cell microlocalisation to the airway smooth muscle (ASM) bundle is a feature of asthma. The number of mast cells in the ASM was increased in the subjects with eosinophilic asthma compared to all the other groups (p < 0.001; table). The number of mast cells in the ASM was increased in the subjects with eosinophilic asthma compared to healthy controls (p < 0.001; table).

**Conclusion:** Mast cells in the ASM are a feature of eosinophilic and non-eosinophilic asthma. The mast cell activation was different between the asthma phenotypes with increased IL-13 expression from mast cells in eosinophilic asthma compared to those with eosinophilic asthma. This difference in the nature of the mast cell activation between the asthma phenotypes may provide a possible explanation for the differential response to corticosteroids.

Supported by Asthma UK and DoH Clinician Scientist Award.

**S020 THE INDUCTION OF ANTIVIRAL RESPONSES IN HUMAN AIRWAY SMOOTH MUSCLE AND EPITHELIAL CELLS**


Respiratory infections trigger inflammatory responses, leading to leukocyte recruitment, epithelial damage, mucus hypersecretion, and bronchoconstriction. This has the potential to exacerbate many airways diseases, for example asthma, by sensitising the tissue micro-environment to allergens. Toll-like receptors (TLRs) 3, 7, and 8 have been described as sensors of viral infection, with TLR3 recognising the double-stranded RNA produced during viral replication, while TLRs 7 and 8 detect single-stranded viral RNA. Thus, TLRs may provide a dynamic system for host defence against pathogenic respiratory viruses if present and functional in the airway. Our results reveal TLR3 is expressed intracellularly in primary human airway smooth muscle cells (HASMCs) and confirm TLR3 expression (extra- and intra-cellularly) on the BEAS-2B human airway epithelial cell line. Stimulation of both cell types with poly(C):dDNA mimics which acts via TLR3, caused the release of a repertoire of pro-inflammatory cytokines (CXCL8, CXCL10, IL-6, and CCL5) and upregulated ICAM-1 expression, an adhesion molecule utilised by some respiratory viruses to gain access to tissue cells. These responses were significantly enhanced by coinoculation with the proinflammatory cytokines IL-1β or TNFα. Peripheral blood mononuclear cells (PBMCs) defend against infection and modulate immune responses in the lung, thus their role as mediators of lung antiviral responses was investigated using an in vitro coculture system. We have previously shown that PBMCs are necessary for LPS-induced cytokine release from HASMCs (Morris et al. AJRCCM 2005;171:814–22); here we report that PBMCs also enhance LPS-induced cytokine release from BEAS-2B cells, and were required for tissue cell responses to agonists of TLR7/8. Exposure to multiple TLR agonists may also occur at inflammatory sites, so we therefore stimulated cocultures of PBMCs with either BEAS-2B cells or HASMCs, with agonists of both TLR3 (acting principally on the tissue cell) and TLR7/8 (acting principally on the immune cell) and observed cooperative responses leading to a synergistic enhancement of cytokine generation from the cocultured PBMCs and tissue cells. These data indicate that the inflammatory response is regulated by cooperative networks that can be modelled in vitro with primary human cells, furthermore it suggests these will be of more importance than the response of an individual cell when examining the processes of acute TLR-driven inflammation.

Some of the data have previously been presented at Toll2006: Recent advances in Pattern Recognition, Salvador, Brazil.

**S021 ACTIVATION OF NEUTROPHILS BY THE REPAIRING BRONCHIAL EPITHELIUM ARE REGULATED VIA PI3-KINASE/AKT/PROTEIN KINASE C DELTA-MEDIATED SIGNALS**

M. Uddin, G. Seunois, L. C. Lau, D. E. Davies, R. Djukanovic. Division of Infection, Inflammation and Repair, School of Medicine, Southampton General Hospital, Southampton SO16 6YD, UK.

Malfunctioning of the bronchial epithelium is a recognised feature of both acute infections and chronic inflammatory disorders of the airways as seen in severe asthma, and this may contribute to enhanced neutrophil responsiveness. We set out to determine the modulatory role of the repairing human bronchial epithelium by studying the way the bronchial epithelial cell line, 16HBE 14o- impacts on neutrophil activation and its downstream signalling pathways. Culture conditioned medium (Cm) was selected from subconfluent 16HBE cells (16HBE-CM) and to mimic the phenotype of the repairing asthmatic epithelium, 16HBE cells were treated with EGF (10 ng/ml). While EGF itself was not most assesseable ASM (area>0.1 mm²) were available from 7 subjects in each group. We enumerated inflammatory cells and IL-13+ cells in the ASM using immunohistochemistry.

**Results:** The number of IL-13+ cells in the ASM was increased in eosinophilic asthma compared to all the other groups (p < 0.001; table). The number of mast cells in the ASM was increased in the subjects with eosinophilic asthma compared to healthy controls (p < 0.001; table).

**Conclusion:** Mast cells in the ASM are a feature of eosinophilic and non-eosinophilic asthma. The mast cell activation was different between the asthma phenotypes with increased IL-13 expression from mast cells in eosinophilic asthma compared to those with eosinophilic asthma. This difference in the nature of the mast cell activation between the asthma phenotypes may provide a possible explanation for the differential response to corticosteroids.

Supported by Asthma UK and DoH Clinician Scientist Award.
The role of TGF-β in lung disease

**S023** CHARACTERISATION OF BONE MORPHOGENETIC PROTEIN AND TGF-β SIGNALLING PATHWAYS IN MONOCROTALINE AND HYPOXIA-INDUCED PULMONARY ARTERIAL HYPERTENSION IN THE RAT

L. Long*, A. Crosby†, M. Southwood, P. D. Upton, N. W. Morrell. Division of Respiratory Medicine, University of Cambridge School of Clinical Medicine, Cambridge, UK

Idiopathic pulmonary arterial hypertension (PAH) is an often fatal disease characterised by proliferation of endothelial and smooth muscle cells in small pulmonary arteries. Approximately 70% of familial PAH cases are due to heterozygous germline mutations in the gene encoding the bone morphogenetic protein receptor type II (BMPR-II), a receptor for the transforming growth factor-β (TGF-β) superfamily. Dysfunctional BMP signalling is now emerging as a feature of diverse forms of PAH. We questioned whether dysfunctional BMP/TGF-β signaling was a feature of two commonly used models of PAH; the chronically hypoxic and the monocrotaline treated rat models. Male Sprague-Dawley rats received a single intraperitoneal injection (60 mg/kg) of the pyrroldizidine alkaloid monocrotaline (M) or were exposed to normobaric hypoxia (FiO₂ 10%) (H) for 3 weeks. Control rats were maintained in room air. After three weeks the M and H rats had a significant increase in pulmonary arterial pressure, right ventricular hypertrophy and vascular remodeling, compared with control rats. In both experimental groups there was a reduction in the lung expression of both BMP1A and BMPR-II mRNA (∼60%) as determined by real-time RT-PCR. In addition there was a reduction in the expression of the inhibitory Smad6, a transcriptional target of BMP signaling. In the M rats western blot analysis of lung protein revealed that there was a trend for a reduction in the expression of Smad7, a downstream target of TGF-β signaling.

*These authors contributed equally.

**S024** ANALYSIS OF THE HHT3 LOCUS ON CHROMOSOME 5, ENCODING A NEW GENE FOR HEREDITARY HEMORRHYAGIC TELANGiectASIA

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The majority of patients with pulmonary arteriovenous malformations (PAVMs) have underlying hereditary haemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome) in which abnormal vascular structures develop throughout life. HHT is inherited as an autosomal dominant trait and is genetically heterogeneous. Three disease genes have been identified to date, resulting in HHT type 1 (endothelin), HHT type 2 (ALK1), or HHT-JP, an HHT-juvenile polyposis overlap syndrome (Smad4). PAVMs occur in all
types of HHT, most commonly in HHT type 1 due to endoglin mutations. HHT type 2 patients with ALK-1 mutations are also at risk of HHT-associated pulmonary hypertension. Endoglin and ALK-1 encode proteins expressed on vascular endothelial cells, and all three gene products modulate or transduce transforming growth factor (TGF-β) signals.

We recently identified a new locus for HHT on chromosome 5 (Cole SG, Begbie ME, Wallace GMF, Shovlin CL. J Med Genet 2005;42:577–82). First we demonstrated that the HHT gene in a Hammersmith PAVM/HHT family was unlinked to the known HHT genes endoglin, ALK-1, or Smad4. The 3 known HHT genes were also sequenced, and no mutations were identified. A genome-wide linkage study was used to identify the HHT3 locus on chromosome 5 where a single haplotype was inherited by all affected members of the pedigree (Zmax 3.45, q = 0, fully informative markers). The consideration of the genome was excluded to a 2.5-Mb resolution. Fine mapping narrowed the interval to a 5.4-cM/6-Mb region that contains 28 genes including 10 novel genes (http://www.ensembl.org).

In order to narrow the interval further, additional polymorphic markers have been studied. Candidate genes in the interval were initially selected based on known function and/or expression on vascular endothelial cells. Having sequenced database-submitted sequences, we have used endothelial cell cDNA library screening and 5′RACE in order to identify additional endothelial cell-expressed sequences in our favoured candidate genes. This work is supported by the British Heart Foundation.

**S025**

**ACTIVATION OF PROTEINASE ACTIVATED RECEPTOR-1 ON MESOTHELIAL CELLS INDUCES ACTIVATION OF TRANSFORMING GROWTH FACTOR-BETA VIA UPREGULATION OF THROMBOSPONDIN-1**

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**Rationale:** TGFβ1 is a potent pro-fibrotic cytokine with immunomodulating actions, known to be important in human pleural diseases. We have previously shown that intra-serosal thrombin levels are elevated in pleural disease, and that thrombin stimulates release of TGFβ from mesothelial cells via activation of PAR-1. TGFβ is mainly secreted in a latent form, and its activity is tightly regulated by post-translational activation. The aims of this study are to establish (1) the presence and (2) the significance of activators of latent TGFβ on mesothelial cells.

**Methods:** (1) Expression of known activators of TGFβ - thrombospordinin (TSP-1) and avb6 and avb8 integrins - at mRNA and protein levels was determined using RT-PCR, FACS and immuno-precipitation in cultured mesothelial cells. (2) Mesothelial cells (Met5A) were exposed to thrombin or TFLR-NH2 (a PAR-1 agonist peptide) and the expression of the activators of latent TGFβ was measured by real-time RT-PCR. In order to test if TSP-1 or PAR-1 activator (latent TGFβ) was investigated using LSKL, a competitive inhibitor of TSP-1 mediated TGFβ activation. Active TGFβ levels were measured using a modified mink lung epithelial cell bioassay. Total TGFβ levels were measured by heat treating the samples before assay.

**Results:** (1) TSP-1 and avb6 and avb8 integrins are expressed by all six benign and malignant mesothelial cell lines tested. TSP-1 expression was further confirmed by RT-PCR in human pleural tissue samples (n = 15) of various benign and malignant pleural diseases. (2) Thrombin stimulated a time- and dose-dependent increase in active and total TGFβ released from mesothelial cells (p < 0.01) both. This was accompanied by a time-dependent upregulation of TSP-1 expression (up to sevenfold v control, p < 0.001), but not that of avb6 or avb8 integrin subunits in mesothelial cells. The addition of LSKL, (but not the scrambled control peptide SLK) reduced the basal level of active TGFβ by 24%, and both the thrombin and the TFLR-NH2 induced secretion of latent TGFβ by over 2-fold (all p < 0.05).

**Summary:** Mesothelial cells express all the known potent activators of latent TGFβ. Activation of PAR-1 induces significant increases in active TGFβ by increasing the release of total TGFβ and by upregulating TSP-1.

**S026**

**FAILURE OF BONE MORPHOGENETIC PROTEIN RECEPTOR TRAFFICKING IN PULMONARY ARTERIAL HYPERTENSION: POTENTIAL FOR RESCUE?**

A. Sobolewski, N. Rudarakanchana, T. K. Jeffery, R. C. Trembath, N. W. Morrell. Department of Medicine, University of Cambridge School of Clinical Medicine, Cambridge, UK

Heterozygous germline mutations in the gene encoding the bone morphogenetic protein type II receptor (BMPR-II) have been shown to cause familial pulmonary arterial hypertension (PAH). We have previously demonstrated that substitution of cysteine residues in the ligand binding or kinase domain of BMPR-II prevented trafficking to the cell membrane. Agents able to increase cell membrane expression of functional BMPR-II may have therapeutic implications for the treatment of PAH. The aim of this study was to investigate the effects of chemical agents on BMPR-II cell membrane expression and function. Transient transfection of Hela cells with wild type and mutant BMPR-II constructs were used for all experiments. Immunolocalisation studies using an anti-KDEL-recombinant human BMPR-II antibody demonstrated retention of the cysteine mutant BMPR-II mutations mainly in the ER. Importantly, mutations leading to cysteine substitutions in the ligand-binding domain showed intact kinase activity and ability to interact with type I receptors. Confocal microscopy and FACS analysis were used to assess cell membrane expression of wild type and mutant BMPR-II. Following treatment with thapsigargin, glycerol and sodium 4-phenylbutyrate, FACS analysis showed an increase in tagged-BMPR-II at the cell membrane of cells transfected with either wild type or mutant constructs. These results were confirmed by immunocytochemistry and confocal microscopy. Subsequent experiments investigated whether this increase in cell membrane expression translated to an enhanced functional response. Sodium 4-phenylbutyrate pre-treatment followed by BMP4 or 6 stimulation of both wild type and mutant BMPR-II transfected cells showed increased phospho-Smad1/5 activity compared to BMP4/6 alone, by immunoblotting. These findings suggest that certain agents can modulate cell surface expression of BMPR-II by increasing trafficking of both wild type and mutant protein, and that cysteine-substituted ligand binding domain mutants of BMPR-II have intact signaling pathways that appear to be capable of responding to agonists. Rescue of mutant BMPR-II receptors may have therapeutic applications in some cases of familial PAH.

**S027**

**EPITHELIAL MESENCHYMAL TRANSITION OCCURS IN PRIMARY AIRWAY EPITHELIAL CELLS IN RESPONSE TO TRANSFORMING GROWTH FACTOR-BETA AND EPIDERMAL GROWTH FACTOR**

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**Introduction:** Epithelial to mesenchymal transition (EMT) is a process by which an epithelial cell changes its phenotype to that of a fibroblast or myofibroblast. EMT is believed to play a significant role in epithelial and fibrogenesis in chronic kidney and liver diseases yet data on its role in chronic lung disease is much more limited. During EMT cells lose their epithelial properties, such as ability to form tight junctions and gain features of a mesenchymal cell such as invasion and reduced production. We have recently shown a marker of EMT in airway biopsies from lung transplant recipients (Ward et al, Thorax 2005) suggesting this phenomenon could play a role in the airway remodelling seen after lung transplantation.

**Aims:** This study investigated whether the growth factors, TGFβ and EGF, could induce in airway epithelial cells the typical phenotype change and the changes in protein expression characteristic of EMT.

**Methods:** Primary human small airway epithelial cells (Cambrex) were grown to ~50% confluence on vitrogen and were then stimulated with TGFβ (10 ng/ml) and EGF (200 ng/ml). The phenotype of the cells was monitored by phase contrast microscopy. After 72 hours some cells were fixed and expression of the tight function, E-cadherin, and Collagen I was assessed by confocal microscopy. The remaining cells were harvested for western blotting and probed for E-cadherin and Collagen I expression.

**Results:** In the absence of exogenous stimulus, control cells showed a uniform epithelial morphology with a high level of E-cadherin expression and no expression of collagen I. Stimulation with TGFβ and EGF for 72 hours induced numerous cells to adopt a fibroblast-like morphology and E-cadherin and Collagen I was expressed by almost all cells. The remaining cells were harvested for western blotting and probed for E-cadherin and Collagen I expression.

**Conclusion:** This study demonstrates that TGFβ and EGF can drive EMT in primary airway epithelial cells and that this is associated with rapid activation of the SMAD signalling pathway. EMT may play a role in airway fibrogenesis and additional studies are needed to assess the clinical relevance of these observations to chronic airway diseases associated with remodelling. AJP is supported by a GSK Clinical Fellowship.
Pathomechanisms of COPD

**S029** THE IMPACT OF A LEGISLATIVE BAN ON SMOKING IN PUBLIC PLACES ON THE QUALITY OF LIFE, PULMONARY FUNCTION, AND INFLAMMATION OF BAR-WORKERS IN SCOTLAND

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Background: Scotland has recently introduced a legislative ban on smoking in confined public places. We sought to investigate the impact of this ban on the health of bar-workers.

Methods: A prospective observational study was undertaken in non-smoking bar-workers from Tayside, Scotland. Data on exposure to environmental smoke, symptoms, pulmonary function, and airway and systemic inflammation were gathered one month before and one month after the introduction of the ban.

Findings: The percentage of bar-workers with respiratory or sensory symptoms fell by 26% (95% CI: 13.8 to 38.1) and 32.5% (19.8 to 42.5) at one and two months after the ban. FEV1 increased by 8.2% (3.9 to 8.0) and 5.1% (2.1 to 8.0) of predicted (p<0.005) at one and two months, with significant changes in both asthmatic and non-asthmatic workers. Serum cortisol levels fell by 1.93 ng/ml (2.83 to 1.03) and 2.23 ng/ml (3.10 to 1.34) at one and two months (p<0.001). The total white cell and neutrophil count was reduced by 630 cells/mm3 (1010 to 260, p=0.002) and 410 cells/mm3 (740 to 90, p=0.028) respectively at two months. Compared with baseline, asthmatic and rhinitic bar-workers also had less airway inflammation at one month with a 0.8-fold reduction (0.67 to 0.96, p=0.036) in exhaled nitric oxide, and better Juniper quality of life scores by 7.3 points (p<0.001). Specifically, after adjustment, indivi-
duals with a CRP over 264 m/g/cm2 of talc. This was mirrored by a corresponding increase in a semi-quantitative score of microscopic thickening of 7.1-fold (p<0.05) for mice receiving 50 mg talc over saline controls. Trichrome staining showed that the thickening was predominantly due to a result of increased extracellular matrix deposition. TGFb levels increased in a dose-related fashion, with a fold increase of 1.33 and 2.59 (p<0.05) in mice given 25 and 50 mg of talc respectively. Talc also induced a significant dose-dependent increase in neutrophil influx (×107/ml lavage fluid) in the visceral cavity: 2.6 ± 1.2 (saline) × 17.5 ± 10.7 (25 mg talc) × 115.1 ± 18.7 (50 mg talc). These results were reproduced using another talc preparation (Sigma).

Summary: Talc induces the release of total TGFb from mesothelial cells in vitro. In vivo, talc induces a dose-dependent increase in active TGFb levels, proliferation and thickening of mesothelial cell layer, collagen deposition, and formation of adhesions.

**S030** C-REACTIVE PROTEIN AND LUNG FUNCTION IN MIDDLE-AGED MEN IN NORTHERN IRELAND

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Background: Systemic inflammation may be related to reduced pulmonary function. We tested the hypothesis that small increases in C-reactive protein (CRP), within the “normal” range, were associated with reduced forced expiratory volume in one second (FEV1) in apparently healthy middle-aged men in Northern Ireland.

Methods: 10600 French and Northern Irish men aged 50 to 59 years were recruited mainly at their place of work from 1991 to 1994 as part of the Prospective Epidemiological Study of Myocardial Infarction (PRIME). The French cohort was selected at the same time. This involved a questionnaire and physical measurements including lung function by spirometry. Aliquots of plasma were frozen immediately at ~80°C for later high sensitivity CRP analysis. We present a cross sectional analysis of the 1273 rescreened men for whom a high sensitivity CRP measurement and a valid spirometry trace had been obtained.

Results: The men had a mean age of 64 years and 42% had never smoked. The table shows a significant reduction in the mean percentage predicted FEV1 (FEV1%) with increasing CRP (p<0.001). After adjustment for confounders (including smoking status, education, BMI, alcohol intake, waist-hip ratio, age, height, and social status), this association remained (p<0.001). Specifically, after adjustment, indivi-
duals with a CRP over 264 μg/dl had a reduced FEV1% of on average 8.7 compared with individuals with CRP below 102 μg/dl.

Conclusions: There is a strong negative relationship between high sensitivity C-reactive protein and percent predicted FEV1 in middle-aged men in Northern Ireland. This association suggests a link between systemic inflammation and reduced FEV1.

Abstract S030 Percentage predicted FEV1 by CRP (in fourths)

<table>
<thead>
<tr>
<th>CRP (μg/dl)</th>
<th>FEV1.0% Mean</th>
<th>Adjusted effect* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;102</td>
<td>94.1 (15.9)</td>
<td>ref cat</td>
</tr>
<tr>
<td>102–153.8</td>
<td>90.5 (18.4)</td>
<td>–1.9 (4.4 to 0.7)</td>
</tr>
<tr>
<td>153–264.5</td>
<td>86.6 (15.6)</td>
<td>–2.7 (5.3 to –0.6)</td>
</tr>
<tr>
<td>&gt;264</td>
<td>80.9 (17.7)</td>
<td>–8.7 (11.3 to –6.0)</td>
</tr>
</tbody>
</table>

*pMean difference in percentage predicted FEV1 in category of CRP compared with reference category, adjusting for confounders (mentioned above) using linear regression.

**S031** INCREASED CIRCULATING IL-6 AFTER WHOLE BODY AND INSPIRATORY MUSCLE EXERCISE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Circulating interleukin-6 (IL-6) increases with low intensity exercise in adults with cystic fibrosis. We hypothesised a similar increase after whole body and inspiratory muscle exercise (IME) in patients with pulmonary obstructive pulmonary disease (COPD). Patients (22) mean (SD) age 70.4 (6.7) years and 12 age matched healthy subjects (HS) performed cycle ergometry and resistive IME on different days. Cycling
started with 3 min unloaded pedalling at 60 rpm, then increments of 5–
10 watts/min at 60 rpm until voluntary exhaustion. During IME forced
inspiratory effort at 75% of maximum inspiratory pressure (MIP) was
maintained with progressively shorter recovery time between repeat
manoeuvres. Plasma IL-6 and TNFa sr I and II were measured at start, end of exercise and 15, 30, 60, and 120 minutes later. FEV1/FVC for
patients was 55.7 (9.0)% BMI and fat free mass were in the healthy
range. No patient was hypoaemic at rest. The power achieved during
cycling (80–100 watts) was similar to activities of daily living. IL-6 and
TNFa sr I and II were greater for patients than HS at all time points
(p<0.05). IL-6 increased with cycling and IME for patients, but not in HS.
Neither TNFa sr I nor II changed after cycling or IME. In nutritionally
replete patients with moderate severity COPD cycling or IME were
associated with increased circulating IL-6. This effect during activities
during daily living could add to the persistent systemic inflammation in COPD.

Some of these data are due to be presented at the ERS 2006.

S032 THE EFFECTS OF CANNABIS ON PULMONARY STRUCTURE, FUNCTION AND SYMPTOMS
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Background: Cannabis is one of the most widely used illegal drugs worldwide. Long-term use of cannabis is known to cause chronic bronchitis and airflow obstruction, however the frequency of macroscopic emphysema, the dose-response relationship and the dose equivalence of cannabis with tobacco has not been determined.

Methods: A convenience sample of adults from the Greater Wellington Region was recruited into four smoking groups; cannabis only, tobacco only, combined cannabis and tobacco and non-smokers of either substance. Their respiratory status was assessed using high resolution CT scanning, pulmonary function tests and a respiratory and smoking questionnaire. Associations between respiratory status and cannabis use were examined by analysis of covariance and logistic regression.

Results: A total of 339 subjects were recruited into the four groups. A dose-response relationship was found between cannabis smoking and reduced FEV1/FVC and sGaw, and increased TLC. For adverse respiratory effects one cannabis joint was equivalent to between 2.5 and 6 tobacco cigarettes, depending on the lung function variable measured. Cannabis smoking was associated with decreased lung density on HRCT scans. Macroscopic emphysema was detected in 1/75 (1.3%), 15/92 (16.3%), 17/91 (18.9%) and 0/81 subjects in the cannabis only, combined cannabis and tobacco, tobacco alone and non-smoking groups respectively.

Conclusions: Smoking cannabis is associated with a dose-related impairment of larger airways function resulting in airflow obstruction and hyperinflation. The 1:2.5 to 6 dose equivalence between cannabis and tobacco cigarettes for adverse effects on lung function is of major public health significance.

S033 SERUM GAMMA-Glutamyl TRANSFERASE IN LUNG DISEASE

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Introduction: Serum gamma-glutamyl-transferase (GGT) is elevated in 26.6% of patients with alpha-1-antitrypsin deficiency (AATD), independent
of the presence of previous liver disease (Stockley. ATS 2006). GGT regulates transport and synthesis of the antioxidant glutathione. Its expression is increased in rat lung epithelial cells in response to oxidative stress (Liu. Am J Physiol 274:1330) and serum GGT correlates with CRP as a systemic marker of inflammation in humans (Lee. Atherosclerosis 178:327). We hypothesised therefore, that serum GGT may be related to lung disease and its severity in AATD.

Method: The database for the UK AATD registry was searched to find baseline lung function, smoking information and clinical features regarding sputum production and colour, along with exacerbation data for 338 subjects. Any relationship between these factors and baseline serum GGT were then assessed.

Results: Serum GGT correlated negatively with forced expiratory volume in 1 second (FEV1)% predicted (r = 0.158, p = 0.002). Mean serum GGT increased as the GOLD stage increased from 33.4 ± 7.9 iU/l to 39.1 ± 8.2 iU/l and 49.2 ± 11 iU/l in stage 4 (p = 0.002). Mean serum GGT was significantly higher in patients who had chronic bronchitis (49.3 ± 11 iU/l vs 39.1 ± 7 iU/l) (p = 0.002), suggesting a relationship to bronchial inflammation. There was, however, no significant difference between mean serum GGT for subjects who produced sputum of various colour categories as defined by a sputum colour chart. (p = 0.966) Nor was there a relationship between serum GGT and the numbers of exacerbations over the previous 1 year. A difference in mean GGT was, however observed for never smokers (37.1 ± 7 iU/l vs 4.29 ± 10 iU/l) (p = 0.002). Nevertheless serum GGT was not shown to be significantly correlated with pack years smoking (r = 0.092, p = 0.73).

Conclusion: Serum GGT is related to the severity of airflow obstruction (GOLD stage) in AATD, smoking status and chronic bronchitis. The relationship to this regulator of glutathione is consistent with an anti-inflammatory role of this systemic biomarker.

S034 OXIDATIVE STRESS INDUCES EPITHELIAL TO MESENCHYMAL TRANSITION IN BRONCHIAL EPITHELIAL CELLS: A POSSIBLE ROLE IN AIRWAY REMODELLING
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A. J. Fisher. Applied Immunobiology and Transplantation Research Group,
Institute of Cellular Medicine, Newcastle University, UK

Introduction: Excessive oxidative stress may play a role in airway injury and contribute to airway remodelling seen in chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or post-transplant ablative bronchiolitis. The mechanism by which oxidative stress may contribute to airway remodelling is poorly understood. We hypothesised that oxidative stress may induce epithelial to mesenchymal transition (EMT) in airway epithelial cells. EMT is a process by which an epithelial cell loses epithelial properties such as forming tight junctions and develops a myofibroblast phenotype with increased expression of collagen and mesenchymal markers. Recent markers of EMT have been demonstrated in airway biopsies from lung transplant recipients (Ward et al, Thorax 2005).

Aims: To investigate the effect of an environment high in oxidative stress on cell morphology and expression of epithelial and mesenchymal markers in human bronchial epithelial cells.

Methods: Human bronchial epithelial cells (16HBE14o-1) were exposed to low dose hydrogen peroxide, at concentrations between 0 and 25 M, or to 40% hyperoxia for 7 and 14 days. The production of intracellular reactive oxygen species (ROS) was assessed by FAC analysis using DHR and MitoSOX staining. Change in cell morphology was monitored by phase contrast microscopy. At the end of treatment cells were either fixed for confocal microscopy or harvested and protein expression was assessed by Western blotting.

Results: In the absence of oxidative stress, 16HBE14o-1 cells show a uniform epithelial morphology with high level expression of the tight junction protein, E-cadherin. Levels of the mesenchymal markers S100A4, alpha-smooth muscle actin (a-SMA), and collagen type I/III were very low or undetectable. Treatment with hydrogen peroxide or 40% hyperoxic resulted in significantly increased expression of the mesenchymal marker, S100A4 (250% increase) after only 7 days. After 14 days in hyperoxic levels of a-SMA, collagen type I and collagen type III were increased (200%, 100%, 150% respectively) and E-cadherin expression was decreased by 46%. Coincubation with the anti-oxidant N-acetylcysteine (NAC) almost completely inhibited collagen type III expression in 16HBE14o-1 cells in response to hydrogen peroxide.

Conclusions: Oxidative stress can induce EMT in bronchial epithelial cells and provides a potential mechanism for increased fibrogenesis in the airway microenvironment and may contribute to airway remodelling. MN has a Marie Curie EU funded studentship and AJF is supported by a GSK Clinical Fellowship.
Diagnosing procedures in lung cancer

S035 THE ROLE OF TRANSBRONCHIAL NEEDLE ASPIRATION IN AN INTEGRATED CARE PATHWAY FOR ASSESSMENT OF PATIENTS WITH SUSPECTED LUNG CANCER
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Introduction: Transbronchial needle aspiration (TBNA) is a safe, simple yet underutilised sampling modality for patients with suspected lung cancer and mediastinal lymphadenopathy. It may be the sole diagnostic test, or as a staging modality to prevent unnecessary mediastinoscopic biopsies.

Methods: We prospectively evaluated the value of TBNA in patients with suspected lung cancer and mediastinal lymphadenopathy. Patients attending the linked Rapid Access Chest clinics of the two hospitals between December 1999 and June 2003, who underwent bronchoscopy as part of an integrated care pathway were included. Standard methods for bronchoscopy and TBNA were used. Particular care was taken to prevent contamination of TBNA samples from the distal airway secretions, thus minimising false positive results. Two dedicated respiratory cytopathologists assessed TBNA samples for adequacy of sample, presence of lymphocytes representing a lymph node aspirate, and the presence or absence of malignant cells. Patients without a positive TBNA result proceeded to positron emission tomography (PET) and/or mediastinoscopy. In patients with a negative TBNA and no further investigations due to clinical confidence of non-malignancy, a true negative TBNA was only assigned after 18 months follow up without evidence of malignancy. An additional analysis, the number needed to diagnose (NND) was calculated in the same way as number needed to treat. It represents the number of TBNAIs needed to be performed to provide a positive result, and is calculated as 1/[sensitivity – (1-specificity)].

Results: Of 827 patients referred for which prospective data were gathered, 561 had a final diagnosis of malignancy, with pathological confirmation in 502 (89%) patients. The initial CT scan provided evidence of malignancy in 37.9%(n=11) had chemotherapy and/or radiotherapy. Mean stent survival was 87.7 [3 to 340] days with one patient surviving more than 10 years to date.

Conclusions: Our study provides further evidence on the role of stent placement in malignant vena caval obstruction (SVCO) in accordance with NICE guidelines on this subject. With locally available expertise, our practice was found to be safe and effective in providing rapid symptom palliation in advanced lung cancer.

S036 STENTING IN SUPERIOR VENA CAVA OBSTRUCTION: A FIVE YEAR EXPERIENCE WITH LUNG CANCER N. Banerjee1, T. J. Fletcher2, A. D. Mackay2, D. K. Petkova2, M. Cleasby2. 1SpR Respiratory; 2Consultant Chest Physician; 2Consultant Radiologist, Good Hope Hospital, Sutton Coldfield, W Midlands, UK

Introduction: Superior vena cava obstruction (SVCO) causes significant morbidity in lung cancer with distressing symptoms and shortened survival. The aim of this study was to evaluate the efficacy and report our experience with metallic stents in SVCO at our hospital. Data gathering was done by retrospective review of case notes and hospital information systems.

Methods: Twenty nine patients aged between 47 and 91 (mean 70.7) years underwent stenting as primary treatment for clinical and/or radiological SVCO between Jan 2001–Dec 2005. The diagnoses of lung cancer was established in 69%(n=20); non small cell lung cancer 34.5% (n=10), small cell lung cancer 27.5% (n=8), and mesothelioma 6.9% (n=2) and tissue diagnosis could not be ascertained in 9 (31%) cases. Obstruction to the superior vena cava was found to be due to stricture and/or thrombus in all patients (n=29).

Results: Immediate response to treatment was measured radiologically by the following three parameters: while central venous pressure (CVP) recorded in 48.3% (n=14) cases demonstrated a mean fall in pressure 6.48 (1.41) mm Hg, establishment of free flow to the right atrium and disappearance of collaterals were reported in 51.7% (n=15) and 10.3% (n=3) subjects respectively. Clinical improvement in breathlessness and/or oedema was noted in 10.3% (n=3) patients immediately after stenting. Long term stent patency was achieved in all cases. We encountered four minor and one major complication. Minor problems occurred in 4 (13.8%) patients, one each had shoulder pain, graft haematoma, stern thrombus and contrast leak. One patient had major complication of pulmonary embolism within 48 hours of stenting requiring anti coagulant therapy. More than a third of patients 37.9%(n=11) had chemotherapy and/or radiotherapy. Mean stent survival was 87.7 [3 to 340] days with one patient surviving more than 10 years to date.

Conclusions: The new videobronchoscope is superior as a diagnostic tool compared to older scopes and we presume this is a function of the clarity of the on-screen image. The AF mode performed well but false positives were still a problem. There was no added diagnostic benefit from the AF mode, perhaps because the white light images were so clear. Another reason may be the low incidence of pre-invasive lesions in this patient population, less highly selected than in other studies (Chiyo et al. Lung Cancer 2005;48:307–13). The optimum design and use of autofluorescence systems continues to be refined.
Introduction: Patients with lung cancer often have no visible endobronchial lesion, despite the presence of centrally based pathology on radiological examination of the chest. In these cases, the clinician may be prompted to obtain a histological diagnosis via another route, potentially delaying the patient journey and increasing the resource requirements. To circumvent this, we have adopted a policy of fine needle aspiration (FNA), bronchial brushings (BBB), blind bronchial biopsy (BBB), and bronchial lavage (BAL) via the original bronchoscopy. We report the additional diagnostic yield using this approach.

Method: We looked at all patients attending our large cancer unit over an 18 month period who had the above investigations performed when no endobronchial cancer was seen. Demographic and radiological data were collected, and the diagnostic yield and any further investigations performed were noted.

Results: Thirty one patients (mean age 69 years, mean FEV1 1.71 litres, WHO PS mean 0.95 (range 0–2); 17 male), fulfilled the criteria. All had pre-bronchoscopy staging CT scans with evidence of mediastinal lymphadenopathy (subcarinal (13), hilar (7), pre/paratracheal (13)). 24 patients had lung masses and 1 pleural thickening (MRI/CT). All patients had FNA (29), trachea (5), main/lobar bronchi (6), by an SP in 23 cases (74%). FNA was positive in 10 (32%) (9 malignancy, 1 sarcoidosis); in only 3 cases was insufficient tissue obtained. Consultants had a higher success rate (50% vs 26%), and the yield was greatest through the bronchial route (62% vs 25%). 9 patients underwent BBB which was positive in 3 (33%) (BAL 25 cases) and BBB (13) were positive in 1 case each. Overall, the combination of these procedures produced a diagnostic yield in 15 cases (48%). No complications were recorded. The remaining patients underwent mediastinoscopy (4), percutaneous needle biopsy (3), VATS (1), and ultrasound guided biopsy (1). Despite this, 7 patients ultimately had a clinical diagnosis of malignancy.

Conclusion: The addition of these sampling methods at bronchoscopy increased the yield in this selected group of patients who had no visible endobronchial lesion, obviating the need for further invasive and resource intensive investigations in up to half of them. Other clinicians may wish to consider adding these simple to perform diagnostic tests to their routine bronchoscopy practice.

## S039

### MINIMISING INTERVENTIONS IN THE DIAGNOSIS AND STAGING OF LUNG CANCER THROUGH BIOPSY OF METASTASES AND MEDIASTINAL NODES AS AN INITIAL PROCEDURE

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Introduction: Rapid assessment of suspected lung cancer is important for patients to minimise uncertainty and to ensure treatment is commenced as soon as reasonably possible. The aim is to diagnose and stage with the minimum number of investigations and ideally the safest and least costly test. Use of this modality in the investigation of lung cancer.

Results: 151 patients were identified; 24 were excluded (diagnosis not lung malignancy or still under investigation). Notes were unavailable on a further 5, leaving 122 for analysis. 72% were non-small cell lung cancer, 8% small cell, 10% mesothelioma and 1% carcinoid (diagnosed on surgical excision). 9% had a clinical or radiological diagnosis of lung cancer with no formal tissue type identified. 11% of patients, but only one patient from the metastatic biopsy group, underwent more than one procedure to establish a tissue diagnosis.

Discussion: These data for image guided lung biopsy give diagnostic rates comparable to that in the literature (Schreiber et al. Chest 2003;123:1155–1285). In this series, a fifth of patients with lung cancer underwent metastatic biopsy with a superior diagnostic rate to other interventions, with the additional benefit of having undergone a single diagnostic and staging procedure, and the potential for reduced morbidity and time to first treatment. There may be a role for increased use of this modality in the investigation of lung cancer.

Paediatric respiratory disease: bench to bedside

## S040

### CONGENITAL HEART DISEASE AND OTHER HETEROACTIVE DEFECTS IN A LARGE COHORT OF PATIENTS WITH PRIMARY CILIARY DYSKINESIA

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Background: Primary ciliary dyskinesia (PCD), a recessive genetic disorder with a prevalence of 1/12–17 000, is characterised by sino-pulmonary disease and reflects abnormal ciliary structure and function. Situs inversus totalis (SI) occurs in ~50% of PCD patients (Kartagener’s syndrome), and there are a few reports of PCD with heterotaxy (situs ambiguous), including cardiovascular anomalies. Advances in diagnosis of PCD, including genetic testing, allow the systematic investigation of this association.

Methods and Results: The prevalence of heterotaxy defects was determined in a cohort of 326 PCD patients by reviewing clinical and radiographic data. Phenotypic markers included anomalies of cardiac, vascular, pulmonary, splenic, gastrointestinal and hepatic anatomy. Situs solitus was identified in 45% and situs inversus totalis in 49% of 326 PCD patients. A substantial fraction (20/326) of PCD patients had heterotaxy defects (6%). Half the patients with heterotaxy had cardiovascular defects (10/20) and most (7/10) had complex congenital heart disease (CHD) requiring surgery. Polysplenia was also prominent (11/20). Genetic analyses in 12 patients with heterotaxy revealed that 7 carried at least one mutation in DNAH5 or DNAI1 and 5 patients had biallelic mutations in DNAH5 (n = 3) or DNAI1 (n = 2).

Conclusions: At least 6% of PCD patients with PCD have heterotaxy, and half of these have cardiovascular abnormalities. The prevalence of CHD with heterotaxy is 200 fold higher in PCD than in the general population (1:50 vs 1:10 000). Mutations in genes causing defective cilia are a significant cause of heterotaxy and CHD, and screening for PCD should be undertaken in these patients, particularly if there is concomitant sino-pulmonary disease.

## S041

### TRENDS IN PNEUMONIA AND EMPYEMA IN SCOTTISH CHILDREN IN THE PAST 25 YEARS

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Introduction: Empyema thoracis is a complication of pneumonia. The incidence of empyema in children has increased in UK and North America over the last 10 years and this increase is most marked in the 1–4 year group; reasons for this increase are unclear, but could include an increase in the incidence of pneumonia. We report on the number of children admitted to hospital in Scotland for empyema over the past 25 years in the context of pneumonia admissions over the same period.

Methods: Admissions for children <15 years with empyema and pneumonia were analysed using ICD-9 and ICD-10 coding obtained from the Scottish Information Services Division. The period of interest was between 1 January 1981 and 31 December 2005 and changes in...
the total population over this period was considered in the analysis. Data was divided by age (groupings <1 year, 1–4 years, 5–9 years, and 10–14 years).

**Results:** There were 24,312 admissions for pneumonia in children (11,299 between 1 and 4 years) and 217 for empyema (76 between 1 and 4 years). Empyema admissions increased from <10 per annum up to 1999 to reach a peak of 33 in 2005. Among the 1–4 year age groupempyema admissions rose from <2/year 1981–85 to 7.4/year between 2001–05. When all children were considered, annual admission rates for pneumonia remained unchanged. However among 1–4 year olds, admissions/year rose progressively during the early nineties reaching a plateau by 2000 (mean admissions/year (SD) between 1981–85 was 394 (47.7) compared with 520 (40) between 2001–05).

**Discussion:** Our whole population study shows that the incidence of childhood empyema has risen recently in Scotland and continues to rise. The incidence of pneumonia in young children has also risen over the last 25 years and this preceded the rise in empyema by approximately 10 years. Our observations suggest that the rise in empyema is unlikely to be related to an increase in pneumonia. Changes in bacterial pathogenicity and/or host susceptibility could be important.

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**SO42**

**DO ESTIMATIONS OF HABITUAL ACTIVITY IN CHILDREN WITH CYSTIC FIBROSIS PREDICT AEROBIC FITNESS?**

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Exercise is of benefit to all individuals, but may benefit those with CF to an even greater extent and further prolong life expectancy. In addition the deep breathing associated with exercise has been shown to improve sputum clearance [Zach et al. Lancet 1981; 2:1201–3]. Despite this there is limited knowledge of the habitual activity levels of children with CF and the relationship to aerobic fitness. Most studies have used questionnaires, which depend on recall; objective measures of activity are now available and have been validated in healthy children.

We studied 17 children with cystic fibrosis (mean age 12.5 (3.5)l, and obtained estimates of habitual activity in three ways. Each child wore an accelerometer (Actiwatch, Cambridge Neurotechnology Ltd, UK) on non-dominant wrist, and a heart rate monitor (Polar Heart Rate monitor, Polar Electro Oy, Finland) for a period of 4 days (2 school days and 2 weekend days), and completed an activity questionnaire (HAES) for one typical weekday and weekend day. Actiwatch counts were converted to levels of energy expenditure [Puyau et al. Med Sci Sports Exerc 2004;36;1625–31] (‘awake time’ was counted as all epochs with count >0, and ‘active’ as epochs with counts >700. For heart rate data, activity was calculated as proportion time spent >50% above resting heart rate (PAHR-50) (Logan et al. Med Sci Sports Exerc 2000;32;162–6). Aerobic fitness was assessed using an incremental ramp protocol with breath by breath analysis and expressed as peak oxygen consumption (VO2peak).

Mean (SD) percentage of awake time spent active as reported by HAES was 47.5 (15.7) and as measured by Actiwatch was 28.1 (12.6). Mean (SD) VO2peak was 39.2 ml kg-1·min-1 (9.2). The correlations between these three estimates of activity and VO2peak were assessed.

The measures of regular activity all correlated to some degree with aerobic fitness, but this relationship was strongest for the heart rate estimates. The HAES questionnaire correlated rather weakly with direct measures of activity, particularly PAHR-50. Ambulatory heart rate monitoring appears to be useful in assessing levels of activity which influence aerobic fitness; questionnaire data may not be sufficiently reliable.
at e20.5 (n = 6) and e21.5 (n = 3) were also equivalent between the groups.

Conclusions: Pulmonary Ang-1 and Tie-2 are developmentally regulated during perinatal transition suggesting a key role in adaption at birth. However pulmonary vasculopathy in fetal CDH is not associated with Ang-1/Tie-2 upregulation: therefore their hyperactivation may be the consequence rather than cause of pulmonary vascular remodelling in adult human PHT.

NATIONAL SURVEY OF CHILDREN WITH POST-INFECTIOUS OBLITERATIVE BRONCHIOLITIS: A PROGRESS REPORT
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Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne, UK; University of Newcastle upon Tyne, UK

Introduction: Obliterative bronchiolitis (OB) is reported to be relatively common in some developing countries, but has previously been thought to be rare in developed countries. Increased suspicion and improving diagnostic methods now identify many more paediatric cases in the UK. Little is known about the true incidence of this problem and so a national study began in October 2005 with the aim of ascertaining all cases diagnosed in the last 10 years. The study will describe the epidemiology of OB including causative organism, degree of diagnostic delay, overall severity of disease, mortality and quality of life of patients and their families.

Methods: Four sources of ascertainment are being used: (1) all consultant general paediatricians; (2) respiratory paediatricians in regional centres; (3) British Paediatric Orphan Lung Disease Registry; (4) mortality data from the Office for National Statistics. Radiological findings will be assessed by two pairs of blinded radiologists, and this component of the study will provide a unique consensus on HRCT diagnostic criteria. Cases will be reassessed 5 years after completion of the initial study.

Results: Over 1700 consultants were mailed and to date 52% have replied. 290 cases have been reported. There are large regional variations, but estimated overall incidence of disease is 2.5 per million children per year aged 0–15 years. The number of cases notified by region is shown in the table.

Conclusions: Further data are awaited, but this is already by far the largest series of children ever reported. This condition is not nearly as common in some developing countries, but has previously been thought to be rare in developed countries. Increased suspicion and improving diagnostic methods now identify many more paediatric cases in the UK. Little is known about the true incidence of this problem and so a national study began in October 2005 with the aim of ascertaining all cases diagnosed in the last 10 years. The study will describe the epidemiology of OB including causative organism, degree of diagnostic delay, overall severity of disease, mortality and quality of life of patients and their families.

Occupational asthma

IS FEV1 DECLINE SLOWER IN WORKERS WITH OCCUPATIONAL ASTHMA WITH NORMAL EXHALED NO?
A. D. Vellore, V. C. Moore, C. B. S. G. Burge, A. S. Robertson, W. Anees, P. S. Burge. Occupational Lung Disease Unit, Birmingham Heartlands Hospital, UK

We have found two phenotypes of occupational asthma separated on exhaled breath Nitric Oxide (FENO). We postulate that the rate of FEV1 decline during continued exposure is less in those with normal FE(NO) compared to those with raised FE(NO). Fifty one consecutive workers, presenting at an occupational lung disease clinic, had measurements of exhaled breath NO and induced sputum whilst exposed to the causative agent. They were followed with regular FEV1 measurements until complete removal from the causative agent. All were advised to avoid continuing exposure at diagnosis. They were divided into those with normal and raised FE(NO) (+/- 9.6 ppb with the Logan meter, flow rate 200 l/min, corresponding to induced sputum eosinophilia +/- 2.2%). The rate of FEV1 decline was computed by linear regression using all measurements made over a follow up period of at least 1 year. Thirty six of eight workers had a normal FE(NO); of these, 32 completed >1 year before complete removal from exposure. This group had DFEV1 of 6.86 ml/year (SEM = 17), only 5/32 had an annual FEV1 decline of >60 ml/year. In the raised FE(NO) group only 7/13 workers remained exposed for >1 year before complete removal from exposure; making DFEV1 assessment unreliable. Our previous work showed DFEV1 100.9 ml/year (SEM 17.7) in 90 workers with occupational asthma and continuing exposure (not phenotyped for FE(NO)) who were followed-up over a mean of 2.9 years (Thorax online first 10.1136/thorax.2005.054080). Therefore, those with normal FE(NO) at presentation may be a group with a better prognosis despite continuing exposure to the causative agent.
The region has a recognised high rainfall and requires indoor animal husbandry during the winter months. Most were asymptomatic, 20 had symptoms of asthma (7 non smokers) which was significantly related to IgE level (p<0.007), and 13 of HP (10 M faeni precipitin positive, 11 non smokers).

Respirable dust (mainly from stored and then crushed barley feed mix) concentrations varied between 2.0–45 mg/m³ in barns which were all poorly ventilated. Skin tests indicated that storage mite (Leptoglyphus destructor) sensitivity was most common (93/119, 19/20; p<0.001), with lesser reactions to grain (33/119, 12/20), animal dander (33/119, 10/20). Grass pollen sensitivity was less than expected (9/119, 3/20; p=NS) when compared with non-farming background atopic asthma in the practice.

A review suggested that while asthma in this population is not unusual, it is mainly related to occupational sensitisers, with a notable dominance over common inhalant sensitisation, perhaps as a response to the high dust levels and allergens encountered in the farm buildings.

**S049 OCCUPATIONAL ASTHMA CAUSED BY ARABIDOPSIS THALIANA**

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A 36 year old never-smoker with an 8 year history of hay fever but no past history of asthma undertook a 3 year research project involving the plant Arabidopsis thaliana (wall cress). He was based in a small laboratory with an attached growing room that was maintained at 22–24°C and 30–55% humidity. The laboratory and growing room did not have specific ventilation but there was no obvious damp or mould. After 2 years research he began to develop breathlessness within 5–10 minutes of entering the laboratory. Initial investigations confirmed asthma with airflow obstruction (FEV1/FVC 0.31; predicted values 0.67/4.43 litres) and increased airway responsiveness (PD20 methacholine: asthma range 11–200 mg). Skin prick tests showed positive responses to mixed grass pollen (4 mm), rape pollen (4 mm) and house dust mite (4 mm) with 7 mm positive and 0 mm negative controls. Serial PEF measurements showed a work related pattern with an OASYS score of 4 (asthma likely with scores >2.5). A supervised workplace challenge test led to a fall in FEV1 from the baseline value of 3.10 litres to 2.55 litres within 5 minutes of entering the laboratory. There was a further fall over the next 10 minutes to 1.95 litres and the test was terminated. Skin prick solutions were prepared from Arabidopsis leaves and flower heads. There were positive 4 mm responses to the flower heads (pollen) but no response to the leaves or to a genetically modified plant. A control subject did not show positive skin responses.

Arabidopsis is a member of the Brassicaceae (mustard) family. It is related to radish, rape and birch. It is used extensively in plant biology research as its genome is small, has been fully sequenced and is easily manipulated. Previous studies have identified its lipid transfer protein as a potential allergen (Int Arch Allergy Immunol 2003;131:85–90).

**S050 SODIUM METABISULPHITE INDUCED AIRWAYS OBSTRUCTION IN WORKERS IN THE FISH PROCESSING INDUSTRY**

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**Introduction:** Sodium metabisulphite (SMBS) is widely used in the fishing industry as a preservative, antioxidant and bleaching agent. At sea its use may be poorly controlled resulting in high exposure among fishermen. It has been described as causing occupational asthma and dermatitis in workers. Aim: To investigate the lung function response of two patients with suspected occupational asthma exposed to sodium metabisulphite. Methods: Both patients provided serial peak expiratory flow readings. Blood samples were taken for total IgE and RAST. Methacholine challenge testing was performed before and after two days after specific challenge testing with (1) seawater and (2) sodium metabisulphite in an exposure challenge chamber. Sodium metabisulphite handling tasks were simulated for 5, 10, 15, and 60 minutes for one patient with measurement of SCo2 concentration.

**Results:** Both patients showed a work related pattern in peak flow changes. Total IgE was negative in one and moderately elevated in the other; RAST levels for shrimps were negative in both patients.
additional genetic or environmental factors are necessary for disease manifestation. Since mitogen-activated protein kinase (MAPK) pathways are essential for cell proliferation and have been reported to inhibit Smad signaling we determined the importance of this interaction in PASMCs isolated from small pulmonary arteries (<3 mm external diameter). In initial experiments we confirmed that BMP2 and 6 led to concentration dependent phosphorylation of Smad1, and extracellular signal-related kinase 1/2 (ERK1/2) in PASMCs by immunoblotting. Inhibition of ERK1/2 with the selective inhibitor, U0126, increased phosphorylation of Smad1 following BMP stimulation, increased nuclear translocation of Smad1 and increased activation of a BMP responsive luciferase reporter gene. Activation of ERK1/2 by exogenous platelet-derived growth factor-BB (PDGF-BB) also antagonised BMP-stimulated Smad1 phosphorylation in PASMCs. Using phosho-specific antibodies we determined that PDGF stimulation increased phosphorylation of the serine 206 residue of the linker region of Smad1, and not the c-terminal serine typically responsible for BMP transcriptional responses. In PASMCs harbouring mutations in the kinase domain of BMPR-II, BMP stimulation was associated with reduced c-terminal Smad1 phosphorylation and reduced activation of Ras/ERK pathways. We conclude that phosphorylation of the Smad1 linker region by ERK1/2 inhibits c-terminal Smad1 phosphorylation, nuclear import and BMP dependent gene transcription in PASMCs. Activation of ERK1/2 pathways by growth factors implicated in the pathogenesis of pulmonary hypertension, such as PDGF, may contribute to the defect in BMP signaling and have a permissive effect on disease manifestation in PAH.

**S053 ACETYLATION OF HISTONE H4 AT NF-kB SITES IN PREDICTED ET-1 PROMOTER IS INVOLVED IN SYNERGISTIC SYNTHESIS OF ET-1 IN HUMAN PULMONARY ARTERY SMOOTH MUSCLE CELLS TREATED WITH TNF-α AND IFN-γ**

S. J. Wart, S. McMaster, J. A. Mitchell, T. W. Evans, M. Ito, K. Ito, I. M. Adcock. Unit of Critical Care, National Heart and Lung Institute, Dovehouse Street, London SW3 6NP, UK

**Introduction:** Endothelin-1 (ET-1) has been implicated in vascular remodeling and the development of pulmonary arterial hypertension (PAH). Vascular smooth muscle is also an important source of ET-1, although the mechanisms controlling its synthesis and release are poorly understood. We have previously reported a synergistic release of ET-1 by human pulmonary artery smooth muscle (HPASM) cells when stimulated with the inflammatory cytokines, tumour necrosis factor (TNF) α and interferon (IFN) γ. We sought to determine possible mechanisms.

**Methods:** HPASM cells were grown from explanted vessels taken at lung surgery, under local ethical approval. Cultured cells were treated with either 10% fetal calf serum (FCS), 10% FCS plus TNF-α (10 ng/ml), 10% FCS plus IFN-γ (10 ng/ml) or 10% FCS and a combination of the cytokines, for 18 hours. Complementary DNA was produced and real-time quantitative PCR performed using primers for the pre-pro ET-1 gene. In further experiments, chromatin immunoprecipitation (ChIP) was performed using an antibody against acetylated histone H4, on HPASM cells treated under the same conditions for 2 hours (previously optimised by time course experiments). DNA/histone interactions were fixed with formaldehyde. To investigate transcriptional activity at putative nuclear factor (NF)-κB and interferon regulatory factor (IRF)-1 binding sites on the pre-pro ET-1 promoter, primers were designed and real-time quantitative PCR performed on the acetyl-histone H4/DNA pull-downs.

**Results:** We show that the combination of TNF-α and IFN-γ induced synergistic transcription of prepro-ET-1 mRNA as determined by real-time PCR, compared to the cytokines alone (ET-1/GAPDH copy number ratio: control, 0.003 (0.00077); IFN, 0.007 (0.00214); TNF, 0.0025 (0.00108); TNF/IFN, 0.0213 (0.0049); p = 0.0041). Furthermore, using ChIP we have demonstrated that there is enhanced acetylation of histone H4 at the NF-κB sites positioned at 891, 1214, 2093, and 2424 bp from the start codon. Interestingly, there was no acetylation of histone H4 at a single IRF-1 site with the different cytokine combinations, and several of the remaining NF-κB sites appeared redundant.

**Conclusion:** Enhanced synthesis of ET-1 by the combination of TNF-α and IFN-γ in HPASM involves synergy at the level of transcription of the prepro-ET-1 gene. During this process there is enhanced acetylation of histone H4 at several NF-κB binding sites. As far as we are aware, this is the first report of epigenetic control of ET-1 synthesis, and the use of ChIP to identify human cells to investigate such mechanisms. Understanding such mechanisms may lead to novel therapies directed against PAH.

**S054 FLUVASTATIN SELECTIVELY INHIBITS HYPOXIC PROLIFERATION AND ACTIVATION OF P38 MAP KINASE IN PULMONARY ARTERY FIBROBLASTS: IMPLICATIONS FOR PULMONARY HYPERTENSION TREATMENT**

C. M. Carlin, A. J. Peacock, D. J. Welsh. Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow, UK

**Background:** Excessive pulmonary vascular cell proliferation is a key aspect in the development of severe pulmonary hypertension. Exploring the differential effects of any proposed antiproliferative treatment on the cell types resident to the pulmonary artery is important if we are to determine how best to exploit these drugs. Statin drugs have antiproliferative effects and reverse pulmonary hypertension in animal models. In particular, we have reported fluvastatin inhibition of hypoxia-induced pulmonary adventitial fibroblast (PAF) proliferation (Carlin et al, BTS, 2005). It is unknown whether statins would be effective in the treatment of pulmonary hypertension in humans at standard doses or which statin would be best suited to this indication. Also unknown is whether established or novel therapies would complement or simply duplicate the effects of statins and whether we should expect all forms of pulmonary hypertension to respond similarly. To address some of these questions we studied proliferative responses of PAFs, pulmonary artery smooth muscle cells (PASMCs) and systemic adventitial fibroblasts (SAFs) to incremental doses of serum, platelet-derived growth factor and acute hypoxia (5%). We studied the effects of different statins across a range of doses. The cellular mechanisms in the PAF-hypoxia model were assessed by studying effects of statins, prenyl intermediates and related inhibitors on proliferation and MAP kinase activation.

**Methods:** Proliferation of vascular cells was assessed by [3H] thymidine uptake and cell counting. MAP kinase activation was assessed by Western blot analysis.

**Results:** Fluvastatin at pharmacological doses inhibited hypoxic proliferation and p38 MAP kinase phosphorylation in PAFs. This effect was reversed by the prenyl compound geranylgeranyl pyrophosphate and mimicked by a geranylgeranylated transferase inhibitor, suggesting that hypoxia-induced p38 phosphorylation is mediated via pathways such as RhoA or Rac1. The Rho kinase inhibitor hydroxyfasudil had no effect. PASMCs and SAFs showed no increased proliferation in acute hypoxia. Serum and PDGF-induced proliferation of PAFs, PASMCs, and SAFs was only influenced by fluvastatin at doses 10–100 fold higher than achieved in vivo, with no evidence of a circulation specific effect. Simvastatin and atorvastatin had similar effects to fluvastatin, but in contrast to fluvastatin the doses of these required are much greater than those achieved in vivo, in humans.

**Conclusion:** An important hypoxic signaling pathway in PAFs has been identified and it is selectively inhibited by fluvastatin at pharmacological dosage. Fluvastatin would seem to have specific potential for hypoxia-associated pulmonary hypertension.

**S055 TRANSFORMING GROWTH FACTOR p1 REGULATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN PULMONARY ARTERY SMOOTH MUSCLE CELLS**

R. Clifford, K. Deacon, L. Corbett, A. Knox. University of Nottingham, City Hospital, Nottingham, UK

**Background:** Pulmonary hypertension (PH) is a rare disorder of the pulmonary vasculature characterised by abnormal vasoconstruction and remodelling of the pulmonary arteries. It is widely that pulmonary artery smooth muscle cells (PASMC) proliferation leads to the remodelling that underlies severe PH. Interest in vascular endothelial growth factor to PH arose through two observations. (1) The lumen of small and medium precapillary pulmonary arteries of PH patients contain plexiform lesions which have been described as “dynamic angiogenic lesions” as they express angiogenic molecules including VEGF and VEGF receptor 2. (2) Numerous animal studies have shown the introduction of increased VEGF by various methods to alleviate PH. The aim of this research was to study the regulation of VEGF in PASMCs. From the cytokines and growth factors tested (TGFβ1, bradykinin, interleukin-1β, prostaglandin E2, tumour necrosis factor α and endothelin-1), only TGFβ1 caused a significant increase in VEGF protein and, therefore, became the focus of the project. This has added interest due to the past discovery of the BMPR2 mutation (a receptor in the TGFβ1 superfamily) in familial PH and the emerging concept of aberrant BMPR2 signalling having a positive impact on TGFβ1 signalling.

**Methods:** Studies were performed in PASMCs at passage 6. VEGF proliferation production was measured by EUSA. Transcriptional regulation was assessed by transient transfection of promoter reporter constructs using either Lipofectamine 2000 or Fugene 6 according to
Abstract S054 (A) PAF proliferation is significantly increased in acute hypoxia; this effect is blocked by fluvastatin at a pharmacological dose of 1 μM. SAFs do not proliferate to hypoxia. Fluvastatin 1 μM has no effect on serum-normoxic proliferation of either PAFs or SAFs but 10 μM reduces proliferation levels to control values (∗significantly increased v serum-normoxia, p<0.05; **significantly reduced v serum-normoxia p<0.05). (B) Lipophilic statins inhibit acute hypoxia-induced PAF proliferation; no significant difference in potency is identified. (C) The inhibitory effects of fluvastatin on hypoxia-induced PAF proliferation are completely reversed by repletion with mevalonate (M), farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP); repletion with squalene (Sq) has no effect. Prenyl compounds alone have no effect on serum-normoxic or hypoxic proliferation. (∗significantly increased v serum-normoxia, p<0.05). (D) The inhibitory effects of fluvastatin on hypoxia-induced PAF proliferation are mimicked by a geranylgeranylation transferase inhibitor (GGTI). Hypoxic PAF proliferation is unaffected by the farnesyltransferase inhibitor (FTI), the squalene synthase inhibitor (ZA), cholesterol depletion (MBCD) or the rho kinase inhibitor, hydroxyfasudil (HF). (∗significantly increased vs serum-normoxia, p<0.05). (E) Pulmonary artery smooth muscle cells exhibit increased proliferation to serum and PDGF-BB. Fluvastatin 1 μM has no effect but partial inhibition of both serum and PDGF-induced proliferation is achieved at the 10 μM dose. (∗significantly reduced v serum/PDGF-BB alone, p<0.05). (F) Acute hypoxia for 16 hours induces phosphorylation of p38 MAP kinase. This is completely blocked by fluvastatin 1 μM. As with proliferation this inhibitory effect is completely reversed by repletion with M, FPP and GGPP but not Sq.

Abstract S056 Absolute cell counts at day 6 (SEM)

<table>
<thead>
<tr>
<th></th>
<th>10% FBS</th>
<th>10% FBS + TGF-β</th>
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<tbody>
<tr>
<td>Control human PASMC</td>
<td>38.4 ± 10^3 (0.77)</td>
<td>22.9 ± 10^3 (2.11)</td>
</tr>
<tr>
<td>BMPRII mutant human PASMC</td>
<td>42.3 ± 10^3 (12.6)</td>
<td>54.0 ± 10^3 (16.24)</td>
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</table>

*p<0.05 TGF-β compared with 10% FBS alone.

Abstract S057

**BMPRII DYSFUNCTION IN PULMONARY ARTERY SMOOTH MUSCLE CELLS CAUSES ABNORMAL GROWTH RESPONSE TO TGF-β**

R. J. Davies, P. D. Upton, R. C. Trembath, N. W. Morrell. Department of Medicine, Addenbrooke’s Hospital, Cambridge CB2 2QQ, UK

**Introduction:** Pulmonary arterial hypertension (PAH) is characterised by increased growth of pulmonary vascular endothelial and smooth muscle cells. The familial variant of this condition (FPAH) is mainly caused by mutations in the bone morphogenetic protein type II receptor (BMPRII), a receptor in the TGF-β1/BMPsuperfamily. Although mechanisms underlying this dysregulated cell growth are not yet fully understood, our previous results have implicated TGF-β1. Here we characterise more comprehensively the abnormal growth response to TGF-β in cells harbouring disrupted BMPRII.

**Methods:** Pulmonary arterial smooth muscle cells (PASMCs) were harvested from explanted lungs from patients undergoing lung transplantation for FPAH as well as from labectomy tissue in non-PAH control patients. Cells were maintained under standard tissue culture conditions. Cells from 3 control and 3 mutant cell lines were seeded at 1.5 x 10^4 cells/well and quiesced for 24 hours. Cells were then incubated in DMEM/10% FBS in the absence or presence of TGF-β1 (10 ng/ml), treatments being replenished every 48 hours. Cells were counted on alternate days and viability assessed by trypan blue exclusion. Similar studies were also performed on cells harvested from mice heterozygous for a null allele BMPRII as well as human control cells in which BMPRII was knocked down by transfection with siRNA for BMPRII.

**Results:** The growth of control cells, both human (table) and mouse, was significantly inhibited when treated with TGF-β1. However, cells harbouring a BMPRII mutation or with reduced expression of BMPRII receptors, due to either a null allele or as a result of transfection with siRNA for BMPRII, were not susceptible to the growth inhibitory effect of TGF-β1. Western blot analysis of protein from cells transfected with BMPRII siRNA, has demonstrated that this TGF-β1 mediated effect is not due to increased activation of the TGF-β1 signaling intermediaries, Smad 2 or 3.

**Conclusions:** These results show that BMPRII dysfunction is central to the abnormal growth response to TGF-β. Although the mechanism of this response remains to be defined our initial results suggest a Smad independent mechanism.

Abstract S057

**Remodelling score**

<table>
<thead>
<tr>
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<th>Median</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>Media score</td>
<td>2 (0–3)</td>
<td>5 (5–5)</td>
</tr>
<tr>
<td>Total vessel score</td>
<td>5.5 (3–8)</td>
<td>9 (9–11)</td>
</tr>
<tr>
<td>Hue</td>
<td>199 (182–220)</td>
<td>202 (188–223)</td>
</tr>
<tr>
<td>Saturation</td>
<td>101 (86–129)</td>
<td>97 (80–118)</td>
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</table>
Smoking cessation

**S058** CAN RESPIRATORY OUTREACH SERVICE INFLUENCE SMOKING CESSATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE FOLLOWING ACUTE EXACERBATION?

M. Redfern, H. Lydon, K. Garrod, R. Sundar, M. A. Greenstone, J. A. Kastelik. Castle Hill Hospital, Cottingham, Hull and East Yorkshire NHS Trust, UK

**Introduction:** Smoking cessation is one of the most important aspects of managing patients with chronic obstructive pulmonary disease (COPD), as it slows the rate of decline of lung function and benefits patients in terms of symptom progression and survival. Smoking cessation intervention is associated with a variable short and long term quit rates.

**Aim:** To assess the effectiveness of smoking cessation advice given during and after an acute exacerbation COPD in the community by ROS in the Hull and East Yorkshire area.

**Methods:** Smoking cessation intervention was provided by a trained nurse as a part of a respiratory outreach service (ROS) to patients during an acute exacerbation in the hospital followed up in the community, in the form of support, verbal advice and nicotine replacement therapy. They were followed up in 1, 3, 6, and 12 months.

**Results:** Over a period of 18 months, 91 patients were qualified, 12 (13%) patients died and in the remaining 79 patients (39 women) mean age was 65 (51–87) years. Smoking history was 62.2 pack years with a range of 10 to 228 pack years. After intervention, 41 (51%) patients managed to stop smoking in 4 weeks. At 3 months 33% and at 6 months 30% managed to stop smoking. However 17 started smoking again. At 18 months 20 (25%) of them managed to stop smoking.

**Conclusion:** The national COPD audit conducts a high mortality rate following an acute exacerbation. Smoking intervention has a high success rate at 4 weeks following an acute exacerbation, which was maintained at the end of 18 months. We suggest a routine smoking cessation intervention during an acute exacerbation and as a part of hospital at home service and might emphasis similarity with pulmonary rehabilitation regarding effectiveness of early intervention following exacerbation.

**S059** CAN SMOKERS PASS SEAMLESSLY FROM A HOSPITAL BASED TO A COMMUNITY BASED SMOKING CESSATION SERVICE? A RANDOMISED CONTROLLED TRIAL

K. E. Lewis,1,2, H. Dixon1, V. M. Edwards1, C. Whitehead1, L. Durgan1, R. Sykes1.1 Carmarthenshire NHS Trust, UK; 2School of Medicine, University of Wales Swansea, UK; 3All Wales Smoking Cessation Service

**Background:** Most smoking cessation programmes are based either in secondary care or primary care/community. We tested a model where hospitalised smokers are first counselled in secondary care and then referred to the community service for ongoing support and relapse prevention. To validate quitters, they must first attend.

**Methods:** Open-label, randomised, controlled, intervention trial. Smokers attending two hospitals, who wanted to quit, were randomised to (A) single session and generic advice from the Stop Smoking Counsellor (SSC), /– NRT or (B) 4 weeks’ support by the SSC, /– NRT and then advised to contact the community smoking cessation service on a provided leaflet, (B) 4 weeks’ support by the SSC, /– NRT and then given a specific appointment with the community service before leaving the SSC office. Non-attenders were sent a reminder letter and were phoned once. Those with active psychiatric illness, substance misuse, were pregnant or who were housebound were not recruited. We compared attendance at each time point between the three groups.

**Results:** We present interim data on 344 patients. The three groups did not differ significantly on age, gender, pack-years, comorbidity, self-reported daily consumption, comorbidity, number of outpatients, and baseline modified Fagerstrom score. The table shows % attendance (from number eligible to attend at each time point).

**Conclusion:** Despite good attendance within secondary care, later attendance to the community service is very poor, even when specific appointments are made and smokers are individually reminded. Although there is an 11% difference in attendance rates at 3 months between groups B and C, by 6 months this difference has disappeared.

**S060** SMOKING HISTORY AND CESSATION IN ACUTE MEDICAL ADMISSIONS: A FOLLOW UP STUDY

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**Introduction:** Smoking is the greatest preventable cause of respiratory disease in the developed world. A smoking history should be taken from all patients, and smokers advised to stop and given support.1 We have previously reported on smoking history and cessation support in acute medical admissions to our hospital, and the effect of a clerking proforma;2 this is a follow up study after the introduction of a smoking cessation strategy and service.

**Methods:** We obtained a sample of casenotes of patients admitted as medical emergencies in January 2006, after the introduction of a smoking cessation strategy (including guidelines for support and pharmacotherapy, and training for all health professionals). We collected demographic and diagnostic information, the documented smoking history and cessation advice given. We carried out descriptive and univariate analysis (using smoking history and cessation as outcomes), and compared results with those of our previous study using STATA 8.

**Results:** We reviewed casenotes of 99 patients, mean age 59 years, 55 (56%) male, 47 (49%) with smoking-related diagnoses. 82 (83%) had a smoking history recorded. Of the 30 current smokers identified, only 6 (20%) were given advice to stop, although those with smoking-related diagnoses were more likely to be given advice compared to unrelated conditions (33% v 7%, x^2 = 3.0, p = 0.08). Smoking history was significantly better compared to results from 2004 (recorded in 83% v 61%, x^2 = 11.2, p = 0.001), before the introduction of the smoking cessation strategy and service, although the proportion of smokers given smoking cessation advice was no different (20% v 16%, x^2 = 0.9, p = 0.36).

**Conclusion:** Although we have shown a significant improvement in smoking history in acute medical admissions, smoking cessation advice remained poor despite the introduction of a smoking cessation strategy and service. This study highlights the continued need for education of medical staff in smoking cessation.

Background: Intensive intervention with inpatients who smoke improves smoking cessation rates. Smoking cessation (SC) services for inpatients started at the Whittington Hospital in July 2004 and in July 2005 the premises became “smoke free”. However, junior doctors need to know where to refer patients for smoking advice. Over a 16 month period we measured smoking rates in inpatients, documentation of smoking status and provision of SC advice by junior doctors.

Method: Three cross sectional surveys of all adult medical and surgical inpatients were carried out on single days in October 2004, June 2005, and January 2006. Patients were interviewed by medical house officers using a standardised anonymous questionnaire. Questions included current smoking status, whether smokers had smoked since admission, and whether smokers had received SC advice during their admission. Documentation in the medical record of smoking status and SC plan was also recorded. Junior doctor education on SC was provided with audit feedback after each survey. After the first survey, the investigators added a prompt to the admission proforma reminding junior doctors to discuss SC and giving details of how to refer patients to SC services.

Results: A total of 616 in-patients were interviewed. The response rate for each survey was 74.3 (1.4)% (mean (SEM)). The percentage of in-patients who were smokers did not change at 19.6 (1.4)% consistently lower than the community smoking prevalence of ~35%. Smoking status was well-documented (84%–91% of patients). In October 2004 only 15/45 (33%) in-patients were advised about SC. This increased significantly to 26/46 (57%) in January 2006 (p<0.05). SC plan was documented for only 3/45 (7%) smokers initially, but increased significantly over the period (p<0.05), although only to 10/46 (22%). There was no significant trend for patients smoking during their admission: 21/45 (42%) admitted smoking in hospital in October 2004 and 14/46 (30%) were still smoking during their admission in January 2006 despite being on “smoke-free” premises.

Conclusions: Approximately one in five inpatients smoke. Only 30% of patients were given SC advice initially, despite having a SC service. Our data suggest that SC education and feedback for junior doctors had a significant impact on increasing provision, and documentation, of SC advice. This is important for SC services to be used optimally. More still needs to be done as only 60% of smokers were given advice and this is still poorly recorded. Of concern, despite the premises being smoke free, 30% of patients continue to smoke during admission. More training of junior doctors as well as inpatient SC advisors are needed to help inpatients quit.

The NHS STOP SMOKING SERVICES: HOSPITAL STAFF AWARENESS AND THE PATTERN OF REFERRAL TO THE LOCAL (BASILDON AND THURROCK) SERVICES

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Introduction: Smoking cessation services (SCS) have a quit rate of between 13–19% (abstinence for six months or longer) when compared to 5% following GP advice alone and 2–3% if no advice is given.1 The effort of SCS has largely focused on primary care practices. However close links between secondary and primary care are important for delivery of effective services. Promotion and awareness schemes have been orchestrated in the past for the hospital setting. The aim is to audit and review what is needed to promote this further.

Objectives: (1) To assess the level of awareness of the local SCS among hospital medical and nursing staff in a 652-bedded District General Hospital. (2) To identify the pattern of referral to the SCS and to assess the effectiveness of our two local SCS (the Basildon and Thurrock services).

Methods: (1) A survey was undertaken among the staff at Basildon Hospital to assess awareness and frequency of referral to the SCS. (2) The database of the Basildon and Thurrock SCS was reviewed.

Results: Forty eight hospital staff participated in the survey (12 nurses, 12 junior doctors, 12 middle grade doctors, and 12 senior doctors). Thirty six participants (75%) reported that they were aware of the local SCS. Only 10 participants (21%) had received advice from the local SCS. During the period April 2004 to March 2005, Basildon SCS received 776 referrals including 619 self referrals (79%), 157 GP referrals (20%) and 10 direct hospital referrals (1%). It is possible that some individuals who self-referred had done so following hospital staff advice. Of the 776 referrals to the Basildon SCS, 457 attended the SCS clinic at least once and 301 completed the whole program. The 12 month quit rate for this group was 27%. During the same period, the Thurrock SCS received 1069 referrals including 643 self referrals (67%), 271 GP referrals (28%), 4 direct hospital referrals (0.4%) and 45 from other sources (4.6%). Out of the 963 referrals, 413 attended at least one clinic and 290 completed the program. No data are currently available for the 12 month quit rate for this group.

Conclusion: Although many hospital staff are aware of the presence of the local SCS, the pattern of referral suggests poor attempt from the hospital staff to use the service directly. Judging by the 12 months quit rate for Basildon SCS, the service has higher success rates relative to the expected figures of 13–19%. Increase awareness of SCS and encourage more collaboration between secondary care and SCS is recommended.


KNOWLEDGE OF QUIT SMOKING SERVICES BY HOSPITAL PAEDIATRIC STAFF

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Aims: Parental smoking is associated with increased rates and severity of childhood respiratory illness.1 Many parents want to quit smoking, but need professional support.2 We questioned staff within the Paediatric Department to determine what level of knowledge they had about smoking cessation services available locally and how confident they felt to advise a patient about quitting smoking.

Methods: We sent an anonymous questionnaire to all the 237 nursing, medical and support staff in the Child Health department of our hospital.

Results: 167 (71%) responded, of whom 81% were nursing staff, 12% doctors, 7% clinical support workers and students. Staff identified passive smoking as being associated predominantly with respiratory problems particularly asthma (55%), otitis media (10%) and SIDS (9%). 59% of respondents were aware of a smoking cessation service within the Trust, but 37% of these were unable to clearly identify what was available or name the service. 49% of all respondents did not know how to refer a patient for smoking cessation support. 56% said that they did discuss the benefits of stopping smoking with the parents of patients, but 69% did not discuss quitting smoking with the children/young people. 71% of staff said they were not confident to advise a parent or patient about how to stop smoking and 73% of the staff liked to receive training in quit smoking interventions.

Conclusion: If attempts are to be made to help families achieve a non-smoking environment for their children, paediatric professionals need training in quit smoking interventions and be better informed of the services available.


MOTIVATIONAL EFFECTS OF SPIROMETRY ON SMOKING CESSATION

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Introduction: For many years clinicians have believed that demonstrating smoking was damaging their lungs would help people to quit, but also worried that if smokers knew they had normal lung function they might be encouraged to continue. We investigated the effect of spirometry on motivation to quit smoking.

Methods: A cohort of smokers was recruited from patients >35 years old attending eight GP practices over one year. Opportunistic spirometry, performed by a trained nurse, was classified as obstructive (OLF) if predicted values were FEV1/FVC < 85% or FEF25–75% < 55%, or normal (NLF). Restrictive changes were excluded (FVC <80% predicted). All smokers were given brief general quit advice plus a specific feedback message on spirometry. OLF group told “Evidence of lung damage due to smoking” and NLF group told “No evidence of lung damage”. The effect of spirometry feedback on shift of stage in the Transtheoretical Model1 (which describes five stages in the process of achieving
long-term smoking cessation) and sustained smoking cessation was assessed after 3 months by self-report.

Results: 328 participants (96% of eligible total) were recruited, 193 in NLF and 135 in OLF groups. Baseline nicotine dependence, cigarette consumption, stages of change distribution, quit confidence and perception scores (VAS) for health, lung damage and quit benefits were similar in both groups. Follow up was successful for 297 (91%). The increase in positive stage shift between OLF and NLF groups was not significant, 39 (31.2%) and 42 (24.4%) respectively (p = 0.399). Negative stage shift was similar (12%) in both OLF and NLF groups. Using multinomial logistic regression, higher perception of health was a significant predictor for positive stage shift compared to negative shift (p = 0.002) while a shorter smoking history (< 20 v > 20 pack years) was not quite significant (p = 0.06). Seventeen participants quit, with 7-day point prevalence cessation rates in the OLF group 50% greater that in the NLF group, but not significantly different at 6.7% and 4.1% respectively (p = 0.311). Successful quitting was associated with shorter smoking history (p = 0.03), lower nicotine dependence (p = 0.003), quit confidence above average (p = 0.008), higher perception of health (p = 0.011) and later stages of change for cessation. Association with category of feedback (OLF v NLF) was not significant (OR 1.65, p = 0.315) but after adjusting for smoking history it was stronger (OR 2.436, p = 0.087).

Conclusion: In selected smokers in primary care, receiving feedback that spirometry showed damage due to smoking was associated with non-significant increases in short-term smoking cessation and positive shift of motivational stage. Feedback that there was no damage was not associated with any decrease in motivation. This is reassuring, as GP contract feedback for chronic obstructive pulmonary disease will be the next stage.

Pulmonary infections

**5064 MICROBIOLOGY INVESTIGATIONS IN COMMUNITY ACQUIRED PNEUMONIA: WHAT IS AVAILABLE FROM ENGLAND AND WALES LABORATORIES?**

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Aims: To assess the availability and usage of microbiological investiga-
tions for the diagnosis of community-acquired pneumonia (CAP).

Methods: Postal questionnaire sent to 212 England and Wales microbiology laboratories. Questions related to the provision of Gram stain for sputum samples, and testing of urine specimens for legionella and pneumococcal antigens.

Results: 203 questionnaires returned (67%) with 133 datasets (10 centres reported jointly). Gram stain on sputum specimens: 52/133 labs (39%) do not provide this service and 81 (61%) labs do (48% special request only). Of the 81 labs, 14 (17%) specify criteria to requesting clinicians and 14 (17%) specify minimum microscopy criteria below reporting specimens. 20 (25%) provide same-day reporting only within working hours. 46 (57%) also provide this out of hours. Legionella urine antigen testing: 131 (99%) labs offer this but 44 (34%) specify criteria to clinicians. 18 (14%) labs specify criteria based upon the 2004 Update to the BTS Management of CAP Guidelines (BTS2004CAP). 97 of these in the 94% (44) run the test on site, and 92 (93%) offer a routine service within 24 hours. 49 labs (50%) provide a result for urgent specimens within 6 hours during working hours; 44 (44%) offer this service out of hours. 61 (62%) of labs refer ‘positives’ to the national reference lab. 43 (69%) refer to support national surveillance. 56 (92%) refer to confirm initial test results. 69 labs (53%) provided data on numbers of tests processed in 2004. The mean number of cases tested per lab was 170 (max 849). The mean number of positive cases per lab was 2.1 (1.2% of tests – total positive cases 145). Pneumococcal urine antigen testing: 71 (53%) labs offer this, and 10 (8%) plan to introduce the test within the next year. Of reporting labs, 23 (32%) specify criteria to requesting clinicians. Most labs (59–83%) provide the service on site, and 55 (93%) offer a routine service within 24 hours, 26 labs (44%) report urgent specimens within six hours (during working hours) and 28 (48%) offer this service out of hours. 33 labs (46%) provided data on the number of tests processed in 2004. The mean number of cases tested per lab was 74 (max 832). The mean number of positive cases per lab was 4.3 (5.8% of tests – total positive cases 304).
Cytokines were measured by Luminex array and ELISA. A laboratory SA was incubated with filter sterilised BALF from WG, IPF, and normal controls. The number of colony forming units (CFU) were counted after 24 hours.

**Results:** Greater than $10^4$ CFU were cultured from 26 (66%) WG patients and in 16 SA was grown. In IPF a pathogen was grown in 12 (39%) patients with one SA. No pathogens were grown in BALF from normal controls. SA was more likely to be grown in the WG relapse and remission compared to acute patients ($p=0.025$). BALF growth of SA is independent of nasal carriage in 15% of cases. IL1RA is elevated ($p=0.05$) and TNFα ($p=0.003$) is reduced, when SA is grown in WG BALF.

Incubating SA in BALF from WG patients resulted in higher numbers of CFU than IPF ($p=0.043$) or normal ($p=0.036$), an effect that is heat labile.

**Conclusion:** SA has a predilection for WG patients where the alveolar environment appears permissive for SA growth. Cytokines reported to stimulate SA growth are elevated in WG BALF compared with controls. Although TNFα is elevated compared with controls, within the WG group, patients that grow SA have lower levels of TNFα which is specifically required for neutrophil killing of SA. Defective clearance mechanisms and a promotive cytokine environment may encourage persistence of SA provoking inflammation and an increased relapse rate.

**Abstract SO66**

### Mean data pg/ml

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<thead>
<tr>
<th>Group</th>
<th>IL1β</th>
<th>IL1RA</th>
<th>IL6</th>
<th>IL8</th>
<th>TNFα</th>
<th>GCSF</th>
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<tbody>
<tr>
<td>WG</td>
<td>161.7</td>
<td>14521.8</td>
<td>17.3</td>
<td>1795</td>
<td>30.91</td>
<td>101.8</td>
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<tr>
<td>WG + N test p value</td>
<td>0.021</td>
<td>0.000</td>
<td>0.025</td>
<td>0.004</td>
<td>0.037</td>
<td>0.015</td>
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<tr>
<td>IPF</td>
<td>16.3</td>
<td>12457.0</td>
<td>13.1</td>
<td>797.8</td>
<td>14.9</td>
<td>73.8</td>
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<tr>
<td>Normal</td>
<td>12.9</td>
<td>323.1</td>
<td>0.5</td>
<td>120.1</td>
<td>12.6</td>
<td>20.3</td>
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</tbody>
</table>

**Abstract SO67**

### C-REACTIVE PROTEIN IS AN INDEPENDENT MARKER PREDICTING SEVERITY IN COMMUNITY ACQUIRED PNEUMONIA

**J. Chalmers, A. Singanayagam, A. Hill.** Department of Respiratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

**Introduction:** National guidelines use CURB score (new mental confusion, urea $>7$ mmol/l, respiratory rate $>30$/minute, systolic blood pressure $<90$ mmHg and/or diastolic blood pressure $<60$ mmHg) for assessment of severity of community acquired pneumonia (CAP). A CURB score $>2$ is regarded as severe pneumonia. The aim of this study was to assess whether the acute phase C-reactive protein (CRP) was an independent marker of predicting severity of CAP.

**Methods:** We studied 187 adult patients admitted with CAP to the Royal Infirmary of Edinburgh between December 2005 and June 2006. Data are presented as median interquartile range (IQR). The Mann Whitney U test and Kruskal-Wallis test was used to compare groups. A $p$ value less than 0.05 (two-tailed) was considered as statistically significant.

**Results:** CRP was an independent marker of severity of CAP: see figure 1. In addition, CRP correlated with patient placement (patients were all assessed in hospital but then were either discharged (hospital stay $<24$ hours), admitted to the Respiratory ward or were admitted to the high dependency (HDU) or intensive care unit (ITU)); see table.

The CRP normal range in our laboratory is from 0–10 mg/l. For CRP $>10$ mg/l, the positive predictive value for severe pneumonia (CURB $>2$) is 83.2% and the negative predictive value for exclusion of severe pneumonia for a CRP $<10$ mg/l is 95.7%.

**Conclusion:** CRP is an independent predictor of severity of CAP. CRP concentrations $<10$ mg/l effectively excludes severe CAP.

<table>
<thead>
<tr>
<th>Group</th>
<th>Median CRP (mg/l) (IQR)</th>
<th>$p$ value (Kruskal-Wallis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>Respiratory ward</td>
<td>146</td>
<td>101</td>
</tr>
<tr>
<td>HDU or ITU</td>
<td>29</td>
<td>216</td>
</tr>
</tbody>
</table>

**Abstract SO67 Boxplot of CRP compared with CURB scores.**

**SO68**

### NEUTROPHIL-MEDIATED IMMUNITY TO MYCOBACTERIUM TUBERCULOSIS INFECTION: ROLE OF LIPocalcin 2

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**Background:** Some individuals exposed to infectious tuberculosis (TB) do not develop evidence of infection. We investigated the factors associated with this phenomenon in a group of TB contacts; independent risk factors for infection were identified with multivariate analysis.

**Methods:** We investigated correlates of host response to mycobacterial infection in 202 adult TB contacts in London, UK, using two whole blood assays, and evaluated the contribution of neutrophils to host response by neutrophil depletion. We determined serum concentrations of the neutrophil antimicrobial peptides HNP 1–3, LL-37 and lipocalin 2 by ELISA, we investigated the effect of recombinant lipocalin 2 and iron restriction on growth of M tuberculosis (MTB) in broth and identified regulators of lipocalin 2 secretion and gene expression in cell culture.

**Results:** We observed a strong and independent inverse relationship between peripheral blood neutrophil count and risk of latent TB infection (LTBI) as indicated by secretion of interferon gamma by whole blood stimulated with the MTB antigens ESAT-6 and CFP-10. The ability of
whole blood to restrict metabolic activity of the recombinant reporter mycobacterium BCG-lux was very significantly impaired by neutrophil depletion, and correlated with serum concentration of lipocalin 2, a neutrophil peptide which binds soluble siderophores of mycobacteria. Lipocalin 2 restricted growth of Mtb in THP-1 broth; this effect was more marked in iron-depleted broth. Black African and south Asian TB contacts had lower serum lipocalin 2 levels, lower neutrophil counts and higher rates of vitamin D deficiency than whites. The active metabolite of vitamin D, 1,25(OH)2 vitamin D3, induced secretion of lipocalin 2 in whole blood and induced lipocalin 2 gene expression in neutrophils in vitro.

Conclusions: High peripheral blood neutrophil count was independently associated with decreased risk of LTBI as diagnosed by a whole blood assay. The vitamin D-inducible peptide lipocalin 2 may contribute to neutrophil-meditated antibiotic activity. Vitamin D deficiency and ethnic neutropenia may combine to increase susceptibility to TB infection in south Asians and black Africans.

Paediatric asthma

S069 CHILDHOOD WHEEZE, PEAK FLOW, AND THE OXFORD TRANSPORT STRATEGY
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Background: Studies of the health effects of traffic interventions are rare.

Methods: Using a before-and-after design between 1999 and 2000, 1389 children aged 6–10 years were visited two to three times a year for five-day periods. On each day of each visit, we measured their PEF and respiratory symptoms among schoolchildren in the city centre of Oxford. In this analysis we report the impact of the Oxford Transport Strategy (OTS) on peak expiratory flow (PEF) and respiratory symptoms among schoolchildren in the city.

Results: Regression analyses adjusting for potential confounders showed a statistically significant improvement in PEF (beta = 5.71 L/min; 95% CI [3.28 to 8.18]) and wheeze (OR = 0.80, 95% CI [0.69 to 0.91]) post-OTS. Children living near roads where traffic decreased post-OTS experienced a greater improvement in PEF than children living on streets where there had been an increase. This association was limited to children currently receiving treatment for asthma and to those in socioeconomic classes III-V.

Conclusion: Our findings suggest that traffic management can lead to localised improvements in childhood respiratory health but that such benefits are especially pertinent to children with pre-existing respiratory problems and those from less affluent backgrounds.

S070 INCIDENCE OF ADRENAL SUPPRESSION IN CHILDREN ON HIGH DOSE INHALED STEROIDS
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Children on high dose inhaled steroids are at potential risk of secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. There appears to be a greater risk of altered adrenal function with higher doses of steroids, but the large degree of inter-individual variability makes it difficult to predict which patients will suffer from this side effect. The British Thoracic Society and Scottish Intercollegiate Guidelines on the management of asthma do not give specific advice to clinicians on which children to screen for possible adrenal suppression. However, clinical adrenal insufficiency has been reported at doses of inhaled fluticasone propionate (FP) >400 mg per day.

We investigated the incidence of adrenal suppression in all asthmatic children on a prescribed daily dose of 500 mg or more of inhaled FP (or the equivalent dose of another steroid) attending the Paediatric respiratory clinic at Nineills Hospital, Dundee. Each child was screened for adrenal suppression using the short synacthen test. 60 patients on at least 500 µg of FP attended the clinic over a two year period. Of these children, 4 had evidence of adrenal suppression on their short synacthen test (peak cortisol response < 500 nmol/L). None of the 29 patients on less than 1000 µg of inhaled FP had biochemical evidence of adrenal suppression. 4 of the 31 patients (12.9%) on 1000 µg or more per day had abnormal short synacthen tests, giving a number needed to treat rate of 7.75 to detect one abnormal short synacthen test in this group.

These results indicate that a significant proportion of children on extremely high dose inhaled steroids are likely to have clinically important, yet undetected, adrenal suppression. Recent reports in the literature have detected even higher levels of impaired adrenal response in children on high dose FP. Routine screening of adrenal function may be indicated in this group of children.

The authors thank Mrs Helen Donald for organising the short synacthen tests.


S071 BODY MASS INDEX, PHYSICAL ACTIVITY, AND BELIEFS ABOUT EXERCISE IN CHILDREN WITH ASTHMA
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Background and Aims: Children with asthma frequently cite exercise as a trigger and this has implications for weight management and mental health.

This study aims to investigate the impact of asthma on children’s customary activity. It is hypothesised that children with asthma will have higher BMI and lower levels of physical activity than children without asthma.

Methods: A controlled, cross sectional study of children aged 7–14 attending hospital outpatient clinics, either for asthma (n = 56), or for ENT or dermatological conditions (n = 61). Outcome measures were BMI, International Task Force classification of obesity, Strengths and Difficulties Questionnaire (SDQ) scores and Physical Activity Questionnaire (PAQ) scores.

Results: The groups were well matched for demographic variables. The asthma group had higher BMI (p = 0.008) and 21.4% were obese compared to 6.6% in the non-asthma group (OR 3.89, 95% CI 1.17 to 12.88). Children with asthma reported fewer physical activities in the previous 24 hours (p = 0.002) but comparable levels of sedentary activities. Obese children were less active (p = 0.038) but regression analysis showed asthma was the strongest predictor of lower activity scores, followed by younger age (adjusted r2 = 0.104). The asthma group had higher levels of emotional difficulties (p = 0.05) and, within this group, PAQ scores negatively correlated with SDQ scores indicating that more active children had better mental health (p = 0.009). More parents (60.7%) and children (66.1%) in the asthma group identified the child’s health as a barrier to exercise compared to the non-asthma group (p < 0.001).

Conclusion: Interventions to promote physical activity in children with asthma may reduce the risk of obesity and improve mental health.

S072 PARENTS CAN DISTINGUISH BETWEEN DIFFERENT CHARACTERISTICS OF WHEEZE AT TWO YEARS OF AGE AND THIS HAS IMPLICATIONS FOR ASTHMA OUTCOME AT FIVE YEARS OF AGE

Introduction: The accuracy of parental reported wheeze in their preschool children has been questioned. The aim of the present study was to compare outcomes at five year of age in children with reported
where wheeze at two years of age where wheeze was characterised by parents as rattling, purring, or whistling.

**Methods:** Participants were part of a whole-population birth cohort study designed to relate early dietary exposures to asthma outcome in later life. At two years of age, parents completed a respiratory questionnaire including the question “Has your child wheezed in the previous year?” Wheeze was then categorised as having one of the following characteristics: rattling, purring, whistling, or other. The five year assessment of this cohort included a respiratory questionnaire and a representative proportion also attended for spirometry and skin prick testing. Atopy was defined as at least one positive skin prick test. Spirometry was expressed as a z score adjusting for gender, weight and height.

**Results:** At two years of age, respiratory questionnaire data were available for 1371 of the original 1924 children and 207 had reported wheeze (24 whistle, 49 purr, 124 rattle, and 10 other). The proportion with rattling, purring or whistling did not differ by gender, maternal asthma or maternal smoking. At five years of age, questionnaire data were available in 157 children with reported wheeze at two years of age of whom skin prick reactivity and spirometry were assessed in 95 and 80 respectively. Current wheeze at five years was reported for 74% with previous whistling, 39% with previous purring and 34% with previous rattling (p=0.015), the respective proportions receiving treatment for asthma also differed (40%, 18%, and 11%, p=0.017). The proportion with atopy was higher (67%) among the six children with whistling at 2 years and lower for the 20 with purring (25%) and the 65 with rattling (22%), p= 0.051; 25% of the whole population were atopic. The mean height.

**Background:** In the airway, the presence of the homozygous Arg/Arg genotype (about 15% of patients with asthma in the US and UK) confers relative protection against downregulation by endogenous catecholamines and reverses the benefits from the regular use of short and long acting β₂-agonists in adults. The presence of the Arg16 polymorphism (either Arg/Arg or Arg/Gly) confers bronchoprotective subsensitivity to methacholine and adenosine monophosphate challenge in steroid treated adults with asthma treated with formoterol and salmeterol. However, the consequences of real-life prescribing of long acting β₂-agonists, as an add-on medication to inhaled steroids, in Arg/Arg and Arg/Gly individuals with asthma, have not been explored. **Method:** The study was cross-sectional, involving the collection of information through direct interviews, and the determination of position 16 and 27 of the ADRB2 gene in DNA from mouthwash samples for 546 children and young asthmatics attending paediatric asthma clinics in Tayside, Scotland over 2004-05. Exacerbations of asthma over the previous 6 months constituted the primary outcome measure for the study. **Results:** There was an increased risk of asthma exacerbations across all treatment steps of the British Thoracic Society asthma guidelines, when comparing the homozygous genotypes Arg/Arg vs Gly/Gly (OR 2.05, 95% CI 1.19 to 3.53, p=0.010). This genotype-determined risk was particularly important in those treated with regular inhaled salmeterol. This may be explained by genotype-selective salmeterol induced downregulation and impaired receptor coupling, and associated subsensitivity of response.

**Conclusions:** eNO and asthma symptoms are profoundly suppressed after IM-TAM. Since the reappearance of increase in eNO precedes the deterioration in control, eNO may be useful in guiding the timing and dose of subsequent doses of IM-TAM in this difficult to control group.

**S074 ADRENOCEPTOR GENOTYPE PREDISPOSES TO EXACERBATIONS IN YOUNG ASTHMATICS ON SALMETEROL**

C. N. A. Palmer, B. J. Lipworth, S. Lee, I. Murrie, T. Ismail, D. F. Macgregor, S. Mukhopadhyay. Population Pharmaceutics Group, Biomedical Research Centre, Division of Medicine and Therapeutics and *Maternal and Child Health Sciences, Children’s Asthma and Allergy Unit, Perth Royal Infantile and Ninewells Hospital, University of Dundee, UK

**Background:** The arginine 16 genotype of $\beta_2$-agonist (either Arg/Arg or Arg/Gly) confers bronchoprotective subsensitivity to methacholine and adenosine monophosphate challenge in steroid treated adults with asthma treated with formoterol and salmeterol. However, the consequences of real-life prescribing of long acting $\beta_2$-agonists, as an add-on medication to inhaled steroids, in Arg/Arg and Arg/Gly individuals with asthma, have not been explored.

**Method:** The study was cross-sectional, involving the collection of information through direct interviews, and the determination of position 16 and 27 of the ADRB2 gene in DNA from mouthwash samples for 546 children and young asthmatics attending paediatric asthma clinics in Tayside, Scotland over 2004-05. Exacerbations of asthma over the previous 6 months constituted the primary outcome measure for the study.

**Results:** There was an increased risk of asthma exacerbations across all treatment steps of the British Thoracic Society asthma guidelines, when comparing the homozygous genotypes Arg/Arg vs Gly/Gly (OR 2.05, 95% CI 1.19 to 3.53, p=0.010). This genotype-determined risk was particularly important in those treated with regular inhaled salmeterol. This may be explained by genotype-selective salmeterol induced downregulation and impaired receptor coupling, and associated subsensitivity of response.

**Conclusions:** The arginine 16 genotype of ADRB2 predisposes to exacerbations in children and young adults with asthma. The effect is particularly important in those treated with regular inhaled salmeterol. This may be explained by genotype-selective salmeterol induced downregulation and impaired receptor coupling, and associated subsensitivity of response.

**Characterisation of the COPD exacerbation**

**S075 CHARACTERISATION OF FREQUENT EXACERBATORS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING THE BODY MASS INDEX, AIRFLOW OBSTRUCTION, DYSPNOEA, AND EXERCISE CAPACITY (BODE) INDEX**

J. Lee, J. Miller, J. Barr, A. Deans, C. Poland, M. MacDougall, W. MacNee. ELEGI/COLT Laboratory, MRC/UEC Centre for Inflammation Research, University of Edinburgh, UK

**Introduction:** Chronic obstructive pulmonary disease (COPD) exacerbations represent a major burden to healthcare services. This study aims to characterise COPD patients with respect to exacerbation frequency.

**Methods:** A cross sectional cohort of 62 stable COPD patients, were analysed according to exacerbation frequency for clinical characteristics, including body mass index (BMI), airflow obstruction, dyspnoea and exercise capacity (BODE) index, white cell count (WCC) and health-related quality of life (HRQoL).

**Results:** Compared to infrequent exacerbators (<2 exacerbations/year, n = 40), frequent exacerbators (≥3 exacerbations/year, n = 22) had higher BODE index (frequent v infrequent, 5 (2–9) v 2.5 (0–8), p=0.0003), lower percentage predicted forced expiratory volume in one second (33.5 (18–72%) v 52 (18–83%), p<0.0005), worse dyspnoea (Medical Research Council score 3.5 (2–5) v 2 (1–4),

**Abstract S073.**

![Graph](image-url)
p = 0.0005), shorter 6-minute walking distance (295 ± 16 vs 376 ± 90, p = 0.007) and worse HRQL (St George’s Respiratory Questionnaire total: 60.46 ± 13.45 vs 41.77 ± 17.13, p = 0.0005). Compared to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, BODE index quantifies better correlated with exacerbation frequency (BODE: r = 0.586, p = 0.0002; GOLD: r = 0.487, p = 0.0005) and HRQL (BODE: r = 0.704, p = 0.0005; GOLD: r = 0.517, p = 0.001). BMI and differential WCC were not associated with exacerbation frequency.

Conclusions: Frequent exacerbations are associated with severe COPD, high BODE index, and poor HRQL. The multidimensional BODE index better predicts exacerbation frequency and HRQL than GOLD stage.

Acknowledgments: Study supported by National Institute of Health, grant number RFA-HL-02-005.

**S076 AN EXPERIMENTAL MODEL OF VIRUS INDUCED CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION**


**Background:** Respiratory virus infection is associated with ~50% of acute exacerbations of chronic obstructive pulmonary disease (COPD) (AECOPD) but a causal role is not proven and little is known about the mechanisms of virus-induced exacerbations. We hypothesised that experimental infection of COPD patients with rhinovirus (RV) would induce features of an AECOPD and could be used to develop an experimental model to permit study of mechanisms.

**Subjects and Methods:** 21 subjects (10 COPD and 11 age and smoking matched controls) were studied at baseline and then experimentally inoculated with RV16. Subjects kept daily diary cards of upper and lower respiratory tract symptoms. Lung function, blood, and sputum leukocyte counts were assessed prior to inoculation and during the infection phase. Nasal lavage was collected for detection of RV by RT-PCR.

**Results:** Following inoculation 2 subjects did not develop colds and were excluded from analysis. 19 subjects: 8 COPD (mean FEV1 70% predicted) and 11 controls (mean FEV1 108% predicted) developed symptomatic colds. These were accompanied by lower respiratory tract symptoms of cough, wheeze, increased sputum quantity and change in sputum quality. There were significant increases in total lower respiratory tract score in both groups. Cough and sputum scores increased in both groups but breathlessness increased significantly in the COPD group only (p = 0.0313). PEF fell by 23.5 ml in the controls and 50.5 ml in the COPD group (p = 0.031). Kco fell significantly in the COPD group compared to baseline but not in the controls.

Peripheral blood total leukocyte count increased from 6.85 x 10⁹/l to 9.45 x 10⁶/l in the controls (p = 0.01) and from 7 x 10⁹/ml to 9.65 x 10⁹/ml in the COPD group (p = 0.011). Peripheral neutrophil count increased significantly in both groups (controls from 4.1 x 10⁹/l to 5.75 x 10⁹/l (p = 0.01), COPD from 3.4 x 10⁹/l to 6.7 x 10⁹/l (p = 0.05)). The total sputum non-squamous cell count and neutrophil count did not change significantly after infection in the controls. The total sputum non-squamous cell count increased from 1.1 x 10⁶/g to 4.44 x 10⁹/l (p = 0.05) in the COPD group, and sputum neutrophil number from 0.545 x 10⁹/l to 3.18 x 10⁹/l (p = 0.01). RV was detected in nasal lavage fluid in all subjects. There were no adverse events.

**Conclusion:** Experimental RV infection in COPD results in symptoms, lung function changes and systemic and airway inflammation similar to that seen in naturally occurring exacerbations. These data support a causal relation between rhinovirus infection and COPD exacerbations. This model of AECOPD may be used to gain insight into the molecular and cellular mechanisms of AECOPD.

**S077 QUANTITATIVE DETECTION OF S PNEUMONIAE, H INFLUENZAE, AND M CATARRHALIS IN SPUTUM SAMPLES FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS BY REAL-TIME POLYMERASE CHAIN REACTION**

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**Introduction:** A significant proportion of patients with chronic obstructive pulmonary disease (COPD) will have lower airway bacterial colonisation. Sputum culture has so far been the most important method for identifying bacteria, but there is a need for more sensitive methods for bacterial quantification, such as real-time quantitative polymerase chain reaction (RT-PCR).

**Methods:** To assess the usefulness of RT-PCR, 159 sputum samples collected from 48 COPD patients (54.1% male, FEV1 0.72 (SD 0.38) and FEV1 % predicted 42.8% (SD 16.8)) were prospectively collected at exacerbation onset and at 1, 2 and 5 weeks post exacerbation were examined for S pneumoniae, H influenzae and M catarrhalis by culture and by an in-house multiplex real-time PCR assay using primers and labelled probes for the pil gene of S pneumoniae, the hel gene of H influenzae and the caps gene of M catarrhalis. The assays were performed using the Corbett Research RotorGene. Pilot experiments using samples spiked with known bacterial loads suggested a cut-off of 7.2 x 10⁶ colony forming units (cfu)/ml for S pneumoniae and M catarrhalis and 2.6 x 10⁶ cfu/ml for H influenzae for deciding upon the presence or absence of a specific bacterium.

**Results:** Isolation rates for matched samples were higher by RT-PCR than by culture, for S pneumoniae isolation rate was 35.8% vs 5.5% (x² test; p = 0.007), for M catarrhalis 11.7% vs 9.7% (p = 0.569) and for H influenzae 24.8% vs 22.1% (p = 0.579). The percentage of samples, positive for any of the three bacteria, were 54.5% by RT-PCR and 31.7% by culture (p = 0.001). At baseline (exacerbation-free), the number of patients with a positive sputum for any of the three bacteria was 8/18 (44.4%) by RT-PCR and 5/18 (27.8%) by culture. At exacerbation, these proportions were 19/34 (55.9%) by RT-PCR and 15/34 (44.1%) by culture (Both NS). However, for S pneumoniae at baseline, RT-PCR detected 6/18 (33.3%) compared to 0/18 (0%) by culture (p = 0.007) and at exacerbation, 11/34 (32.3%) compared with 4/34 (11.8%) (p = 0.041).

**Conclusion:** RT-PCR substantially increased the number of pathogenic organisms detected, especially S pneumoniae, in sputum samples from COPD patients at baseline and at exacerbation.

**S078 A PROSPECTIVE STUDY OF COMMUNITY ACQUIRED PNEUMONIA RELATED EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS IMPACT ON MORBIDITY AND MORTALITY**

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**Introduction:** Community acquired pneumonia (CAP) is a recognised cause of acute exacerbation of chronic obstructive pulmonary disease (COPD) and can lead to 15% of acute exacerbation cases. Symptoms like increased cough, increased sputum and breathlessness which are used to define acute exacerbation of COPD are non specific and can be the manifestations of CAP. The choice of antibiotic for CAP varies as per its severity and different from exacerbation of COPD. Cheshire Hospital trust revised its antibiotic guidelines for the management of CAP and recommended the use of the modified CURB-65 score to assess severity. In a prospective study we evaluated the antibiotic use in pneumonic exacerbation of COPD and its impact on morbidity and mortality.

**Methods:** Patients with acute exacerbation admitted to Mid Cheshire Hospital trust on acute medical take were identified. Presence of new radiological consolidation was a prerequisite to define CAP. Severity of CAP was assessed using modified CURB-65 Score. CAP was classified as severe if the CURB 65 score was more than 3 without comorbidities or 2 with comorbidities. Patients with acute exacerbation admitted to Mid Cheshire Hospital trust revised its antibiotic guidelines for the management of CAP and recommended the use of the modified CURB-65 score to assess severity. In a prospective study we evaluated the antibiotic use in pneumonic exacerbation of COPD and its impact on morbidity and mortality.

**Results:** Fifty seven patients (32 males) with a mean age of 72 from January 2006 to July 2006 were studied. The overall mean length of stay was 7 days (range 1 to 26).The mean length of stay in pneumonia exacerbation of COPD and non-pneumonic exacerbation of COPD was 9.5 and 6.13 days. Twelve out of 57 (21%) met criteria for CAP leading to acute exacerbation. Five out of 12 (41%) had non-severe CAP and 59% had severe CAP. Five out of seven pneumonia exacerbations received appropriate IV antibiotics as per hospital antibiotic policy. Two out of seven received oral antibiotics appropriate for acute exacerbation of COPD. In hospital mortality of patient with pneumonic exacerbation of COPD was 25% in comparison to 12% mortality in previous series. The difference in length of stay between pneumonia and non pneumonia exacerbation was statistically significant (p = 0.03).

**Conclusion:** This study highlights that CAP is a significant cause of acute exacerbation of COPD and carries high mortality and morbidity. The choice of antibiotic should be the same as per the CAP guidelines. We recommend that patients admitted with acute exacerbation of COPD should be properly assessed for the presence of CAP and severity assessed using the modified CURB-65 score and treated appropriately with antibiotics as per CAP guidelines.
Introduction: Treatment of chronic obstructive pulmonary disease (COPD) exacerbations is a major burden to the National Health Service. The Met Office has developed a winter service forecasting the risk of exacerbation resulting in hospital admission, combined with anticipatory care to try to reduce the risk and prevent admissions. There is biological evidence to suggest that viruses are important in triggering COPD exacerbations. This study aimed to quantify patterns in COPD admissions, and determine whether influenza surveillance data could be used to forecast risk of COPD exacerbations.

Methods: Daily COPD admissions (ICD10 J40-J44) were extracted for England and five regions from Hospital Episode Statistics for 1997/98-2003/04. Corresponding weekly surveillance data for influenza-like illness consultations (ILI, ICD9 487) in England and Wales were available from the Royal College of General Practitioners’ Weekly Returns Service, by age band. Linear regression against date was used to test for trend. Seasonality was tested using t-tests of monthly averages and Box-Ljung tests for autocorrelation. Relationships between weekly COPD and ILI indicators were tested using linear regression, year-round and winter-only (November–March).

Results: COPD admissions were found to increase in all geographical regions, at rates ranging from 2.1% to 9% per year. Seasonality in both COPD and ILI was found to be significant. Average daily COPD admissions were found to be highest in winter, and about twice as high in January as in July. COPD and ILI were well correlated, with higher correlations in winter than year-round owing to small numbers in non-winter months. ILI in the over 65s age-band gave the best fit to COPD, with COPD leading ILI by 1 week ($r^2=0.43-0.62$ across the regions).

Conclusions: Our data suggest that ILI surveillance could be used as a marker for COPD exacerbations and workload during winter. Availability of real-time COPD data would strengthen this. The seasonal pattern in COPD admissions could be used as a simple forecast of risk of COPD exacerbation: Because ILI lags behind COPD, ILI forecasts rather than seasonality would be needed to forecast COPD.

Clinical studies in asthma pathogenesis

Conclusions: An intermediate care package is associated with a significant reduction in COPD death rate, but no alteration in hospital admission rates. Those in the intervention group were more likely to have self-administered medication at the first sign of an exacerbation and continuation of their therapy in the intervention group may account for the improved survival rate.

Acknowledgement: This study was funded by The Health Foundation. ‘Dr Sridhar died on the 29 June 2006.

S080 THE EFFECTS OF A NURSE-LED INTERMEDIATE CARE PACKAGE IN PATIENTS WHO HAVE BEEN HOSPITALISED FOR AN EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Objectives: To determine the effects of a nurse-led intermediate care programme on the management of patients who have been hospitalised with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods: A randomised controlled trial of 122 patients who had been previously admitted to Hammersmith Hospitals NHS Trust with a diagnosis of AECOPD.

Intervention: A care package incorporating initial pulmonary rehabilitation followed by provision of a COPD self-management action plan, monthly telephone calls and three monthly home visits from a specialist nurse over a two year period.

Main Outcome Measures: Hospital re-admission rates, unscheduled visits to general practitioners, use of self-management, quality of life, mortality.

Results: At the end of two years six (9.8%) patients in the intervention group (IG) had died (1 from COPD) and 12 (19.7%) in the control group (CG) had died (8 from COPD), with a statistically significant difference in COPD deaths (Pearson χ² p=0.015). The number of days alive and out of hospital in both arms were the same (IG, median 726.5 days; CG, median 730 days), as were the total number of admissions (IG, 54 admissions; CG, 37 admissions). Patients in the intervention group were more likely to self administer antibiotics and/or steroid tablet treatments (IG 52% vs CG 23 events) and had a higher total usage of antibiotics and oral steroids (IG 347 courses, median 4.5, range 0–29 v CG 262 courses, median 2, range 0–19), in short courses either self administered or initiated by a doctor or a nurse. At the end of two years, more patients in the intervention group were likely to be receiving regular therapy with inhaled steroids (IG 95% v CG 89%), a long acting beta agonist (IG 93% v CG 71%), and a long acting anti-cholinergic agent (IG 79.1% v CG 42.1%) than in the control group.

Conclusions: Most adult current asthmatics have developed their asthma in later life. The prevalence of chronic cough and phlegm is high among middle age adults, which can be predicted by adolescent current asthma and maternal smoking. However, the risk of wheeze, cough and phlegm at age 44 was highest in those who did not have childhood asthma and have asthma and one in 10 of those who did not have childhood asthma had developed asthma. At age 7 years, exclusively breastfed children with a maternal history of allergy had a marginally lesser risk of current asthma than those who were not exclusively breast fed (OR 0.8, 95% CI 0.6 to 1.0). However, after the age of 7 the risk reversed and exclusively breast fed children were at an increased risk of current asthma by age 44 (OR 1.48, CI 1.08 to 2.03). The prevalence of chronic bronchitis (CB) by age 44 was 8.8% (CI 8.1% to 9.6%). In non-smokers, wheeze at age 13 predicted CB at age 44 (OR 2.71, CI 1.32 to 1.76). Maternal smoking increased chance of asthma up to age 44 but only in current smokers (OR 1.43, CI 1.13 to 1.81). Childhood immunisation protected against asthma to age 44 in those with childhood asthma (OR 0.47, CI 0.25 to 0.9).

Conclusions: Exposures to house dust mite allergen are associated with an increase in bronchial hyperresponsiveness over four years in asthma

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Background: The long term effects of allergen sensitisation and exposure in asthma are not known. We therefore conducted a prospective longitudinal study in a large group of asthmatics to investigate the effects of house dust mite allergen sensitisation and exposure on lung function and bronchial hyperresponsiveness.

Methods: Participants were recruited in 1997/98 and underwent spirometry, direct bronchial challenge and measurement of exhaled nitric oxide (eNO). House dust mite allergen (Der p 1) was measured in mattress dust samples by EUSA and high exposure defined as a level
greater than 2 μg/g. Subjects returned in 2001/02 for repeat measurements of lung function and eNO.

**Results:** Of the 200 subjects who completed both visits, mite allergen exposure was measured in 165 (mean (range) age 45 (10-67) years, FEV1 2.51 (0.71-4.91) l, 82% atopic). Subjects returned for follow up after mean 47 (range 25-68) months. Overall there was no change in spirometry or bronchial responsiveness over the follow-up period. There was a significant but small fall in eNO (geometric mean 1.4 ppb (95% CI 1.2 to 1.6 ppb, p<0.001)). There was no association between exposure to mite allergen and change in spirometry or eNO. However bronchial responsiveness over the four-year period deteriorated in subjects exposed to high mite allergen levels compared to those not exposed (mean (95% CI) doubling dose (DD) change in PD20 -0.44 (1.07 to 0.19) or 0.82 (0.27 to 1.36); mean DD difference 1.26 (95% CI 0.44 to 2.08, p=0.003)). This difference was preserved in the multivariate model (p=0.001; confounders: age, inhaled steroid use and dose, smoking status, baseline PD20, sensitisation to house dust mite). There was no effect of the interaction between house dust mite exposure and sensitisation on change in bronchial responsiveness (p = 0.7).

**Conclusion:** In a large cohort of asthmatics followed prospectively over four years, exposure to high levels of house dust mite allergen at baseline was associated with a subsequent increase in bronchial hyperresponsiveness. This effect is independent of sensitisation to house dust mite.

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structure in NEA and its relationship to airway physiology and treatment response requires further investigation.

**S085** THE SIGNIFICANCE OF ACUTE EXERCISE INDUCED HYPERVENTILATION IN PATIENTS WITH SEVERE ASThma

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Introduction: Hyperventilation and dysfunctional breathing have been linked with asthma though the exact relationship between the two remains obscure. Patients with severe asthma have more symptoms which are more likely to be refractory to conventional asthma therapy. We hypothesised that patients with difficult asthma may have symptoms attributable to hyperventilation.

Methods: Patients with severe asthma as defined by the American Thoracic Society criteria were recruited. Data on demographics, asthma history, respiratory questionnaires, spirometry, airway inflammatory markers, and objective exercise tolerance (incremental shuttle walk test) with concomitant end-tidal partial pressure for carbon dioxide (PETCO2) were collected. Acute exercise induced hyperventilation (AEIH) was defined as any drop in PETCO2 between rest and end-exercise.

Results: Twenty seven subjects were recruited. Five subjects (19%) showed evidence of AEIH. When the AEIH group was compared to remaining 22 subjects as a control group, the AEIH group was similar with FEV1 (72.9% v 72.3%), exhaled nitric oxide and sputum eosinophils. The AEIH group were prescribed more prednisolone (19 mg v 3.2 mg, p = 0.01) and secondary asthma medications (1.4 v 0.7, p = 0.036), had worse University of California Shortness of Breath Questionnaire scores (72.4 v 43.7, p = 0.01) and Juniper Asthma Quality of Life scores (3.2 v 4.4 p = 0.018). In addition, exercise tolerance was markedly reduced in the AEIH group (164 m v 548 m, p = 0.001).

Discussion: AEIH is common in subjects with apparent severe asthma. Its presence is associated with higher medication use, worse symptomatology and reduced exercise tolerance. As such it may cause the true asthma severity to be overestimated. In patients with marked exertional limitation, AEIH may be the limiting factor rather than airflow obstruction.


**S086** REFRACTORY ASTHMA PHENOTYPES AND THE RESPONSE TO SPUTUM EOSINOPHIL DIRECTED THERAPY

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We have previously presented work using multivariate cluster analysis techniques to identify phenotypes of refractory asthma in a population of 270 patients attending our difficult asthma clinic. Our results suggested the presence of two cohorts in which there was discordance between the clinical expression of asthma and the extent of corresponding underlying eosinophilic airway inflammation. One group comprised an older male population with inflammation predominant disease and the other was a largely female, symptom predominant group. The clinical significance of these disease patterns is not known. We tested the hypothesis that these discordant refractory asthma phenotypes respond particularly well to inflammation guided therapy. Data from a recent 12 month prospective study of 73 patients with asthma performed at our centre (Green et al. Lancet 2002) was re-evaluated using cluster analysis techniques. Ward’s hierarchical cluster analysis suggested the presence of 3 clusters. A k-means cluster algorithm predicting a 3-cluster model was then used to allocate individual cases to a cluster on the basis of the following baseline variables: demographic parameters, body mass index, atopic status, symptoms (modified Juniper asthma control score), bronchilator reversibility and % sputum eosinophil count. Outcome measures investigated at 12 months were: change in total corticosteroid dose, number of hospital admissions for asthma and total number of severe asthma exacerbations requiring rescue oral corticosteroid therapy. The study cohort was stratified according to cluster membership and management protocol. Outcome measures were compared between subgroups within each cluster using the independent t test. The clusters identified in the study cohort resembled closely those described in our previous work. Cluster 1 (n = 13) described a discordant symptom predominant (mean modified JACS 2.71, GM eos 0.4%) cohort with a high female preponderance (77%) and elevated BMI (mean 36, SD 5.6). Cluster 2 (n = 27) was an inflammation predominant group (GM eos 5.13, mean modified JACS 0.83) with a higher proportion of males (71%). Cluster 3 (n = 12) was a mixed cohort with both symptoms and eosinophilic airway inflammation. Cluster 2 was the only group showing a significant difference in outcome between management strategies with a fall in exacerbation frequency in the sputum managed subgroup compared with the clinically managed subgroup (mean exacerbation rate per year 0.4 v 4.5, p = 0.01). There was a trend towards requiring a lower dose of corticosteroids in cluster 1 for the sputum managed group (mean Δ steroid dose +842 μg +6583 μg, p = 0.07), this was not associated with a difference in other outcomes. We conclude that monitoring of airway inflammation is a particularly effective strategy in the management of patients cohorts presenting with evidence of discordance between clinical disease expression and underlying eosinophilic airway inflammation.

**Clinical lung cancer highlights**

**S087** CANNABIS AND RESPIRATORY TRACT CANCER: A CASE-CONTROL STUDY


Background: Cannabis may have greater potential than tobacco to cause respiratory tract cancer.

Methods: A case-control study of respiratory tract cancer in adults < 55 years was conducted in eight district health boards in New Zealand. Cases were identified from hospital databases and the Cancer Registry. Controls were randomly selected from the electoral roll with frequency matching to cases in 5 year age groups and district health boards. Interviewer administered questionnaires were used to assess possible risk factors including cannabis use. Logistic regression was used to estimate the relative risk of cancer for two anatomical subgroups: lung or laryngeal cancer, and head and neck cancer.

Results: There were 89 cases of lung and laryngeal cancer, 65 cases of head and neck cancer, and 324 controls. The relative risk of respiratory tract cancer was 3.47 (95% CI 1.13 to 10.7) for the highest tertile of cannabis use (~10 joint-years). The highest tertile of cannabis use was associated with an increased risk of lung or laryngeal cancer, (RR = 4.56, 95% CI 1.35 to 15.5). For each joint-year of exposure, the risk of lung or laryngeal cancer increased 8% (95% CI 2 to 14%), equivalent to one pack-year of cigarette smoking. The association between cannabis use and head and neck cancer (RR = 2.63, 95% CI 0.63 to 10.9) was not statistically significant.

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SURVIVAL SPECTRUM OF RESECTED NEUROENDOCRINE TUMOURS OF LUNG: A SINGLE CENTRE EXPERIENCE

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Introduction: Although lung tumours originating from neuroendocrine (NE) cells represent a spectrum of malignancy, from carcinoids (typical [TC], atypical [AC] or metastatic [MC]), large cell (LC) and small cell (SC) lung cancers, little is known about the survival prospects following resection. We therefore looked at the survival of patients post resection at our unit over a 17 year time period.

Method: The interrogated the comprehensive histology database present in our unit and tracked the survival of all patients who had undergone NE tumour resection between 1987 and 2004 until June 2006.

Results: Of 225 patients with resected NE tumours, 5 were excluded because of histological doubt. Some of the remaining 220 (mean age at resection 61 years (range 14–85), 107 male) had adjuvant chemotherapy. There were 46 (21%) AC, 59 (26.8%) TC, 9 (4%) MC, 53 (24.1%) LC, and 53 (24.1%) SC. Of these, 54 underwent pneumonectomy (36 left), 150 lobectomy and 16 wedge resection. At June 2006 114 were alive, 98 dead, and 8 lost to follow up. To date, median survival is 124 months (mean 128), with an overall 5 year survival of 63% (male 61%, female 65%; p = NS). Type specific 5 year survival was AC 65.6%, TC 85.1%, MC 88.9%, LC 51.8%, and SC 43.7%. At 10 years, overall survival fell to 56.6% and type specific survival 45.8%, 85.1%, 88.9%, 38.9%, and 27.1% respectively. There was significant difference in survival between AC and TC (p = 0.01), LC (p = 0.05), and SC (p = 0.001) at five years which remained for TC and SC at 10 years. There was no significant difference in survival between LC and SC at any time period.

Conclusion: Survival in resected NE tumours varies with cell type. In our series there was significant difference in progression between typical carcinoids and the remainder. We also found that patients with even the most malignant variety (SC) can survive if the tumour is suitable for resection. This study shows the importance of histological distinction in this group of tumours, since it may have implications for survival.
proportion of patients with lung cancer that require interval imaging before the diagnosis is confirmed, but also to analyse other factors that contribute to failures to meet the 62 day wait target.

**Method:** A retrospective casenote audit in the 7 Lung Cancer Units which make up the Merseyside and Cheshire Network, looking at the last 489 patients diagnosed with lung cancer.

**Results:** Of these 489 patients, 30% presented as inpatients, 43% as outpatients under the “two week rule” and the remaining 27% as outpatients on another route. Sixty nine per cent of patients had NSCLC, 23% SCC, and 8% mesothelioma. In total, 27 (9 inpatients and 18 outpatients) (6%) required an interval CT scan before the diagnosis of lung cancer was confirmed. Ninety five per cent of patients referred under the 2 week rule were compliant with the target and 97% patients presented within 31 days of decision to treat. However, 22% of patients failed to meet the 62 day wait target. Of the patients who failed the 62 day wait target, 2% had interval CT scans, 24% had CT and PET imaging, but 74% had CT scans and a histological or clinical diagnosis without PET. Forty seven of the 489 patients (10%) were referred for a PET scan, but had NICE guidelines for lung cancer been followed a further 77 patients should also have been referred. The median interval from PET request to PET scan was 28 days (range 12–197).

**Discussion:** Achieving the 62 day wait target for lung cancer with 95% compliance would be improved if the DoH agreed to temporarily “suspend” patients requiring interval CTs from monitoring. Delay in access to PET scanning in the Merseyside and Cheshire CNG contributes significantly to “62 day rule breaches” and would be exacerbated further if all patients who qualify for PET scans were referred. However, the majority of patients who breached the 62 day target had neither a PET or interval CT. A detailed analysis of factors contributing to these breaches will be presented.

**S091 PEMETREXED BASED CHEMOTHERAPY FOR MALIGNANT MESOTHELIOMA; A RETROSPECTIVE ANALYSIS OF 100 CONSECUTIVELY TREATED PATIENTS**

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Malignant mesothelioma is an aggressive tumour associated with asbestos exposure. It has a latency of 30–40 years and in 90% arises in the pleura. The median survival with supportive treatment is 6 months.1 In 2001 malignant mesothelioma was responsible for 1848 deaths in Britain and the incidence is expected to rise until 2015.2 In the registration phase III trial, pemetrexed, a multi-targeted agent, compared to cisplatin, had a median survival of 12.1 months compared to cisplatin alone, 9.3 months in patients with malignant pleural mesothelioma.

We assessed within an audit, the survival benefit and toxicity of pemetrexed in 100 malignant mesothelioma patients treated consecutively at Wythenshawe Hospital since 2003. Patients with WHO performance status (PS) 0–2 were treated with pemetrexed in combination with cisplatin (CisP) or carboplatin (CarbP), or pemetrexed alone (P), 58, 37 and 5 patients respectively. The choice of regimen was determined by renal function and comorbidity. All patients were supplemented with folate and vitamin B12. Most patients had a restaging CT scan after 4 cycles.

Patients were aged 46 to 86 years, 80% were male and 97% had pleural mesothelioma. A maximum of 6 cycles was given and the mean was 4.2 cycles. Median survival from diagnosis and from start of chemotherapy for all patients was 13.9 months and 10.6 months, respectively. In the registration phase III trial, eligible patients had pleural disease, a Karnofsky performance status >= 70 and no prior chemotherapy or surgery. Comparable patients in our series with PS 0–1 had a median survival for CisP of 12.3 months (n=27) and 11.4 months (n=17) for CarbP. The difference between regimens was not significant. For comparable CisP and CarbP treated patients with PS 2 (n=28), median survival was 10.1 months.

Grade 3 and 4 toxicity occurred in 59.5% of CarbP and 34.5% of CisP patients. Neutropenia (23% of patients), myelosuppression (12%) and febrile neutropenia occurred in 5.3% of CarbP and 5.4% of CisP patients. There was one chemotherapy related death.

This series shows that the results in the registration phase III study can be replicated in a non-trial setting. Toxicity was acceptable and less frequent in the CisP patients. Our patients completed a mean of 4 cycles compared to 6 cycles in the Vogelzang study.1

Abstract S093

**Aims:** To identify total bacterial community present in CF sputum. To determine the prevalence of bacterial species not traditional associated with CF lung disease.

**Methods:** 102 whole sputum samples from 34 adult CF patients were analysed by T-RFLP using previously published techniques (Rogers GR, et al 2003, 2004, 2005). In brief, bacterial DNA was first extracted from the sputum samples. The DNA region of interest was then amplified, and cleaved using a restriction enzyme. The resulting segments of DNA were then separated by length using an automated DNA sequencer. This process generated profiles, comprised of different bands, each derived from a different individual bacterial species.

**Results:** 248 different bacterial species were identified, with a mean of 13.3 (7.9) species per sample. For each sample, bacterial species were ranked in order of relative prevalence within the sample (fig).

**Discussion:** With a mean of 13.3 species per sputum sample the bacterial diversity in CF sputum is higher than identified by traditional culture based techniques. Although *P. aeruginosa* is the most dominant species in 61% of samples, species not traditionally associated with CF lung disease were the most dominant species in 25% of samples, and the second most dominant in 90% of samples. This would suggest that the bacterial community in CF sputum is more diverse than previously recognised, and that organisms not previously considered significant CF pathogens may have important roles to play in what appears to be a complex ecosystem.

**Conclusion:** Bacterial diversity in the CF lung, as identified by T-RFLP, is far greater than previously recognised. Although *P. aeruginosa* is the most dominant species, non-CF organisms are more prevalent. The relative significance of each of organisms identified has yet to be determined.

**S094 OUTCOME OF BURKHOLDERIA CEPACIA COMPLEX PULMONARY INFECTION IN PATIENTS WITH CYSTIC FIBROSIS 1990-2004**

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**Introduction:** *Burkholderia cepacia* complex (*Bcc*) pulmonary infection has been associated with a poor prognosis for patients with cystic fibrosis (CF). It has been demonstrated that clinical course after colonisation with cepacia can vary significantly between individuals. Previous researchers have tried to identify specific risk factors associated with a worse prognosis. The clinical outcome of 111 patients colonised with *Bcc* was assessed during a 15-year period.

**Methods:** Lung function, clinical features and microbiology were recorded for 111 patients until death or the end of follow up. The number of patients who progressed from initial to chronic infection were assessed as well as those who had multiresistant strains. The presence of diabetes and the use of antibiotics and steroids were also documented. Full data were not available in all patients.

**Results:** Age and sex were unrelated to outcome. Seventy five per cent (67/89) of patients infected with *Bcc* already had moderate to severe lung disease at diagnosis; 42% (34/81) had multi-resistant strains and 68% had persistent infection. The annual incidence was 0.3–3.8% and the prevalence 3.7–9.2%; 63 patients died. Compared with a previous study in our Unit, the incidence has decreased over the last ten years, while prevalence and the number of deaths have decreased over the last six years. The mean survival was 49 months compared with 11 months in the previous study, however the present study is longer and with larger numbers of patients.

**Conclusions:** Advanced lung disease at acquisition carries a worse five-year clinical outcome (p = 0.001); presence of multi-resistant strains as initial isolates (p = 0.043) and previous use of steroids, (p = 0.007) seems to be associated with a less favourable prognosis. Antibiotic prophylaxis does not lead to the emergence of multi-resistant strains. Patients with advanced CF, multi-resistant strains and persistent *Bcc* infection had a worse outcome. The incidence of *Bcc* appears to be declining.


**S095 FIRST ISOLATION OF PSEUDOMONAS AERUGINOSA: FAILURE OF ERADICATION TREATMENT ASSOCIATED WITH A CLONAL STRAIN**

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**Background:** Early treatment of newly acquired Pseudomonas aeruginosa (*Pa*) infection has a success rate of approximately 80%. (UK CF Trust Infection Control Group 2004.) Suggests that organisms not previously considered significant CF pathogens may have important roles to play in what appears to be a complex ecosystem.

**Objectives:** To identify total bacterial community present in CF sputum. To determine the prevalence of bacterial species not traditional associated with CF lung disease.

**Methods:** 102 whole sputum samples from 34 adult CF patients were analysed by T-RFLP using previously published techniques (Rogers GR, et al 2003, 2004, 2005). In brief, bacterial DNA was first extracted from the sputum samples. The DNA region of interest was then amplified, and cleaved using a restriction enzyme. The resulting segments of DNA were then separated by length using an automated DNA sequencer. This process generated profiles, comprised of different bands, each derived from a different individual bacterial species.

**Results:** 248 different bacterial species were identified, with a mean of 13.3 (7.9) species per sample. For each sample, bacterial species were ranked in order of relative prevalence within the sample (fig).

**Discussion:** With a mean of 13.3 species per sputum sample the bacterial diversity in CF sputum is higher than identified by traditional culture based techniques. Although *P. aeruginosa* is the most dominant species in 61% of samples, species not traditionally associated with CF lung disease were the most dominant species in 25% of samples, and the second most dominant in 90% of samples. This would suggest that the bacterial community in CF sputum is more diverse than previously recognised, and that organisms not previously considered significant CF pathogens may have important roles to play in what appears to be a complex ecosystem.

**Conclusion:** Bacterial diversity in the CF lung, as identified by T-RFLP, is far greater than previously recognised. Although *P. aeruginosa* is the most dominant species, non-CF organisms are more prevalent. The relative significance of each of organisms identified has yet to be determined.

**S096 DEVELOPMENT OF SPUTUM CALPROTECTIN AS A BIOMARKER OF CYSTIC FIBROSIS LUNG DISEASE ACTIVITY: EVIDENCE FROM CROSS SECTIONAL AND LONGITUDINAL STUDIES**

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**Background:** It is difficult to monitor accurately the therapeutic benefit of treatments in cystic fibrosis (CF). We have demonstrated the presence of a number of protein biomarkers in CF sputum using SELDI TOF (Surface enhanced laser desorption time of flight) mass spectrometry. The most abundant of these markers are Calgranulins A and B which form the biologically active heterodimer Calprotectin. Specialised proteomics techniques are a valuable research tool but have limited clinical application. We have therefore developed an in house ELISA to measure sputum Calprotectin which allows us to differentiate between CF and control subjects. We sought to demonstrate the utility of this biomarker in...
the monitoring of infective exacerbations in CF. Furthermore we have compared this to an accepted measurement of inflammation in CF sputum, interleukin 8 (IL8).

**Methods:** Twenty six patients attending the Scottish Adult CF centre were recruited at the time of an exacerbation requiring intravenous antibiotics. Sputum was collected at the start and end of antimicrobial therapy. Sputum Calprotectin and IL 8 levels were assayed with ELISA. Sputum was also assayed with SELDI TOF in tandem.

**Findings:** Sputum Calprotectin levels decreased significantly with antibiotic therapy from 661.9 (496–1039) µg/ml to 379.8 (206–640) (median (interquartile range)) at p = 0.011. Sputum IL8 also decreased but this did not reach statistical significance. 32.87 (19.70–54.86) pg/ml to 22.55 (10.74–60.46) at p = 0.1. Protein profiles of Calgranulins A and B on SELDI TOF also changed accordingly with therapy.

**Interpretation:** These data suggest that Calprotectin levels in sputum reflect the underlying level of inflammation in the CF lung, and may be measured by ELISA as well as SELDI TOF. Proteomics identified sputum markers, such as Calprotectin have a potential application to the assessment of new therapies for CF lung disease. In this study group we demonstrate Calprotectin to be a more significant marker of change in lung inflammation during an exacerbation than IL8. Furthermore this study highlights the importance of longitudinal evaluation in the assessment of new biomarkers.

**S097 ALTERATIONS IN BONE METABOLISM OCCUR AT TIMES OF INFECTIVE EXACERBATION IN ADULTS WITH CYSTIC FIBROSIS**

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Osteoporosis is a disease characterised by low bone mass, bone fragility and an increased risk of fracture. Approximately 25% of cystic fibrosis (CF) adults have low bone mineral density and CF disease severity is the most consistent correlate. Aris et al (AJRCCM 2000) have shown a temporal relationship between inflammatory markers and biochemical markers of bone resorption during CF exacerbations. More recently, Haworth et al (Thorax 2004) have shown interleukin-6 to be an independent predictor of change in bone mineral content over one year in adults with CF.

Inflammation can affect both the formation and activity of osteoclasts and associated alterations in cytokine levels have been implicated in the pathogenesis of osteoporosis, and bone disease associated with rheumatoid arthritis and inflammatory bowel disease. Therefore, variation in levels of cytokines at times of infection (infectious exacerbations) may induce a burst of resorptive activity.

The aim of this study was to investigate levels of receptor activator of nuclear factor-kB ligand (RANKL), osteoprotegerin (OPG) and bone turnover markers (osteocalcin and NTx) before (baseline), during (day 1 and 8) and after (day 42) in patients with CF during infective exacerbations treated with intravenous antibiotics.

Twenty-four patients (14 male, mean (SD) age 24.7 years (6.0), FEV1 48.8% of predicted, BMI 21.3 kg/m²) were recruited at the time of an exacerbation requiring intravenous antibiotics. Twenty-six patients attending the Scottish Adult CF centre were recruited at the time of an exacerbation requiring intravenous antibiotics. Twenty-four patients (14 male, mean (SD) age 24.7 years (6.0), FEV1 48.8% of predicted, BMI 21.3 kg/m²) were recruited at the time of an exacerbation requiring intravenous antibiotics. Twenty-six patients attending the Scottish Adult CF centre were recruited at the time of an exacerbation requiring intravenous antibiotics.

**Findings:** Serum RANKL levels increased significantly by day 14 (p = 0.05) but increased by day 42. OPG levels at baseline were lower than control levels (p<0.05) but increased by day 14 (p<0.05), but had decreased by day 42 to a level comparable to baseline.

**Interpretation:** These data further support the hypothesis that the systemic response to infection results in alterations in bone metabolism in patients with cystic fibrosis. Imbalances in the RANKL/OPG ratio are likely to affect both osteoclast formation and activity, leading to increased bone resorption and hence contributing to bone disease.

**Assessing effectiveness of pulmonary rehabilitation**

**S098 IN-PATIENT PULMONARY REHABILITATION DURING ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: IMMEDIATE EFFECTS ON HEALTH STATUS AND EXERCISE CAPACITY**

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**Aim:** The deleterious effect of hospitalisation in patients with chronic obstructive pulmonary disease (COPD) has been well documented. Inpatient pulmonary rehabilitation (PR) may be able to prevent the observed physical decline. This pilot study evaluates the impact of an in-patient PR programme on the exercise capacity and quality of life, in patients during an acute exacerbation of their COPD.

**Methods:** Fifty patients with COPD were admitted for an acute exacerbation of their disease (27 male, mean (SD) FEV1 0.75 (0.25), % predicted FEV1 38 (12.1) %, age 69.9 (7.96) years) participated in an in-patient PR between May 2005 and May 2006. The programme consisted of educational talks 3 times a week and exercise sessions (endurance and strength) supervised 5 times a week in a gym located on an acute respiratory ward. Prior to commencing the programme patients completed the self reported Chronic Respiratory Questionnaire (CRQ-SR) and performed an incremental and endurance shuttle-walking test, these were repeated at time of discharge from hospital.

**Results:** The results of a paired t-test are shown in the table below. These demonstrate a statistically significant improvement in all of the outcome measures, except the dyspnoea component of the CRQ-SR. The other components of the CRQ-SR exceeded the minimum clinically important difference. There were no adverse events during the exercise sessions.

**Conclusions:** Inpatient PR during acute exacerbation appears to have a significant benefit upon health status and exercise capacity. These pilot data suggest the PR in this population is safe and effective and warrants further investigation.

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>ESWT (secs)</th>
<th>ISWT (m)</th>
<th>CRQ - dyspnoea</th>
<th>CRQ - emotion</th>
<th>CRQ - fatigue</th>
<th>CRQ - mastery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre PR</td>
<td>58.4 (71.8)</td>
<td>34.6 (58.4)</td>
<td>1.97 (0.98)</td>
<td>3.47 (1.25)</td>
<td>2.48 (0.96)</td>
<td>3.13 (1.28)</td>
</tr>
<tr>
<td>Post PR</td>
<td>350.58 (267.2)</td>
<td>76.8 (17.4)</td>
<td>2.37 (1.50)</td>
<td>4.32 (1.12)</td>
<td>3.36 (1.13)</td>
<td>3.84 (1.08)</td>
</tr>
<tr>
<td>Mean change</td>
<td>292.18 (368.96–215.3)</td>
<td>42.2 (61–22)</td>
<td>0.39 (0.79–0.00)</td>
<td>0.84 (1.17–0.52)</td>
<td>0.88 (2.30–0.53)</td>
<td>0.71 (1.03–0.38)</td>
</tr>
</tbody>
</table>

*p<0.05

**Abstract S098**

| Programme: | From February 2005 the INSPIRE Team of East Lincolnshire Primary Care Trust implemented a Primary Care Based Pulmonary Rehabilitation Programme. This ran twice weekly for 8 weeks combining

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exercise and education with a multi-disciplinary team. All patients with a formal diagnosis of COPD, on optimised therapy, and who present with functional disability related to breathlessness, were accepted onto the programme. 76 patients (mean age 69.25 male) were offered a place on the programme after assessment. 75 accepted of which 60 completed with a mean FEV1 of 40.1% of predicted value.

**Results:** The mean improvement in ISWT was 50.5 m (90–200). 80% of the group improved of which 67% improved beyond the Minimal Clinical Important Difference (MCID) of 50 m. Mean HADS for those who completed improved by 0.52 for Anxiety and 1.39 for Depression. The mean score for each domain of the CRQ also increased beyond the MCID of 0.5 for all those completing the programme (Dyspnoea 0.71, Mastery 0.67, Emotion 0.60, Fatigue 0.76). Interestingly, the patients not completing the course demonstrated lower mean scores in all domains of the CRQ compared with those that completed. Of those completing the programme and performing an Endurance Shuttle Walk Test, 42% (25/60) met the criteria for Ambulatory Oxygen Assessment.

**Conclusion:** Delivering a Primary Care Based Pulmonary Rehabilitation Programme has yielded in results that mirror those previously published for outpatient programmes (Withers et al., 1999; Williams et al., 2003). They can also improve accessibility for the patients, thus being congruent to what is important to them, at baseline and reassessment post PR. The Minimal Clinical Important Change (MCIC) for COPM is 2.

**S101**

**FACTORS AFFECTING COMPLETION OF PULMONARY REHABILITATION PROGRAMMES IN SOUTH EAST LONDON**

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**Introduction:** Pulmonary rehabilitation (PR) is the most effective non-pharmacological intervention for chronic obstructive pulmonary disease (COPD). The physiological, psychological, and quality of life benefits of PR are well described (Troosters et al. Am J Respir Crit Care Med, 2005), but are limited by non-adherence rates of 30–40% (Garrod et al. Eur Respir, 2006). Identification of risk factors for non-adherence, followed by appropriate support, is required to improve completion rates. Systematic recording of relevant variables at the time of initial assessment for PR at King’s College Hospital (KCH) has provided a large dataset that is available for such analysis.

**Methods:** We carried out a retrospective analysis of all PR referrals to KCH and its four community PR sites between 01/05/04 and 31/03/06, classifying patients as “completers” (completed 8 sessions), or “non-completers” (assessed and attended <8 sessions). Associations between non-completion and pre-PR demographic (age, sex), physiological (FEV1 % predicted (FEV1 %)), incremental shuttle walk distance (ISWD)), psychological (Hospital Anxiety and Depression Score (HADS)) and quality of life (Chronic Respiratory Questionnaire (CRQ)) variables were assessed by univariate, followed by multivariate, analysis.

**Results:** 327 patients started PR. 244 (74.6%) completed PR and 83 (25.4%) did not complete PR. Non-completers had worse exercise tolerance, higher levels of anxiety and depression, and poorer quality of life than completers in univariate analysis (table), and were more likely to have probable (HADS >10) anxiety (27.0% v 47.0%, p = 0.001) and depression (19.7% v 32.5%, p = 0.02). Only HADS depression score (p = 0.02) and CRQ dyspnoea (p = 0.03) were associated with non-completion in multivariate analysis.

**Conclusion:** The PR non-completion rate in South East London remains high, despite favourable comparison with other figures. Depression was a significant risk factor for non-completion and could be a target for intervention.

**Abstract S101 Data presented as mean (SD)**

<table>
<thead>
<tr>
<th>% male</th>
<th>Age (years)</th>
<th>FEV1 %</th>
<th>ISWD (m)</th>
<th>CRQ-D</th>
<th>CRQ-E</th>
<th>CRQ-F</th>
<th>CRQ-M</th>
<th>HADS-A</th>
<th>HADS-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>43.0</td>
<td>68.1 (10.1)</td>
<td>50.4 (21.0)</td>
<td>209.5 (135.2)</td>
<td>12 (3.77)</td>
<td>6.73 (8.04)</td>
<td>4.32 (3.37)</td>
<td>5.48 (4.08)</td>
<td>8.30 (4.42)</td>
</tr>
<tr>
<td>NC</td>
<td>42.2</td>
<td>65.0 (12.0)</td>
<td>48.5 (19.9)</td>
<td>180.3 (135.2)</td>
<td>23 (2.70)</td>
<td>4.85 (5.67)</td>
<td>3.38 (2.69)</td>
<td>4.20 (2.68)</td>
<td>9.75 (5.09)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.89</td>
<td>0.41</td>
<td>0.56</td>
<td>0.03</td>
<td>0.001</td>
<td>0.01</td>
<td>0.001</td>
<td>0.001</td>
<td>0.03</td>
</tr>
</tbody>
</table>

C, completers; NC, non-completers; CRQ-D, CRQ dyspnoea; CRQ-E, CRQ emotion; CRQ-F, CRQ fatigue; CRQ-M, CRQ mastery; HADS-A, HADS anxiety; HADS-D, HADS depression.
The optimal strategy for maintaining the benefit of pulmonary rehabilitation has yet to be established. A community exercise scheme sponsored by the British Lung Foundation was developed in 10 different locations and the effectiveness assessed. The community exercise scheme was independent of health care professional input.

Methods: Two hundred and twenty five patients with chronic obstructive pulmonary disease (COPD) were recruited to participate (99 male, 96 females 29 missing data), mean age 68.4 (8.5) years, 26 patients were on LTOT. 107 patients had previously attended rehabilitation, mean time since graduation from a rehabilitation programme was 40 months. The programme consisted of weekly exercise sessions offered over 6 months. Sessions were supervised by local gym instructors. Prior to commencing the scheme patients completed the self reported Chronic Respiratory Questionnaire (CRQ-SR), Hospital Anxiety and Depression Score (HAD), and performed an incremental shuttle walking test. These were repeated at 8 weeks and 6 months.

Results: There were no adverse events during the exercise sessions. There was a small increase in SWT distance at 8 weeks from (mean, 95% confidence interval) 273.4 (243.8 to 302.9) m at baseline to 289.3 (263.3 to 315.3) m at eight weeks, this was not statistically significant. In the patients that completed the 6 month course the mean improvement from baseline was 68.2 (45.7 to 90.7) m (n = 85), this increased distance at 6 months was significantly higher than baseline and 8 weeks (p = 0.005). The HAD score showed a significant reduction at 8 weeks in both anxiety and depression (p < 0.05). At 6 months there were no further important improvements observed in either component. The CRQ-SR demonstrated a statistically significant improvement in dyspnoea, fatigue and emotion domain at 8 weeks (p < 0.05), but there were no further improvement at 6 months. The changes in the CRQ-SR did not exceed the minimum clinically important difference except in the dyspnoea domain.

Conclusions: The community exercise scheme supported by the British Lung Foundation appears very effective in not only maintaining but improving exercise performance. It appears that 6 months is required to maximise the effect of physical training. Changes in health status, anxiety and depression occur independently of changes in physical performance and appear to change early on in the programme. Overall this scheme appears to be worthwhile and warrants further support and investigation to establish the optimum maintenance regime.

Clinical and basic science of interstitial lung disease

Autoantibody profile rather than extent of skin disease predicts severity of pulmonary fibrosis in systemic sclerosis


Background: Pulmonary fibrosis in systemic sclerosis (SSc-PF) is associated with significant morbidity and mortality. It has been suggested that SSc-PF occurs predominantly in patients with diffuse cutaneous (dcSSc) rather than limited cutaneous (lcSSc) disease, and in patients carrying the anti-topoisomerase autoantibody (ATA, Scl70); screening in many centres is focused on these subgroups. In addition, the pattern of lung disease shows a marked variability with the extent of skin disease and pulmonary fibrosis. SSc-PF occurs predominantly in patients with diffuse cutaneous disease rather than limited cutaneous disease, and in non-ATA antibody subgroups, strengthening the case for regular screening in subsets previously thought to be minimally at risk. We have highlighted the central predictive role of ATA positivity. Finally, we have shown that the extent of skin and lung disease appear unrelated in this cohort.

The coagulation cascade in fibrotic lung disease progression: local expression of factor X is increased in the injured and fibrotic lung


Introduction: Extravascular pro-coagulant activity is increased in fibroproliferative disorders of the lungs. Circulating coagulation proteinases (usually of hepatic origin) such as factor Xa (FXa) can exert both pro-inflammatory and pro-fibrotic effects via activation of proteinase-activated receptors (PARs). Mice deficient for PAR1 are significantly protected from bleomycin-induced pulmonary fibrosis, indicative of a causative role for coagulation proteinases in this disease model.

Hypothesis: FX is expressed locally in the lung, and thus increases extravascular pro-coagulant activity and contributes to a pro-fibrotic microenvironment.

Results: Microarray analysis of mouse lung following bleomycin instillation revealed 481 genes with increased expression at 7 days, and 346 genes at 14 days compared with saline-treated controls. FX mRNA was detectable and increased twofold and fivefold at 7 and 14 days respectively (p < 0.05). Immunohistochemistry for FX showed a marked increase in FX immunoreactivity post-bleomycin, localised to type II alveolar and bronchial epithelial cells and macrophages. Human tissue arrays containing 18 UIP lung specimens had a similar pattern of FX immunoreactivity. Real-time RT-PCR analysis of microdissected epithelial septate from 5 normal and 5 IPF human lung sections showed a significant fold increase in FX gene expression in IPF (p = 0.053). In vivo analysis confirmed that human bronchial (BEAS-2B) and type II alveolar (A549) epithelial cells express FX mRNA and protein.

Conclusions: Local upregulation of FX following lung injury is consistent with the existence of an inducible extravascular lung coagulation system. FX blockade may represent an attractive target for therapeutic intervention in a number of respiratory conditions associated with local FXa signalling and excessive matrix deposition.

T-bet expression in bronchoalveolar lavage cells from patients with sarcoidosis


Introduction: T-bet is a recently discovered member of the T-box transcription factor family and plays a central role in Th1 development by activating Th1 genetic programs and repressing Th2 cytokine synthesis. GATA-3 in contrast is a Th2 transcription factor promoting the Th2 cytokine secretion and inhibiting IFN-γ production through repression of IL-12 signalling. There is considerable interest in the role of Th1 and Th2 cells in the aetiology of sarcoidosis. We postulate that T-bet expression is increased in sarcoidosis leading to an exaggerated Th1 response which is responsible for granuloma formation.
**Methods:** In order to test this hypothesis 31 patients with sarcoidosis, 20 patients with IPF and 15 normal controls underwent bronchoscopy and bronchoalveolar lavage and real time PCR for T-bet, GATA-3, IFN-γ, and IL-4 performed on recovered cells using specific primer pairs. The same analysis was also performed on peripheral blood to determine whether any associated effects were systemic or confined to the lung environment.

**Results:** Results showed a significant increase in T-bet and interferon-γ mRNA in sarcoid lavage when compared to control subjects (p<br>0.01). The IPF patients also showed significantly lower levels of T-bet and interferon-γ mRNA when compared to control subjects. Interferon-γ was however significantly lower in the IPF patients when compared to the sarcoid group (p<0.05). There was no difference between any of the parameters measured in the peripheral blood sample.

**Conclusions:** These results provide evidence for a Th1 driven inflammatory process in both sarcoidosis and to some extent IPF. The higher levels of interferon-γ mRNA in the lavage fluid from sarcoid patients also provides evidence for a Th1 response. The lack of any significant differences between gene expression in peripheral blood suggests that these cells are localised within the lung.

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**Abstract S107**

**DETERMINANTS OF BRONCHOALVEOLAR ALVAGE FLUID CHEMOTACTIC ACTIVITY IN WEGENER’S GRANULOMATOSIS: THE INTERDEPENDENCE OF IL-1 AND IL-8**


**Introduction:** Neutrophil counts are persistently elevated in the bronchoalveolar lavage fluid (BALF) of patients with Wegener’s granulomatosis (WG), even when patients are in disease remission. Ongoing neutrophil recruitment and the release of neutrophil products may damage local lung tissue. The molecular determinants of neutrophilic inflammation within the lung in WG are unknown.

**Methods:** Under agarose chemotaxis was performed using neutrophils from a normal control and incubated with BALF from 31 WG and 6 normal controls. BALF chemokine levels were measured by Luminex array and myeloperoxidase by colorimetric assay. WG activity was determined using the BVAS system.

**Results:** WG BALF had significantly elevated neutrophil %, MPO, IL-1β, IL-8 and G-CSF compared to controls (see table). The neutrophil % correlated with IL-1 (r = 0.59, p = 0.001) and IL-8 (r = 0.466, p = 0.012) but not with other chemokine levels.

**Conclusion:** Balchemotactic effect was increased in WG patients compared with normal controls (p<0.001). WG lavage during relapse had the greatest increase in chemotactic response (mean = 4.44 mm) compared to acute (3.53 mm) and remission (2.81 mm) groups and controls (1.734 mm). BALF chemotactic activity strongly correlated with IL-1β (r = 0.761, p = 0.001) and IL-8 (r = 0.64, p = 0.012) but not with other measured chemokine levels. To ascertain the relative importance of IL-1β and IL-8 in determining the chemotactic response, experiments were repeated using neutralising antibodies and a CCXR2 antagonist. Both anti-IL-1β and anti-IL-8 antibody inhibited BALF chemotaxis by 80% (p = 0.001). The combination of anti-IL-1β and anti-IL-8 or CCXR2 antagonist virtually abrogated (95%, p = 0.001) the chemotactic potential of BALF. To determine any interrelationship between IL-1β and IL-8 in our system, their effects were blocked with anti-IL-1β and anti-IL-8. The chemotactic effect of IL-1β was significantly blocked by anti-IL-8 (91%, p = 0.004) suggesting that IL-1β chemotactant actions are IL-8 dependent.

**Conclusion:** Our data show that even during remission WG BALF is a stronger neutrophil chemotactant than normal BALF with a resulting increase in the neutrophil product MPO. Neutrophilic chemokines are elevated in the BALF of WG patients compared with normal controls. IL-1β and IL-8 are the predominant determinants of neutrophil chemotactic activity in WG BALF. IL-1β appears to have its effects via IL-8 and the CCXR2 receptor. Anti-CCXR2 therapy may have potential to limit neutrophilic inflammation in patients with WG.

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**Abstract S108**

**THE FREQUENCY OF OCCURRENCE OF CT FEATURES OF DIFFUSE PARENCHYMAL LUNG DISEASE IN SECONDARY CARE**

F. A. Woodhead1, J. Curtin2, B. D. W. Harrison3, 1Specialist Registrar, Eastern Deanery, 2Norfolk & Norwich University Hospital, 3formerly at Norfolk & Norwich University Hospital, UK

**Introduction:** Over the last decade there has been an increasing use of thoracic CT to help diagnose diffuse parenchymal lung disease (DPLD). To our knowledge no published studies have examined the frequency of occurrence of CT features of DPLD in an unsellected population.

**Methods:** A retrospective search was made of thoracic CT reports at the Norfolk & Norwich University Hospital (NNUH) over a 2 ½ year period from June 2001 to December 2003 looking for diagnostic labels and radiological features of DPLD. The NNUH is a secondary hospital with a
catchment area of 750,000 people in the East of England. On the basis of referral source (rheumatologist vs chest physician), report diagnosis or radiological features (pleural disease or mosaic attenuation) disease likely to be secondary was classified as "Connective Tissue Disease" (CTD), "Asbestosis" or "HP/RBILD". All other cases were thought to be primary, either "IPF" if this or UIP was thought the likely diagnosis with no differential or otherwise "IIP" (Idiopathic Interstitial Pneumonia). The frequency of emphysema was recorded as was the age, spirometry and gas transfer and frequency of biopsy. Incident cases were those first diagnosed during the study period. Prevalent cases were those identified still living on the final day of the study.

Results: A total of 232 cases were identified. 183 were prevalent and 172 incident. Overall prevalence was 24.4/100,000 with a maximum of 214/100,000 men aged 80-84 and 106/100,000 women aged 85-89. Overall incidence was 9.1/100,000/year, highest at 71/100,000 men/year and 48/100,000 women/year aged 85-89. Patients with CTD had better lung function but there were no other physiological differences between groups.

Conclusions: Radiological features of DPLD are common in secondary care, especially with increasing age. Average age is higher than in the BTS CFA study Mean age of CTD and HP/RBILD was lower than other care, especially with increasing age. Average age is higher than in the TORCH was a 3 year, double blind, placebo (usual care)

Therapeutic approaches to COPD management

The TORCH (TOWARDS A REVOLUTION IN COPD HEALTH) STUDY: SALMETEROL/FLUTICASONE PROPIONATE IMPROVES QUALITY ADJUSTED SURVIVAL OVER THREE YEARS

A. Briggs1, G. Hlick2, G. Lozano-Ortega3, M. Spencer4, J. Vestbo5, P. Calverley6, on behalf of the TORCH investigators. 1University of Glasgow, Glasgow, UK; 2University of Pennsylvania, Philadelphia, US; 3Oxford Outcomes Ltd, Vancouver, Canada; 4GlasoSmithKline, Greenford, UK; 5Wythenshawe Hospital, Manchester, UK; 6University Hospital, Liverpool, UK

Background: TORCH was a 3-year, double-blind, placebo (usual care) controlled multicentre trial of 6112 (ITT population) patients: salmeterol (SAL) 50 mg (n = 1521), fluticasone propionate (FP) 500 mg (1534), salmeterol/fluticasone propionate (SFC) 500/50 (1533), or placebo (PL) (1524). The primary aim was to investigate the effect of SFC on all cause mortality over 3 years and it was shown that SFC reduced the risk of death by 17.5% versus placebo (p = 0.052 adjusted for interim analysis). Here we explore differences between treatment arms in terms of quality adjusted survival.

Methods: Health related quality of life (HRQoL) was measured at baseline and at approximately six month intervals using the St George’s Respiratory Questionnaire (SGRQ) and the EQ-5D generic utility instrument (collected in 22 countries n = 4114). Quality adjusted survival time with each treatment over the 3 year study time was calculated by integrating the quality of life score with the probability of survival. The SGRQ score was transformed to a 0–1 scale by reversing the 0–100 scores and dividing by 100. Missing values due to withdrawal were imputed using a previously published method (Briggs et al. Value Health 2006;9:227–35.) that imputes from observed values with a similar propensity to be missing.

Results: The propensity method indicated that withdrawal was associated with lower health status. The table shows the estimated quality adjusted survival time (95% CI) following imputation for each of the treatment arms of the trial, for the subsample that provided EQ-5D data. Conclusions: Results show a significant benefit of treatment in terms of quality adjusted survival, with the greatest increases in the SFC group. It is important to account for the informative nature of withdrawal and results are sensitive to this. SGRQ results provide an interesting comparison in terms of the difference between treatments based on a disease specific HRQoL instrument. However, the EQ-5D results have the advantage of representing Quality Adjusted Life Years, the preferred measure for economic appraisal.

Abstract S109

<table>
<thead>
<tr>
<th></th>
<th>SGRQ (n = 4114)</th>
<th>EQ-5D (n = 4114)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.444 (1.414 to 1.467)</td>
<td>2.007 (1.967 to 2.025)</td>
</tr>
<tr>
<td>SAL</td>
<td>1.474 (1.463 to 1.497)</td>
<td>2.038 (2.003 to 2.056)</td>
</tr>
<tr>
<td>FP</td>
<td>1.476 (1.461 to 1.493)</td>
<td>2.058 (2.049 to 2.083)</td>
</tr>
<tr>
<td>SFC (SAL+FP)</td>
<td>1.561 (1.544 to 1.568)</td>
<td>2.139 (2.104 to 2.154)</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001
tensions lead to CO₂ retention, CO₂ retention is associated with acidosis, and acidosis is associated with death.

**FUNCTIONAL STATUS MEASUREMENT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE VALUE OF THE FUNCTIONAL STATUS DOMAIN OF THE CLINICAL COPD QUESTIONNAIRE**

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**Introduction:** Improvement of HRQoL is an important treatment goal in COPD; the assessment of health status is therefore relevant for caregivers and for the patient, both in daily clinical practice as well as in research setting, short and validated outcome measures are needed. The Clinical COPD Questionnaire (CCQ) is a recently introduced short 10-item validated health status questionnaire which contains three domains: symptoms, functional status, and mental status. The functional status of a patient is one of the main determinants of health status and improving functional physical capacity by itself is a major treatment goal.

**Purpose:** To assess the value of the functional status domain of the CCQ in measuring functional status of COPD patients.

**Methods:** Datasets of two studies were re-analysed. Dataset 1: 88 COPD patients completed the CCQ before lung function assessments and after 2 weeks this was repeated and a global rating of change was assessed. Dataset 2: 210 COPD patients, hospitalised because of an acute exacerbation, completed the CCQ at days 1–7 and at day 42. Day 42 data were used for the current analysis. A validation process similar to the validation of the total CCQ was performed. We measured floor and ceiling effects, internal consistency using Cronbach’s α and test-retest using the Intra Class Coefficient (Study 1). We hypothesised that the CCQ functional domain score correlated stronger with SGRQ activities using the Intra Class Coefficient (Study 2). We furthered that the BORG dyspnoea scores would correlate only modestly with the individual (functional status related) CCQ items (Study 2).

**Results:** Minimal (floor) and maximal (ceiling) scores occurred in 8% and 0% of the 88 patients respectively. Cronbach’s α was 0.89. The ICC was 0.82. The a priori hypotheses were confirmed (see table).

**Conclusion:** CCQ functional status domain shows good measurement properties and can be used to measure functional status in COPD patients.

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**S112 A RANDOMISED STUDY OF TIOTROPium RESPimat SOFT MIST INHALER VERSUS IPRATROPIum PMDI IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

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**Background:** Tiotropium provides prolonged muscarinic M₃ receptor blockade and sustained bronchodilatation with once-daily dosing. The aim of this study was to compare the efficacy and safety of tiotropium, delivered via Respimat Soft Mist Inhaler (SMI), an innovative propellant-free device, with ipratropium pMDI and placebo in patients with chronic obstructive pulmonary disease (COPD).

**Methods:** Two identical, 12-week, randomised, double dummy, placebo controlled studies were performed in 64 centres worldwide. COPD patients were randomised to inhaled tiotropium 5 μg or 10 μg Respimat SMI, ipratropium 36 μg pMDI or placebo. The primary endpoint was the change in morning pre-dose FEV1 after 12 weeks of treatment. Secondary endpoints included FVC, PEFR, rescue medication use, COPD symptom scores, and the Physician’s Global Evaluation (PGE). Safety was monitored from adverse events.

**Results:** The majority of patients (n = 719) were male, with a mean age of 64 years, and mean FEV1 (% predicted) of 40.7%. At week 12, tiotropium (both doses) significantly improved the primary endpoint compared with ipratropium or placebo (table). The increases in peak FEV1, FEV1 AUC(0-6h), and FVC for both tiotropium doses were superior to placebo and ipratropium. PEFR was significantly improved after tiotropium (large: p < 0.001 vs placebo and ipratropium). Rescue medication use was significantly reduced for all active treatments (largest: p = 0.03 vs placebo). Both doses of tiotropium significantly improved the ‘tightness of chest score’ compared with ipratropium and the PGE score compared with placebo. Adverse events were comparable across groups. Dry mouth was more common with tiotropium (8.3% (5 μg) and 10% (10 μg)) than ipratropium (3.9%) or placebo (2.2%).

**Conclusion:** Tiotropium (5 μg and 10 μg), delivered via Respimat SMI, significantly improved lung function compared with ipratropium pMDI and placebo. Tiotropium Respimat also provided a number of symptomatic improvements over ipratropium pMDI.

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**S113 PREDICTING AND PLANNING END OF LIFE CARE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: MRC SCORE IS AN IMPORTANT MARKER**

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**Introduction:** Predicting survival time for patients with severe chronic obstructive pulmonary disease (COPD) is difficult, despite there being a number of well validated prognostic factors. FEV₁ is reported to be the best single correlate of mortality (Celli et al, 1995). Although dyspnoea has been shown to be even more discriminating than FEV₁ in terms of mortality (Nishimura et al, 2002), MRC score is not usually included as a prognostic indicator. We characterised a group of patients who died whilst under a Chronic Respiratory Support (CRS) team. Patients under CRS have, by entry criteria, had ≥2 admissions for exacerbations of COPD in 1 year, and the annual mortality of this group is high (16%). We assessed whether known prognostic indicators were predictive of death, and therefore useful in guiding the most appropriate time to introduce end of life planning.

**Method:** Case notes of 29 CRS patients with COPD who had died over a 24 month period (December 2003–December 2005), were retrospectively analysed and compared with 29 living COPD patients under CRS over the same period. Factors analysed included: age, FEV₁, body mass index (BMI), number of exacerbations in the year prior to death, Medical Research Council (MRC) Dyspnoea score, smoking status, use of long term oxygen therapy (LTO) and optimised resting respirometry, comorbidities, and social factors, including living alone and alcohol excess. The rapidity and place of death was assessed for deceased patients, as was the use of advance directives. A further case-note analysis of COPD patients, not under CRS, (n = 16) who had died during the same period, was also undertaken.

**Results:** There were no significant differences in age, FEV₁, BMI, number of exacerbations, use of LTO or optimised respirometry, smoking status, comorbidities or social factors between patients who had died and patients alive under CRS. However, deceased CRS patients had an MRC score of 4.3 (0.17) (mean (SEM), n = 29), which was significantly (p = 0.005 high) higher than the MRC score of living CRS patients which was 3.8 (0.13) (n = 29). In the group that died, there was no documentation of a living will despite the fact that only 8 deaths (24%) were sudden (that is, the
Training tomorrow’s chest physicians

M. Thririmaran, D. C. Currie. Dewsbury & District Hospital, MidYorkshire Hospitals NHS Trust, UK

Specialist training in the UK has changed over the 10 years. Since the introduction of Calman training programme there has been numerous changes to the structure of training programmes. We cannot ignore the facts that our training is based on service provision. Supervision and training by experienced consultants is vital to how and what we learn. All respiratory Specialist Registrars (SpR’s) in Yorkshire region were asked to fill in a questionnaire as a part of their preparation for the annual assessment (RITA) in June 2005. The question from the Programme Director was phrased as follows: “I am keen to find out in which part of your SpR experience you are learning the most. Please estimate the percentage of your SpR learning in each of the following areas …”. The trainees were given five potential categories for learning.

Results: See table.

Conclusion: Respiratory trainees in Yorkshire report that nearly two thirds of their training is based on hands-on experience, especially working closely with the consultants. Those involved in organising SpR training should take note of this important finding. Each year there are more requests for SpR’s to take time out for structured training days and for self-directed learning. It is important that training through experience is given a higher profile and not further compromised.

BTS QUESTIONNAIRE SURVEY OF FLEXIBLE TRAINING AND ATTITUDES SURROUNDING FLEXIBLE TRAINING AND WORKING IN SPECIALIST REGISTRARS IN UK


A questionnaire survey of training and working patterns and associated attitudes was carried out in all respiratory specialist registrars in UK in March 2006. This was a second survey following a survey in 2003. In total 286/507 (56%) responded, median age 32 years (26-45), 120/286 (42%) female, 166/286 (58%) male. There were 23/286 (8%) part time trainees, 22F:1M, (8% in 2003, all female). The median number of sessions worked was 6 (5-8) and 23/13 (18%) were in a slot share, 15/23 (65%) supernumerary, 4/23 (17%) in a whole time post and 1/23 (4%) in research. For these part time trainees 13% intended to return to full time training at some point and 87% (55% in 2003) had no such intention whereas 52% (89% in 2003) intended not to work full time as a consultant but 22% intended to return to full time work in <5 years and 26% in 5-10 years. There were 263 full time trainees and 190/263 (73%) had no intention of training flexibly of which 21% were female, 20 (7.6%) definitely planned to train flexibly in the future of which 90% female, and 51 (19.5%) probably planned to train flexibly of which 76% were female. As a consultant 138/263 (53%) did not plan to work flexibly (12% female), and 60/263 (23%) did plan possibly to work flexibly (58% female), 45/263 did plan probably to work flexibly (74% female), and 19/263 (7.3%) did plan definitely to work flexibly (74% female) as a consultant. Five trainees had been flexible and returned to full time work. All the trainees were asked if they would feel welcome, neutral, worried or resist if a trainee colleague was to be supernumerary, slot share or whole time. There was a substantial swing from welcome 193/286 (67%), worried 16/286 (5.6%) when the trainee colleague

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<table>
<thead>
<tr>
<th>Area for learning SpR year</th>
<th>Structured teaching, courses and society meetings</th>
<th>Working closely with consultants on a day to day basis</th>
<th>During other service work (eg working independently on call)</th>
<th>Self directed private study</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 1, 2</td>
<td>21.7</td>
<td>37.5</td>
<td>24.2</td>
<td>14.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Years 3, 4, 5</td>
<td>19.6</td>
<td>43.1</td>
<td>24.6</td>
<td>11.8</td>
<td>0</td>
</tr>
<tr>
<td>All SpRs</td>
<td>20.6</td>
<td>40.5</td>
<td>24.5</td>
<td>13.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Thirty of the 31 SpRs answered the question. Seven trainees were females. Questionnaires were coded for sex and year of training.
was to be in a supernumery post, to welcome 128/286 (45%), worried 54/286 (19%) when in a slot share post, to welcome 72/286 (25%), worried 118/286 (41%) when in a whole time post. In total 32/286 (11%) reported coming across bad attitudes to flexible training while 65/286 (23%) reported good attitudes. In total 18 trainees reported having considered giving up respiratory medicine due to their experiences and 99/286 (35%) indicated that they would leave if they could not start flexible training when they wished.

Conclusions: Flexible training remains at 8% with 42% of trainees female. A high proportion of full time trainees, predominantly female, expected to train flexibly at some time and to work flexibly as a consultant but not necessarily for their entire career. The trainees reported some support but also overt criticism and the type of post and organisation of the posts seems likely to be important. A failure to allow for flexible training/work will lead to many trainees leaving respiratory medicine.

**S117 PLOTTING THE DECLINE IN UK BASED RESPIRATORY RESEARCH: AN INTERNET BASED ANALYSIS**

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There is genuine concern among UK based respiratory clinicians that research opportunities in UK based institutions have been on the decline over the past two decades. Reasons for this are probably multifactorial but direct supportive evidence at best anecdotal; further, whether the same is true of research from other countries etc is uncertain. Using an internet based research we have analysed citations (approximately 80% from each journal source and excluding editorials, conference abstracts, and letters) taken at four yearly intervals back to 1989 and drawn the analysis from six of the top 10 English language respiratory journals reporting the highest impact factors in 2004. Using these methods as a surrogate for the amount of research being undertaken, as anticipated, there has remained a dominance of publications from the USA. Surprisingly, however, collective evidence represented as a percentage of the total analysed indicates a downward comparative trend (see fig) not only in published research from the UK (from 16.6% to 10.6%) but also from the USA (52.4% to 34.5%). During this period representation both in proportion of the total and absolute numbers increased from Asia (8.3% to 13.8%) but more so from Europe (18.9% to 35.6%). Specifically analysing the UK citations, major falls have predominantly been in the traditional non-US based journals with publications in Thorax (60%; down to 35%) and Respiratory Medicine (75% down to 13%) with less of an impact from the European Respiratory Journal. Specific reasons for these observations can only be speculated but probably include both scientific merit and editorial direction as well as market influences with wider distribution and readership. Whether the decline particularly in UK based research is in part also due the lesser demand on clinicians in training or more specifically simply funding issues cannot necessarily be deduced but both are likely to be important determinants.

Abstract S117 Table 1

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<tbody>
<tr>
<td>UK</td>
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<td>50</td>
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<td>Europe</td>
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<tr>
<td>Other</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
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</table>

Methods: Attendance at outpatient clinics, and bronchoscopy list and the number of bronchoscopies undertaken by SpRs were used as markers of training. Work days missed due to annual leave, study leave and on-call commitments were calculated. A comparison was made between the periods October 2002–03 and October 2004–05. The change over, to EWTD compliant rotas occurred in the intervening year. Data was collected from a teaching hospital, and a district general hospital (DGH) within Yorkshire, from hospital files and SpR training records. The teaching hospital rota changed from a 3 month general medicine partial shift to full shift. The teaching hospital SpR continued to spend 9 months each year on a non-resident specially on-call rota. The DGH changed from 1 in 6 on-call rota to 1 in 8 full shift, throughout the year. Full day educational events have replaced evening sessions.

Results: Missed working days, due to annual and study leave, on-call commitments including night shifts and compulsory rest days increased in both hospitals, the greater impact being in the DGH. Both hospitals demonstrated a reduction in SpR outpatient clinic attendance, bronchoscopy list attendance and bronchoscopies performed by SpRs. These reductions being greater in the DGH.

Conclusions: Specially training opportunities have been reduced by the change to EWTD compliant working patterns. This is likely to be compounded by further time constraints to be imposed in 2009. Action must be taken to enhance quality of training as quantity is reduced.

**S119 INTERESTS OF RESPIRATORY SPECIALIST REGISTRARS IN ASPECTS OF RESPIRATORY CRITICAL CARE**

H. Pattani, S. Wharton. Queens Medical Centre, Nottingham, UK

The Respiratory Critical Care Group is a subcommittee of the Education and Training Committee of the British Thoracic Society (BTS). This group is interested in the interface between Respiratory and Critical Care Medicine (CCM). The remit of the group is as follows:

- To recommend training requirements in CCM for Specialist Registrars (SpRs) in Respiratory Medicine
- To be a link between the BTS and the Intensive Care Society
- To develop research priorities in CCM
- To develop standards of care in this area
- To be a support group for BTS members practicing in the area.

In order to evaluate the current state of training in CCM for Respiratory SpRs the group sent out a survey to all SpRs registered with the BTS in May 2005. One of the aims of this questionnaire was to establish the level of interest in respiratory critical care amongst the trainees. There was an overall response rate of 54% (208/389). 69% of responders expressed an interest in developing a special interest in at least one area of respiratory critical care (intensive care, medical high dependency, non-invasive ventilation, weaning). 36% were interested in one area, 20% in two areas, 7% in three areas and 6% in all four areas. Looking at these areas individually; intensive care was considered an area of special interest by 19% of responders, medical high dependency by 33%, non-invasive ventilation by 57% and weaning by 3%.

Our survey data may be biased since those interested in respiratory critical care might be more likely to respond. However if it is assumed that all non-responders have no interest in respiratory critical care, 37%
of all Respiratory SpRs still have a special interest in at least one of these areas.

Our survey shows that a significant proportion of SpRs in Respiratory Medicine intend to develop a special interest in at least one aspect of respiratory critical care. This highlights the need for the development subspecialty training programs in the various aspects of respiratory critical care.

Basic mechanisms of lung disease

S120 RETINOIC ACID INDUCES ALVEOLAR REGENERATION IN THE ADULT MOUSE LUNG OF DIFFERENT OUTBRED MOUSE STRAINS

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Rationale: In emphysema the lung is unable to spontaneously regenerate lost alveolar tissue. Treatment with Retinoic Acid (RA) in rodent models of emphysema induces alveolar regeneration (Massaro GD, Massaro D. Am J Physiol 2000;278:L955–60). However some studies using different species and strains of animal have failed to show this effect (Fujita M et al. Thorax 2004;59:224–30). We have previously shown that Dexamethasone (Dex) treatment of newborn TO outbred strain mice disrupts alveolar development, causing substantial and permanent reduction in alveolar surface area (SA). Later RA treatment restores lung architecture to normal (Hind M, Maden M. Eur Respir J 2004;23:20–7). In order to determine whether this model of alveolar regeneration is strain-specific, our protocol was repeated with CD1 outbred strain mice.

Method: Male CD1 mice were all Dex-treated (0.4 mg/kg Dex in PBS, daily subcutaneous injection) from postnatal day 4–15 (P4–P15). From P46–57 animals received either RA (2 mg/kg in DMSO/oil) or 5xRA (10 mg/kg in DMSO/oil) or vehicle (DMSO/oil) by intraperitoneal injection. Control group received vehicle at both treatment points. All mice were sacrificed at P90 and lung morphology analysed (mean alveolar chord length (Lm), alveolar SA, lung volume (LV)).

Results: Dex-treated mice showed increased Lm and reduced SA and SA/LV compared with Controls, consistent with inhibition of alveolar septation during postnatal development. RA group results were similar, indicating failure of RA treatment to regenerate alveoli. 5xRA mice showed return of Lm, SA and SA/LV towards normal values, indicating successful alveolar regeneration (see table and figs 1–3). (Results from a repeat study in NIHs outbred mouse strain pending.)

Conclusion: The Dex-treated mouse model of emphysema is robust and repeatable in different strains. RA dose threshold for inducing alveolar regeneration is higher in CD1 mice, suggesting a difference in retinoid pharmacokinetics and/or metabolism between strains. However, RA-induced regeneration of mouse lung architecture in our model is not strain specific. This supports the theory that RA plays a central role in mammalian alveolar maintenance, repair and regeneration, and may provide a novel therapy for emphysema in the future.
cytology in the assessment of asthma and chronic obstructive pulmonary disease (COPD), and the fluid component of sputum contains important mediators and biomarkers of inflammation such as cytokines, but these proteins may be liable to the action of proteases such as neutrophil elastase. The presence of sputum iron in inflammatory lung disease is well documented. We therefore hypothesised that other metal ions present in sputum may be affected by airway inflammation and sought to assess their value as biomarkers for the investigation and monitoring of respiratory diseases.

Methods: Induced sputum was obtained from 20 healthy control subjects and a range of patients with inflammatory pulmonary diseases: 23 patients with cystic fibrosis (CF), 16 with (non-CF) bronchiectasis, 17 with asthma, and 23 with COPD. The fluid phase of processed sputum was subjected to inductively coupled plasma optical emission spectrometry to detect levels of iron, zinc, manganese and copper. 14 patients with CF were also followed through an exacerbation cycle, with sputum being collected and analysed at the beginning and end of antibiotic therapy.

Findings: Sputum zinc differentiated CF and bronchiectasis from controls with p < 0.001 at the following levels in µg/l: SE(α) control: 17.6 (3.0), bronchiectasis 112.1 (20.6), CF 150.0 (23.4), COPD 34.6 (7.1), asthma 36.2 (13.6). Sputum iron also differentiated CF and bronchiectasis from controls at p < 0.001. Levels of manganese and copper were numerically lower, but were elevated for CF (p < 0.05), bronchiectasis and asthma (p < 0.01) versus controls for manganese, and were elevated for all diseases (p < 0.05) compared with controls for copper. Sputum zinc level decreased significantly following antimicrobial therapy for an exacerbation in CF subjects from 236 µg/l (47.1) to 140 (30.1) (p < 0.0086).

Interpretation: Increased zinc and iron represent markers of airway inflammation in CF and bronchiectasis, but zinc has better potential to monitor disease activity. While there is a wealth of information about the significance of iron in lung inflammation, the role of fluctuating zinc remains unexplored.

Conclusions: Sputum zinc might be a valuable biomarker in the investigation and monitoring of respiratory disease.

S122 MURINE MESENCHYMAL STEM CELLS GENERATE OSTEOSARCOMA-LIKE LESIONS IN THE LUNG: IMPLICATIONS FOR STEM CELL THERAPY
S. Aguilar,1,2 E. Nye,3 D. Bonner,3 S. Jones,3 1Centre for Respiratory Research, Rayne Institute, London, UK; 2Cancer Research UK, London, UK

Rationale: Recent studies have demonstrated the ability of donor bone marrow stem cells (BMSC), both haematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) to engraft as alveolar epithelium after bone marrow transplantation (BMT). These observations raise the possibilities that circulating BMSC contribute to repair of the alveolar epithelium and that this process may be supplemented and manipulated with therapeutic benefit. Importantly however, several early studies have been difficult to reproduce and indeed recent studies have shown that subpopulations of BMSC may exacerbate lung damage. In addition, MSC populations that were previously thought to be ‘pure’ have now been shown to be contaminated with HSC. Our objective was to determine the engraftment potential of a highly purified population of MSC.

Methods: Murine MSC were selected based on CD45/Cd11b- adherent cells. They were infected with lentivirus expressing eGFP with 96% transduction efficiency. These cells were injected into mice following whole body gamma irradiation of 375 cGy to ablate their bone marrow. Lungs were harvested and fixed at 1, 2, 7, 14, and 28 days. The lungs were subsequently stained with antibodies against epithelial markers TFF1, AE1/3, T1-antitrypsin, SP-A, SP-D; and endothelial marker CD31; and bone markers. Results: Transplanted mice were sacrificed at 28 days owing to breathlessness. Donor derived bronchiolar epithelium and rare pneumocytes were identified by co-expression of eGFP and with specific markers. However, a large percentage of the lung parenchyma at 28 days after MSC transplant showed bone tumor formation explaining the breathlessness. Posterior karyotype analysis showed chromosomal instability in MSC at the time of injection (passage 4 or 5) but not at early passages.

Conclusions: MSC engraft into the lung after transplant but remain multi-potent with uncontrolled differentiation into inappropriate lineages causing fatality. This malignant transformation can be explained, at least partially, due to chromosomal abnormalities.

S123 STEPWISE INCREMENTAL CHANGES IN ADAM33 EXPRESSION DURING MOUSE LUNG DEVELOPMENT
H. M. Haitch, R. M. Powell, S. T. Holgate, D. E. Davies. The Roger Brooke Laboratories, Division of Infection Inflammation & Repair, University of Southampton, Southampton, UK


Methods: MF-1 mice were time mated and lungs were harvested by microdissection at embryonic day (ED) 11–19, postpartum day (PD) 1 and 8 and adult mice (AM) (n = 5–8). Samples were processed for mRNA analysis by RT-qPCR. To establish the most stable genes for normalising, control gene expression was measured in embryonic, postpartum and adult lungs. 12 normalising gene control kits were selected for analysis and the 3 most stably expressed “house-keeping genes” (HKGs) were determined by GeNorm analysis. These were used for normalisation of ADAM33 and α-smooth muscle actin (α-SMA) expression.

Results: The best HKGs for normalisation of mRNA expression in developing lung were found to be GAPDH, cytosome C1 and ATP synthase subunit. Using these HKGs, ADAM33 mRNA expression increased in 4 significant (all p < 0.002) steps during normal mouse lung development. These steps corresponded to the progression from the embryonic stage (ED11) to pseudoglandular stage (ED12–15), to the canalicular stage (ED16, 17), to the saccular alveolar stage (PD18) and to the adult stage (AM). The greatest increases in ADAM33 expression could be observed from ED11 to 12 and postpartum. The smooth muscle marker, α-SMA, showed a similar stepwise incremental pattern of expression.

Conclusion: ADAM33 is expressed at all stages of murine lung development. The marked increase in expression in the early stages of lung development and postpartum suggest that ADAM33 might be induced by tubular contraction that starts in the pseudoglandular stage around ED12/13 and mechanical stretch from breathing after birth. Polymorphisms in ADAM33 might be involved in mechanical stretch-induced abnormal bronchial smooth muscle development.

Funded by Asthma Allergy & Inflammation Research (AAIR) Charity (UK), British Lung Foundation (UK) and Roger Brooke Charitable Trust (UK).

Some of this work has been presented at the ERS 2006.

S124 IL-13 SIGNALING POLYMORPHISMS PREDICT ASTHMA AND ATOPY PHENOTYPES IN AN UNSELECTED POPULATION
G. A. Davies, M. Moller, D. Gopalakrishnan, P. Bikhchandani, S. Benjamin, M. Sansbury, M. B. Gravenor, J. M. Hopkin. School of Medicine, Swansea University, Wales, UK

Background: The interleukin(IL)-13 signaling pathway is central to the pathogenesis of asthma and atopy. Case-control studies have shown genetic variants of IL13, its shared receptor subunit IL4RA and the transcription factor STAT6 to be associated with asthma and atopy. We assessed the association of these loci with asthma and atopy phenotypes at a population level.

Abstract S124 Summary of significant genetic predictors of clinical outcomes

<table>
<thead>
<tr>
<th>ID</th>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL13 Arg110Gln</td>
<td>Asthma ever</td>
<td>1.38 (1.06–1.79)</td>
<td>0.015</td>
</tr>
<tr>
<td>IL4RA Ile50Val</td>
<td>Asthma ever</td>
<td>1.38 (1.06–1.79)</td>
<td>0.015</td>
</tr>
<tr>
<td>STAT6 rs324015</td>
<td>Current eczema</td>
<td>2.62 (1.40–4.91)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Current hayfever</td>
<td>1.99 (1.19–3.32)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Carriage of at least one mutant allele v wildtype homozygote.
†Mutant homozygote v other genotypes.
Methods: Twenty two polymorphisms were genotyped in IL13, IL4RA and STAT6 genes in 1614 unselected volunteers aged 18–30 years. Data included physician-diagnosed asthma, eczema and hayfever (validated questionnaire) and total IgE levels. Results were analysed by multiple logistic and linear regression, adjusting for relevant covariates.

Results: Physician diagnosed “asthma ever”, “eczema ever”, and hayfever were recorded by 22.6%, 23.1%, and 32.5% of our population respectively. Geometric mean total IgE was higher in males (p < 0.001). Genetic data are presented for the Caucasian group (n = 1443). Significant predictors are summarised in the table. IL13, IL4RA, and STAT6 loci were associated with physician-diagnosed “asthma ever”, current eczema and hayfever. A novel prediction was seen between a 3’UTR variant of IL13 and total IgE (p < 0.05). Novel predictions of IgE were also demonstrated for IL4RA 3’UTR and intron variants and previously reported associations were confirmed at a population level (p < 0.01).

Conclusion: Although the genetics of asthma is complex, involving polygenic and heterogeneous effects, we have shown that common variants of IL-13 signaling have identifiable predictive effects in an unselected population. Novel predictions demonstrated between IL13, IL4RA, and STAT6 with clinical atopy and total IgE levels offer new targets for therapeutic manipulation and improve our understanding of the underlying complex genetic associations underpinning asthma and atopy.

S125 CHRONOLOGICAL EXPRESSION OF CILIATED BRONCHIAL EPITHELIUM 1 IN MOUSE AND HUMAN PULMONARY DIFFERENTIATION

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Rationale: Cilia play a critical role in mammalian embryogenesis, especially for normal positioning of internal organs. The expression of ciliated bronchial epithelium (CBE) 1 is highly associated with bronchial ciliated epithelial cells (ABCC8:337.1491-500). In order to explore the role of CBE1 during differentiation in lung development, we have studied its expression in mouse embryonic and adult lungs and human embryonic lungs (HEL) in vitro and in vivo.

Methods: MF-1 mice were time mated and embryonic lungs were harvested at embryonic day (ED) 11–19 and postpartum day (PD) 1 and 8 and from adult mice (AM) (n = 5–8); human embryonic lungs (HEL) (7–10 weeks) were collected following the Polkhome Committee guidelines after informed consent and ethical approval. HELs were dissected and explants were cultured in vitro for 3–18 days. Samples were processed for mRNA analysis using RT-qPCR and embedded in glycol methacrylate resin for immunohistochemistry (IHC).

Results: In the mouse lungs, CBE1 was strongly induced at ED11, declined between ED12–15 and then increased again from ED16, with highest levels postpartum and in the adult lung (p < 0.001). In contrast, expression of Foxj1, a forkhead transcription factor which regulates expression of ciliated cell genes, was low at ED11 but increased from ED15. In HELs, CBE1 mRNA was first detectable at about 10 weeks post conception (wpc), whereas that of Foxj1 was detected from 7 wpc. No expression of tektin-1 was observed up to 10 wpc. IHC showed that CBE1 was hardly visible at 10 wpc, but was strong at 12.3 wpc, with concomitant appearance of visible cilium. When HELs at 9 wpc were cultured in vitro, CBE1 mRNA was temporally increased with more than a one-hundred-fold increase in mRNA expression at day 12 (p = 0.03) and day 18 (p < 0.01) compared to day 0 (start of the culture). IHC showed no expression at day 0 and 6 but could be strongly detected in the developing epithelium at day 18.

Conclusions: The timing of induction of CBE1 was similar to that of Foxj1, consistent with a role for CBE1 in cilogenesis. However, the high expression of CBE1 in murine lung primordia (ED11) suggests that it may play an additional early role in asymmetric lung development, possibly as a regulator of monociliary function.

Diagnosis and management of pleural disease

S126 THE EXTENT OF SURGERY FOR MALIGNANT MESOTHELIOMA IN PATIENTS OVER THE AGE OF 65: A THERAPEUTIC DILEMMA?

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Background: Great controversy still exists regarding the role of radical versus less invasive surgery for the management of malignant pleural mesothelioma (MPM). While there is initial evidence that radical surgery may benefit younger patients there is no information available regarding the procedure of choice for the older age group. Standard of care in the elderly is symptom control. Radical excision has been offered to this age group but remains controversial. VATS debulking offers a probably less morbid therapeutic alternative. We aimed to evaluate the results of these alternative methods.

Methods: We retrospectively analysed the data for 63 consecutive patients with MPM undergoing therapeutic surgery, Stage I-II pleuro-pneumonectomies (n = 13) and radical decortications (n = 8) and non-radical (VATS decortications n = 42) surgery in our unit over a period of 9 years. Survival data were analysed with the Kaplan Meier method and peroperative variables were compared.

Results: In the pleuro-pneumonectomy (EPP) group 30 day mortality was 3/13 (23%) and the median survival was 247 days (8.2 months). In the Radical Decortication Group 30 day mortality was 1/8 (12.5%) and the median survival was 373 days (12.4 months). In the VATS Decortication Group 30 day mortality was 3/42 (7.1%) and median survival was 433 days (14.4 months).

Conclusion: In the over the age of 65 patients with malignant pleural mesothelioma minimally invasive debulking surgery is the preferred therapeutic option.

S127 EPIDEMIOLOGY OF SPONTANEOUS PNEUMOTHORAX: A HOSPITAL BASED STUDY

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Background: Pneumothorax is the presence of air in the pleural cavity. Spontaneous pneumothorax (SP) occurs without a preceding cause and can be subdivided into primary spontaneous pneumothorax (PSP), occurring in otherwise healthy individuals and secondary spontaneous pneumothorax (SSP) which occurs in patients with an underlying lung disease. There is a paucity of data on the epidemiology of pneumothorax, especially from the Indian Subcontinent.

Aim: This study describes the aetiology and clinical profile of patients admitted with a diagnosis of SP to a large hospital in India.

Methods: This was a descriptive prospective hospital based study. All the patients admitted at a tertiary care hospital with a diagnosis of SP over a two year period were included in the study. Relevant clinical and epidemiological details were recorded on a proforma for analysis. Patients were considered as having a PSP if an underlying aetiology could not be found and a SSP when the cause could be established. Risk factor analysis for PSP was done for variables like age, sex, smoking, body mass index, height, upper to lower segment ratio and presence of
Exertion at the onset using patients with SSP as controls. Comparison was made between the PSP and SSP groups. \( p = 0.05 \) was taken as being significant.

**Results:** The most common cause of SSP was found to be pulmonary tuberculosis (41.66%). Age distribution showed a bivac pattern, the first peak occurring between 20 to 30 years of age and second between 40 to 50 years. Male to female ratio was 5:1. Incidence of SP was found to be 99.94/year/100 000 hospital admissions. Incidence figures for PSP and SSP were 19.98 and 79.96/year/100 000 hospital admissions respectively.

**Conclusions:** The epidemiology of SP in India is slightly different from that seen in the West. The relative incidence of SSP was comparatively higher as compared to reports from the West. Pulmonary tuberculosis was the most common cause of SSP as compared to chronic obstructive pulmonary disease in the West.

**Abstract S129**

**AN AUDIT OF SELDINGER INTERCOSTAL CHEST DRAIN COMPLICATIONS**

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**Introduction:** The British Thoracic Society Pleural Disease guidelines were introduced when most hospitals were using blunt dissection for chest drain insertion (BTS Pleural Disease Group. Thorax 2003;58[Suppl II]). It is now routine practice in most UK centres to use small (10–14F) bore chest drains inserted by the Seldinger technique and in our hospital 12F Seldinger tubes are used initially in all medical patients requiring pleural drainage. A complication rate of 18% has been quoted for chest drain insertion for all indications (Chan L, et al. Am J Emerg Med 1997;15:368–70) but comparable data for Seldinger systems are lacking.

**Aim:** To quantify the frequency of complications from 12F Seldinger chest drains.

**Method:** A retrospective case note audit of 100 randomly selected patients (59M, 41F/mean age 61 years [range 19–92 years]) requiring pleural drainage between March 2005 and 2006 was performed.

**Results:** 74% were emergency admissions. Symptomatic malignant effusions were the most frequent indication (46%) for chest tube insertion, followed by pneumothorax (23%) and empyema (14%). Ultrasound guidance was utilised in 24% (20% insertion, 4% skin site marked). The mean time to drain removal was 1.5 days. 13% required chest drain replacement (9% had “fallen out” and in 4% the initial chest drain was blocked), 4% were re-sited with radiological assistance. There were two cases of trapped lung and 8% of the audit population were referred for cardiothoracic input (2% as outpatients). Pleurodesis was delayed in 10% of cases as a result of chest drain complications.

**Conclusion:** Serious complications from Seldinger small bore chest drains are few with aberrant tube placement rates comparing favourably to those previously quoted (1% v 6%). There were no empyemas on initial tube insertion (other series report up to 6%). However, there is a substantial rate of chest tube displacement necessitating further pleural procedures which add to patient morbidity and prolong hospital stay.

**Abstract S130**

**THE EFFECT OF BLIND PERCUTANEOUS PLEURAL BIOPSY ON SUBSEQUENT VIDEO ASSISTED THORACOSCOPY**

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**Background:** Blind percutaneous pleural biopsy (BPPB) is an established investigative tool for pleural effusion, with a reported diagnostic rate of...
Therapeutics for tuberculosis

**Tuberculosis drug related hepatitis in patients treated with standard rifampicin/isoniazid/pyrazinamide therapy over a 25 year period**

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**Introduction:** Drug-induced hepatitis is known to occur in a proportion of patients on treatment for active tuberculosis (TB). Some colleagues feel that this is increasing in incidence and have reported rates of grade 3 or 4 hepatitis (transaminases either >5× normal; or >20× normal) requiring interruption to treatment in over 10% of patients independent of HIV status.

**Methods:** Drug reactions, together with presumptive drug, have been recorded prospectively since 1981, when short course chemotherapy using rifampicin (R) and isoniazid (H) for 6 months, supplemented by 2 months initial pyrazinamide (Z) was introduced. We examined prospective data on 1710 patients treated between January 1981 and December 2005.

**Results:** 845 (49.4%) were males and 865 (50.6%) were females. 411 (24.03%) were white, and 1278 (74.74%) were of South Asian origin. Only 21 (1.23%) were of Black-African or other ethnic origin. 48 (2.81%) of all patients had drug related hepatitis. This equated to 22 (3.53%) whites and 26 (2.03%) south asian and 0. Other since there were only 21 of other ethnic group with no hepatitis cases this group may explain the longer operation times and lengths of stay in this group. However, it is reassuring that this survey suggests that having a BPPB does not interfere with the diagnostic yield or the complication rate of subsequent VATS, supporting the rationale for including BPPB in the diagnostic pathway for the investigation of unilateral pleural effusions.

**Conclusion:**

- The drug reaction rate over time showed 15/497 (3.02%) for 1981–85; 4/320 (1.25%) for 1986–90; 7/266 (2.63%) for 1991–95; 12/279 (4.31%) for 1996–2000; and 10/328 (3.05%) for 2001–05. There was no statistical trend over time.
- Of the 48 cases of hepatitis 27 (56.3%) were attributed to pyrazinamide, 15 (31.3%) to rifampicin, 5 (10.4%) to isoniazid, and the 1 (2%) fatal case occurred on all 3 drugs.

**Conclusion:** A study of a 25 year prospective cohort shows just over 3% of significant hepatitis overall, which is not rising in incidence. The incidence of hepatitis was highest in the white group overall, but only significantly higher in females. Surprisingly there was no age related effect in either major ethnic group.

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**Outcome of tuberculosis treatment: Blackburn 1986–2005**

L. P. Ormerod, N. Horsfield, R. M. Green. Chest Clinic, Royal Blackburn Hospital, Blackburn, Lancs BB2 3HF, UK


**Methods:** We have added 2 more years’ retrospective data (1986–87) and 5 more years’ data (2001–05) collected prospectively and reported under HPA enhanced surveillance.

**Results:** A total of 1189 cases were notified, with 342 definite (culture positive) pulmonary cases. Of the 328 treated in life, 304 received self-administered treatment (SAT) and 24 directly observed therapy (DOT), with an 89% cure/completion rate and 10.8% deaths. The WHO target is 85% cure/completion rate for confirmed respiratory cases. The relapse rate with SAT was 2/281 (0.6%) and for DOT was 1/24 (4.2%). 150 cases of non-culture confirmed tuberculosis (TB), 207 cases of other respiratory TB (pleural effusion and isolated mediastinal effusions), and 478 non-respiratory TB cases were treated, largely by SAT (all but 5 cases). 12 cases with prior treatment history were treated by DOT. For all cases in the programme, there was a cure/completion rate of 93.7%, a 5.2% death rate, no treatment failures, 0.25% treatment interruption and 0.85% transferred out. The relapse rates for non-culture confirmed pulmonary TB treated by SAT was 1/117 (0.6%), for other respiratory TB 0/207 (0%), and for non-respiratory TB 3/477 (0.6%).

**Conclusion:** Very high cure/completion rates were achieved by regular self-administered treatment (at least monthly) but randomly monitored SAT, with only 41 patients (including 12 with prior treatment histories) or 3.5% of cases having selective DOT. Universal DOT could only at best have improved outcome by under 1% but at greatly increased cost, as the 0.25% with treatment interruptions completed treatment, and most of the 0.85% transferred out to other areas are likely to have done so.

Our 20 year cohort data support a policy of selective rather than universal DOT for TB treatment.
but we are fortunate to have a fairly stable and cooperative local population, with only a small number of "difficult to reach" patients, plus those with a prior treatment history requiring, or those demonstrating non-compliance during treatment, requiring DOT.

### MANAGING MULTI-DRUG RESISTANT TUBERCULOSIS IN THE UK

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**Background:** Past (BTS) and current (NICE) guidelines for the management of multidrug resistant tuberculosis (MDR-TB) recommend that treatment should be carried out by, or in consultation with, physicians who have specific experience with such cases. This study investigates the degree to which this advice is followed.

**Methods:** A postal questionnaire was sent to 259 hospital trusts across the UK, addressed to the individual thought likely to be the principal physician for tuberculosis (TB). Recipients were requested to re-direct the questionnaire if appropriate. A second copy was sent to non-responding hospitals after 3 months.

**Results:** Responses were received from 186 consultants who considered themselves the most experienced TB physician in their hospital (response rate 186/259 hospitals; 72%). Only 15 physicians reported seeing more than one case per year over the previous years of whom 7 worked in London. 100/186 respondents (54%) would refer all MDR-TB to another physician. 38/186 (20%) stated they would manage MDR-TB with advice from another physician. 48/186 (28%) of respondents felt they had the expertise to manage MDR-TB without advice from others. 33 of these 48 (69%) had seen 1 case or fewer per year over the previous 5 years and 8 of them (17%) had seen none in that period. 16 of the consultants seeing 1 or fewer cases/year would also accept MDR-TB referrals from other physicians.

**Discussion:** Even among consultants taking the clinical lead for TB in their hospitals very few encounter more than one case per year of MDR-TB. Some with little or no experience of MDR-TB were willing to manage patients without advice from others, and some who would manage it with advice were uncertain about sources of help. A balance must be struck between the desirability of treatment in an experienced setting, and the patient’s need to be close to home, but our study suggests that this balance is in many cases not the correct one. Developing a more formalised advice network for MDR-TB management may be a step forward.

### FACTORS CONTRIBUTING TO DELAY IN DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

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**Aims:** To study the factors, which contribute to delay in diagnosis and treatment of tuberculosis (TB) in the Borough of Greenwich. The incidence of TB has risen in this catchment area, with infection rates having risen from 36/100 000 to 47/100 000 since 1997.

**Methods:** We reviewed 292 cases of TB treated between 2003–05. We examined the time taken from the first suggestive chest x-ray (CXR) to commencement of treatment. The radiological data were collected and reviewed using the HISS and PACS system. We reviewed all the notes in which there was delay of over 28 days from the initial suggestive CXR to treatment.

**Results:** A total of 56 out of 292 cases had a delay of over 28 days from the initial suggestive CXR to commencement of treatment. The median time of delay was 56 days. The reasons for delay were: patients not keeping their clinic appointments in 9 cases (range of 48–851 days), delays in investigation in 19 cases (range of 32–649 days), CXRs not being acted upon or delays in referrals in 15 cases (range of 41–483 days), diagnosis not suspected due to concomitant lung disease in 6 cases (range of 92–1020 days) and delays in diagnosing pleural effusions in 7 cases (range of 44–793 days). The patients who failed to attend their clinic appointments were all immigrants. Concomitant lung disease was a confounding factor in indigenous white patients in 5 out of 6 cases.

**Conclusion:** There needs to be an increased awareness of the rising incidence of TB, particularly among the immigrant population. The mobility of this group, with some not having fixed addresses and some not having an appointed general practitioner seemed to contribute to poor clinic attendance. In all cases the diagnostic process needs to be speeded up. A high index of suspicion is needed in patients with other chronic lung diseases.
in the chemoreflex gain (from 800 l/min/fraction CO2) resulted in an increase in loop gain of 275 (6)% (p<0.0001) across a wide range of values of steady state CO2 and apnoea thresholds (fig 2). Increasing the apnoea threshold FETCO2 from 0.02 to 0.03 had no effect on system stability. Therefore of the three variables, the only two destabilising factors were high gain and high mean CO2; the apnoea threshold did not independently influence system stability.

Conclusion: This study confirms that a steep chemoreflex slope destabilises cardiorespiratory control. Controversially, it demonstrates quantitatively that it is a high (rather than low) steady state level of carbon dioxide that favours instability. Finally, we conclude that the apnoea threshold itself does not create instability, however in a linear chemoreflex response, it is numerically linked to the true determinants of stability: chemoreflex gain and steady state carbon dioxide.

Method and Results: We studied the effect of repeated alternations in heart rate by 30 bpm and period 60s, on cardiovascular parameters in 22 subjects with implanted cardiac pacemakers and stable breathing patterns (14 with systolic heart failure and 8 subjects with normal systolic function). This pattern of heart rate alternation elicited consistent oscillations in both ETCO2 and ventilation exhibited consistent sinusoidal oscillations with period 60 seconds (fig). The mean amplitude of oscillations in ETCO2 was 4.2 (2.5)% with a mean amplitude of oscillations in ventilation of 12.2 (9.4)% of the mean. The magnitude of the oscillations generated in ETCO2 correlated with the cardiac output produced by the heart rate alternation (r=0.59, p=0.001).

Conclusions: Cardiac output modulation using pacemakers can elicit consistent oscillations in CO2 and ventilation in patients with stable cardiorespiratory control. The size of effect depends on the magnitude of the cardiac output response. This mechanism could be potentially therapeutic, if appropriately harnessed and timed to counteract the fluctuations in CO2 and ventilation seen in periodic breathing and central sleep apnoea, thus avoiding the need for ventilatory support.

Heart rate (bpm)

End tidal CO2 (kPa)

Ventilation (l/min)

Abstract: The effect of acute heart rate alterations on end tidal CO2 and ventilation in one subject (averaged over 6 cycles).

### S137 CAN CARDIAC PACEMAKERS DIRECTLY CONTROL VENTILATION?


Background: In periodic breathing in chronic heart failure and central sleep apnoea, there are repeated oscillations in ventilation and CO2 with unstable cardiorespiratory control. Using patients with pre-existing pacemakers, we tested the hypothesis that dynamic changes in cardiac output acutely affect the delivery of CO2 into the lung, and thereby influence ventilation.

Method and Results: We studied the effect of repeated alternations in heart rate by 30 bpm and period 60s, on cardiovascular parameters in 22 subjects with implanted cardiac pacemakers and stable breathing patterns (14 with systolic heart failure and 8 subjects with normal systolic function). This pattern of heart rate alternation elicited consistent oscillations in both ETCO2 and ventilation exhibited consistent sinusoidal oscillations with period 60 seconds (fig). The mean amplitude of oscillations in ETCO2 was 4.2 (2.5)% with a mean amplitude of oscillations in ventilation of 12.2 (9.4)% of the mean. The magnitude of the oscillations generated in ETCO2 correlated with the cardiac output produced by the heart rate alternation (r=0.59, p=0.001).

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Heart rate (bpm)

End tidal CO2 (kPa)

Ventilation (l/min)

Abstract: The effect of acute heart rate alterations on end tidal CO2 and ventilation in one subject (averaged over 6 cycles).

### S138 COMPARISON OF THE NEP AND FOT TECHNIQUES FOR MEASURING FLOW LIMITATION IN SUBJECTS WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Tidal flow limitation (TFL) is common in patients with severe chronic obstructive pulmonary disease (COPD) and occurs where the tidal expiratory flow loop abuts the forced expiratory flow loop. Patients with FTL are more dyspnoeic and more likely to dynamically hyperinflated during exercise. Flow limitation can be assessed by the negative expiratory pressure (NEP) and forced oscillation technique (FOT) and we have assessed the ease, consistency and usefulness of the two techniques in 32 subjects with moderate to severe COPD (FEV1 = 1.29 (0.64) l, 47 (20)% predicted, FEV1/FVC 0.52 (0.12)). TFL was assessed over 4 minutes tidal breathing using FOT then immediately followed by 5 NEP measurements, also over 4 minutes. This was repeated 20 minutes after administration of 5 mg salbutamol (BD).

A satisfactory measure of FTL using FOT was obtained pre and post BD in all 32 subjects whereas only 53/64 (83%) NEP recordings produced 5 satisfactory traces. One subject produced only 1 satisfactory NEP recording pre and post BD and was excluded from further analysis. In only 41/53 (77%) cases were NEP recordings consistent throughout all 5 measurements—the others showing both FL and non-FL breaths. Subjects were classified as FL or NFL based on the majority result where results were inconsistent. NEP recordings were more likely to be consistent post-BD than pre-BD (p = 0.05). Comparing FOT and NEP, flow status was the same in 48/62 (77%) and different in 14/62 (23%) recordings. Where flow status differed this appeared to be due to breath by breath variation in 4 subjects, upper airway abnormalities in 2 with no obvious explanation in 3 subjects. Flow status changed post-BD in 4 subjects (NEP) and 3 subjects (FOT).

FOT is easier to perform than NEP and, as the measurement is made over a number of minutes rather than a single breath, it appears to be a more consistent measure of flow limitation. Different results were seen commonly and this was likely to be related to breath by breath change in FTL which we speculate is related to change in breathing pattern and/or operating lung volume.

### S139 EXERCISE VENTILATION IN DIFFUSE PLEURAL DISEASE

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This study investigates the causes for an increased exercise ventilation during moderate exercise in men with diffuse pleural disease, but no significant angina, who were referred by Pneumoniosis Medical Panel during 1980-90. Lung function was measured by standard methods and progressive treadmill exercise was performed up to an O2 uptake of 4.5 mmol/min (1.0 l/min). Ventilation at this work rate was considered abnormal if it exceeded the normal range of 17–30 l/min. Pattern of breathing was assessed in terms of tidal volume and respiratory frequency at a ventilation of 30 l/min (designated V30) and R30 respectively for which the reference values were with respect to forced vital capacity. The study aimed to investigate by relatively simple methods the contributions to an increased VEmax of (a) uneven lung function, (b) increased alveolar ventilation sufficient to raise the respiratory exchange ratio (RER >0.91) and (c) a shallow breathing pattern that materially increased the ventilation of the tidal deadspace. A clinical grade of breathlessness of 4 or 5 was taken as evidence for impaired capacity for daily living, whilst a normal transfer factor was assumed to exclude asbestosis.

There were 41 men with a normal transfer factor, who were able to exercise at the designated work level and had radiographic evidence for diffuse pleural thickening, extensive calcified plaques or filling of at least one costophrenic angle. One man was not considered further on account of functional hyperventilation and another had incomplete data. Amongst the remainder VEmax was linearly related to R30. In 4 men the capacity for daily living was impaired; in one the incapacity was due to obesity and in the other three the cause was respiratory. In these men and in 7 others the VEmax was increased. The mechanisms were found to be one or more of those given above, including in two of them dynamic shallow breathing. In two of the three men with incapacity the respiratory impairment would have been apparent from simple spirometry. In the third the principal contributory factor was shallow breathing on exercise without hyperventilation or other evidence for functional overload. The lung compliance was with normal limits.

Heart rate (bpm)

End tidal CO2 (kPa)

Ventilation (l/min)

Abstract: The effect of acute heart rate alterations on end tidal CO2 and ventilation in one subject (averaged over 6 cycles).
Conclusion: In diffuse pleural disease dynamic shallow breathing contributes to disability and respiratory exercise testing may be diagnostic.


FLIGHT ASSESSMENT IN PATIENTS WITH RESPIRATORY DISEASE: AGREEMENT BETWEEN HYPOXIC CHALLENGE TESTING AND PREDICTIVE EQUATIONS

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Background: Predictive equations have been proposed as a simpler and cheaper alternative to hypoxic challenge testing (HCT) for determining the risk of in-flight hypoxia. The aim of this study was to assess agreement between the individual hypoxic response measured during HCT and predictive equations.

Methods: Patients with chronic obstructive pulmonary disease (COPD) n = 15, mean (SD): age (years), 62 (8) FEV1 % predicted, 38 (13); intermittent lung disease (ILD) n = 15: age (years), 69 (13) FEV1 % predicted, 83 (28); cystic fibrosis (CF) n = 15: age (years), 66 (6) FEV1 % predicted, 44 (19) were studied. Spirometry was recorded pre testing and oxygen saturations (SpO2) were recorded pre, post and during HCT. Capillary earlobe samples were collected and analysed for pH, PCO2 and PO2 pre and post testing and when SpO2 = 85%. A HCT performed using the Ventimask method. The PaO2 at altitude was estimated for each group using four published predictive equations which use values of PaO2 at sea level (breathing room air) and lung function measurements to predict altitude PaO2. The results were interpreted using the BTS recommendations for prescription of in-flight oxygen post HCT; PaO2Alt >7.4 kPa in-flight oxygen not required; PaO2Alt = 6.6–7.4 kPa in-flight oxygen required; PaO2Alt < 6.6 kPa borderline for in-flight oxygen which may require further investigation.

Analysis: The Stuart Maxwell test of overall homogeneity was used to assess agreement between hypoxic challenge test results and each of the predictive equations.

Results: During HCT the PaO2 (ground) kPa mean (SD) in each disease group decreased; COPD from 8.37 (0.85) to 6.9 (0.65); ILD from 8.9 (0.53) to 7.3 (0.64); CF 9.6 (0.86) to 7.5 (0.91). In each group the results show that fewer patients would require in-flight O2 if prescription was based on HCT compared to the four predictive equations; COPD, HCT n = 6, equations n = 13–15; ILD, HCT n = 1, equations n = 1–15; CF, HCT n = 2, equations n = 7–12. With the exception of equation 3, these differences reached statistical significance (p<0.05).

Conclusions: Predictive equations tend to overestimate the need for in-flight supplemental oxygen. The cost of in-flight oxygen can be cheaper and as some airlines do not permit its use, HCTs should be performed to ensure accurate in-flight oxygen prescription for patients with respiratory disease.

Differential effects of vascular endothelial growth factor isoforms on primary human lung microvascular endothelial cell proliferation

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Vascular endothelial growth factor (VEGF) is a potent permissive and mitogenic factor. It has been detected in high concentrations within the normal lung, compartmentalised to the alveolar space. In patients with acute respiratory distress syndrome we have shown that intrapulmonary levels of VEGF fall and plasma levels increase with a return to normal levels in survivors. Human VEGF commonly occurs as at least three different isoforms formed by pre mRNA splicing: VEGF121, VEGF165 and VEGF189, characterised by their exon number and named according to their base pair number. VEGF165, the dominant form, and VEGF121 are soluble products, whereas VEGF189 remains primarily cell-associated. Another family of VEGF splice variants, VEGF165b has recently been identified, formed by splicing from exon 7 into the previously assumed 3’ untranslated region (UTR) of the VEGF mRNA. VEGF165b has been shown to have significantly differing biological effects to that of VEGF165. We hypothesised that the balance between these two families of VEGF may play a critical role in the development of ARDS. As an initial step we have investigated their effect on primary human pulmonary microvascular endothelial cells (HMVEC-L, Cambrex). In order to explore this hypothesis we cultured HMVEC-L in the presence of serial concentrations of VEGF165 and VEGF165b. Proliferation was assessed by [3H]-thymidine incorporation. VEGF165b significantly increased proliferation but no effect was detected with VEGF165b in comparison to control. However in the presence of VEGF165b, the proliferative effect of VEGF165 was inhibited. These data suggest that VEGF isoforms may have a differential effect on HMVEC-L with significant consequence for functional outcome in the human lung.

HEME OXYGENASE-1 IS INDUCED IN HUMAN NEUTROPHILS FOLLOWING SURGERY REQUIRING CARDIOPULMONARY BYPASS


Introduction: The systemic inflammatory response syndrome (SIRS) is a common consequence of cardiac surgery necessitating cardiopulmonary bypass (CPB). SIRS if severe is associated in some patients with the development of organ dysfunction including the acute respiratory distress syndrome (ARDS). Neutrophil clearance through apoptosis and subsequent ingestion by macrophages is an essential step in the resolution of such inflammation, whilst delayed neutrophil apoptosis is observed following CPB. We have previously shown that haemoglobin, which is released from erythrocytes during haemolysis, induces the anti-apoptotic protein heme oxygenase-1 (HO-1) and delays spontaneous apoptosis in neutrophils from healthy volunteers. We now speculate that HO-1 is induced in neutrophils from patients undergoing surgery requiring CPB.

Methods: Blood was taken from 8 patients undergoing cardiac surgery, before and two hours after the cessation of CPB. Neutrophils were separated by discontinuous gradient centrifugation. mRNA was obtained using TRI reagent. Alternatively, isolated neutrophils were incubated in DME medium for a further 8 hours before collection in cell lysis buffer. mRNA concentrations were estimated by real time PCR and HO-1 protein levels were measured using a commercially available ELISA.

Results: HO-1 mRNA and protein were raised in peripheral blood neutrophils obtained from patients following CPB in comparison with neutrophils obtained prior to bypass.

Conclusion: HO-1 is induced in neutrophils following CPB. This induction may be due to haemolysis and may also contribute to delayed neutrophil apoptosis, and the development of SIRS and its more serious sequelae including ARDS, following CPB.
cause of death. For analysis of matrix deposition, patients were divided into two groups, those receiving assisted ventilation for <96 hours (early) and >22 days (late). In the early group, mean Ashcroft fibrosis scores were highly abnormal (4.54 (0.69); n = 8). Mean Ashcroft fibrosis scores were also elevated in the late group (6.38 (0.27); n = 4) and were significantly higher compared with the early group (p = 0.025). Two patients with elevated fibrosis scores were withdrawn from the analysis as in addition to ARDS, they also had evidence of chronic fibrosing lung disease.

Conclusion: In this study we found that histological evidence of ALI/ARDS correlated with clinical suspicion and was frequently under-reported following postmortem analysis. Clinically relevant ALI/ARDS may be more common than published studies report. Importantly, we also show that significant matrix deposition occurs extremely early in the progression of ALI/ARDS and confirm that pulmonary fibrosis is not a late manifestation of this condition. Pharmacological therapies evaluated for the treatment of this syndrome have predominantly concentrated on modulating the inflammatory response. Novel treatments targeting the early fibrotic response in this condition warrant further evaluation.

**Abstract S144**

**EXHALED BREATH CONDENSATE GLUCOSE LEVELS PREDICT ADVERSE OUTCOME IN ACUTE RESPIRATORY DISTRESS SYNDROME**

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**Introduction:** Exhaled breath condensate (EBC) collection may enable non-invasive real time sampling of respiratory fluid to quantify markers of inflammation and guide intervention. It has been shown previously that bronchial aspirate glucose in ventilator associated pneumonia is elevated during infection with pathogenic bacteria. This study aimed to look at the relationship between EBC glucose and infection/outcome in patients with acute respiratory distress syndrome (ARDS).

**Method:** Fifty seven EBC samples were collected for 20 minutes from patients within 48 hours of developing ARDS. EBC was immediately analysed in the ABG analyser (Rapidlab) for glucose. BAL was performed the same day and cultured quantitatively. Patients were divided into 3 groups: group A with glucose 3–6 mmol/l, group B glucose 3–6 mmol/l and group C with glucose >6 mmol/l.

**Results:** EBC glucose was significantly higher in non-survivors compared to survivors (p = 0.026). There was no statistical difference in serum glucose in these groups (p = 0.4863). Mortality of the groups increased proportionately from group A to C (see table). EBC glucose from infected patients was also significantly higher than non-infected ones (p = 0.009) although here was no statistical difference between serum glucose in these groups (p = 0.3774).

**Conclusions:** EBC glucose is a potential marker of both infection/outcome in ARDS. Since blood glucose did not differ between the groups we suggest that elevated EBC glucose may reflect the severity of epithelial injury. EBC collection may prove to be a useful tool in guiding treatment and intervention in ARDS.

**Abstract S145**

**ALVEOLAR INFECTION SIGNIFICANTLY DRIVES CHEMOTAXIS BUT NOT THE INFLAMMATORY CELL INFILTRATE IN ACUTE RESPIRATORY DISTRESS SYNDROME**


**Introduction:** Chemotaxis is the primary mechanism for directed cell movements and is thought to play a vital role in the migration of inflammatory cells in acute respiratory distress syndrome (ARDS). We were interested in looking at the role of significant alveolar infection and...
its influence on the underlying chemotactic activity and inflammatory cell infiltrate in ARDS. Method: Thirty eight bronchoalveolar lavage fluid samples (BALF) were collected within 48 hours of developing ARDS along with 8 normals. BALF were processed for cell counts immediately after bronchoscopy and quantitatively cultured to detect any significant growth (1×10⁸). Chemotactic activity was measured in all BALF. They were also assayed for various chemokines (IL-1, IL-6, ENA 78, MCP, and RANTES). Results: We found that the mean chemotaxis induced by BALF in ARDS (8.96) was significantly higher when compared to normals (1.90) (p = 0.0001). The mean chemotactic activity of BAL with significant growth was significantly higher (10.08) (n = 24) compared to no growth (7.50) (p = 0.034, n = 14). The mean total cell counts in BAL with significant growth was significantly higher (15.48) compared to no growth (5.50) (p = 0.0337). Although the chemotactic activity and the BAL cell counts were higher in patients with significant growth, they did not correlate with each other (p = 0.2690). BAL cell counts were higher in patients with significant growth, they did not correlate with each other (p = 0.2690). We felt that although the relative difference between neutrophil chemotaxis and apoptosis in the BAL samples. The combined mean chemokine values revealed no difference in BAL with no growth (1431.7) compared to BAL with significant growth (1479.4) (p = 0.9228).

Discussion: Although the cell counts and chemotactic activity is higher in infected BAL there was no direct correlation between the two variables and moreover the combined cytokine levels were not significantly higher. We combined the chemokine values recognising that the role of individual cytokines in chemotaxis and their interactions with each other and the inflammatory cells in ARDS is still unclear. We felt that although the infection in ARDS seems to drive a significant chemotactic activity, the total inflammatory cell infiltrate at the alveolar level would depend on the relative difference between neutrophil chemotaxis and apoptosis effects of ARDS BALF. The net cell count would therefore depend upon the balance between new chemotaxis and reduced cell death due to apoptosis. Conclusion: We have shown for the first time a significantly raised BALF chemotactic activity in ARDS that infection seems to significantly drive further chemotaxis. The cell count is not a direct outcome of chemotactic activity. Reduced apoptosis at alveolar level in ARDS may also be responsible and further work needs to be done to unravel the exact mechanism involved.

MITOCHONDRIAL REACTIVE OXYGEN SPECIES ARE REQUIRED FOR MECHANICAL STRAIN-INDUCED INTERLEUKIN-8 PRODUCTION BY LUNG EPITHELIAL CELLS

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Background: Overdistension of the lung during mechanical ventilation contributes to the mortality of acute lung injury (ALI). Mechanical forces enhance the release of mediators that exacerbate lung damage and contribute to systemic inflammation and death. The neutrophil chemokine interleukin (IL)-8, has been implicated in the pathogenesis of ALI. We have previously demonstrated that stretching monolayers of AS49 cells (a human alveolar epithelial cell line), a model of over-distention, increased IL-8 message expression and release. We aimed to elucidate the signaling pathways underlying this process with a view to mitigating ventilator associated lung injury.

Results: Cyclic mechanical strain (30% stretch at 20 Hz for 2 hours (Flexercell 4000X)) of AS49 cells was associated with increased nuclear factor-kappa B (NFκB; p=0.05) DNA binding activity and phosphorylation of IκBα. The IKK-2 inhibitor AS602868 (Serono, CH) abolished stretch-induced NFκB DNA binding and IL-8 induction, suggesting that activation of the transcription factor NFκB was required. 30% stretch caused intracellular oxidative stress, as evidenced by a decrease, from 1113 to 438 (mean, p = 0.02, n = 8) in the reduced/oxidised glutathione ratio. Stretch-induced oxidative stress was significantly attenuated by N-acetylcysteine (a thiol antioxidant) and rotenone (an inhibitor of mitochondrial complex 1). Finally, AS49 cells lacking mitochondria that were subjected to cyclic mechanical strain did not generate reactive oxygen species, activate NFκB or express IL-8 in response to cyclic mechanical strain, whereas these responses could be induced by IL-1β.

Conclusion: These data suggest a specific role for mitochondria-derived reactive oxygen species acting via the transcription factor NFκB in mechanotransduction in AS49 cells.

Support: British Lung Foundation, The Dr Hadwen Trust. These data have been presented in part at the European Respiratory Society meeting in 2006.

Non-invasive ventilation

THE EFFECT OF SITE AND INSPRIATORY PRESSURE ON THE DELIVERY OF SUPPLEMENTAL OXYGEN THERAPY DURING NON-INVASIVE VENTILATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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Introduction: Supplemental O₂ is frequently added to bi-level non-invasive ventilation (NIV) circuits to maintain S₉O₂ >95%. Oxygen can be added at several points and in the presence of different inspiratory pressures. The effect of varying entrainment sites and inspiratory pressures (IPAP) on PO₂, PCO₂, Fio₂, inspiratory triggering and expiratory triggering in chronic obstructive pulmonary disease (COPD) patients is unknown.

Method: Eighteen patients with stable COPD (mean FEV1 47%) participated in the study. Oxygen was added at 4 sites in the ventilatory circuit (site 1: between mask and exhalation port; site 2: just distal to exhalation port; site 3: at ventilator outlet; site 4: directly into the mask via an inlet). The effect of varying entrainment sites and inspiratory pressures on arterial PO₂, PCO₂, Fio₂ was recorded at 3 minutes. The same face mask (Respironics, Image 3) and ventilator (Respironics, BIPAP ST 30) was used throughout.

Results: Results for PO₂ are shown at IPAP 10/EPAP 4 (table). Anova was used (Statview version 8.0) to analyse the data. Site 4 (via mask) was associated with a significantly higher PO₂ at all flow rates compared with sites 1, 2 and 3 (p < 0.001). Site 3 (at ventilator outlet) was associated with the lowest PO₂ at all flow rates, particularly at 15 l/min (p < 0.001).

Conclusion: During NIV, adding oxygen to the mask at lower IPAPs results in higher oxygen delivery.

AUDIT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH ACUTE TYPE II RESPIRATORY FAILURE: ARE WE GIVING THEM A CHANCE?

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Introduction: The British Thoracic Society recommends the use of non-invasive ventilation (NIV) in COPD patients with an acute exacerbation and persistent respiratory acidosis, despite maximum medical treatment on controlled oxygen therapy.1 Patients who are unsuitable for NIV or in whom NIV has failed should receive early ITU input. Acute Physiological and Chronic Health Evaluation Scores (APACHE) can be used as a predictor of in-hospital mortality for groups of patients.2 The aim of this audit was to assess whether on-call physicians used NIV and requested ITU input appropriately.

Setting: A district general hospital with unselected medical takes. NIV facilities are available on the respiratory ward. ITU/HDU facilities are available on site.

Method: A retrospective audit of 160 case notes from patients with a coded diagnosis of COPD, emphysema, or chronic bronchitis, admitted...
between 1 January and 30 June 2005 was performed. Eight patients were excluded due to incorrect coding. In the remaining patients with persistent type II respiratory failure, an analysis of NIV use, ITU input and APACHE II score was performed.

Results: 29/152 patients (19.1%) had acute type II respiratory failure and fitted the BTS criteria for NIV. In only 11/29 patients (37.9%) was NIV considered and only 5 of those went on to receive NIV. Reasons for failure to progress to NIV were unclear in 4 patients, and no respiratory bed was available for 2 patients. 4/29 (13.8%) patients received ITU review, 3 of whom had received NIV. One patient went on to receive mechanical ventilation due to NIV failure. All of the 29 patients had APACHE II scores of 27 or less, indicating a predicted mortality of less than 51.4% in this group. 23/29 (79%) scored 20 or less, indicating a predicted mortality of less than 28%. There was no correlation between APACHE II score and consideration of NIV or ITU input.

Conclusion: Although NIV is known to reduce in-hospital mortality and the need for invasive ventilation, NIV is still not being utilized appropriately. Only a minority of acutely ill COPD patients are receiving NIV. As a group, the predicted mortality figures using APACHE II were low. Acute physicians should be giving more consideration to NIV and invasive ventilation in patients with COPD and acute type II respiratory failure.


S149 THE OUTCOME OF HOME NON-INVASIVE POSITIVE PRESSURE VENTILATION IN PATIENTS AT THE LONDON CHEST HOSPITAL

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Background: Previous retrospective studies show that long term non-invasive positive pressure ventilation (NIPPV) is effective in patients with extrapolmonary restrictive disorders but less effective in patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis. (Simonds AK, Elliot, MW. Thorax 1995;50:604–9. Leger P. Bedicam JM, et al. Chest 1994;105:100–5). There is no evidence to suggest that NIPPV has a mortality benefit in the management of chronic respiratory failure in COPD. However, it is used in patients with hypercapnic ventilatory failure who have received assisted ventilation during an exacerbation or are hypercapnic or acidic on LTOT in accordance with NICE recommendations. We conducted a retrospective study on patients receiving domiciliary NIPPV at the London Chest Hospital (LCH) to compare current outcome with previously published data and to review the outcome in patients with obesity hypoventilation syndrome (OHS).

Method: For patients commenced on NIPPV at the LCH between 1 July 1993 and 1 June 2005 information was collected on diagnosis, start date, date of death or of stopping NIPPV, and PaCO2 at start, 1 year and 5 years. The 5-year probability of remaining on NIPPV was used as a surrogate for survival. Kaplan-Meir curves were plotted to show the probability of continuing on NIPPV within the different diagnostic groups. Paired student t tests were used to show any significant difference between PaCO2 at the start, 1 year and 5 years for patients within the different diagnostic groups.

Results: Data were available for analysis on 275 patients commenced on NIPPV in the 77 month period. 149 had COPD, 57 thoracic cage abnormalities, of which 18 were post thoracoplasty and 37 had kyphoscoliosis, 46 OHS, 15 progressive neuromuscular disorders and 8 bronchiectasis. Death was the principle cause for withdrawal. The mean (95% confidence interval) 5-year actuarial probability of continuing NIPPV with OHS was 83.3% (100–60), post thoracoplasty 47.7% (92–4), kyphoscoliosis 89% (100–72), COPD 39.8% (38–21), progressive neuromuscular disorders 51% (100–20.8) and bronchiectasis 14.5% (83–0) (fig 1). PaCO2 improved in all patient groups at 1 year including statistically significant falls in OHS (0.87 kPa, p<0.001), COPD (0.52 kPa, p<0.001) kyphoscoliosis (0.81 kPa, p<0.001) and post thoracoplasty (0.6 kPa, p<0.001) (fig 2).

Conclusion: This is one of a small number of studies to show that patients with OHS have a very good long term outcome with NIPPV and the first involving direct comparison against different pathologies. Patients with kyphoscoliosis also have a good outcome, but those post thoracoplasty have much a lower probability of continuation. NIPPV resulted in PaCO2 falls in all groups at 1 year. The outcome in COPD is comparable to previous studies and remains encouraging but more research is awaited.

S150 RESPIRATORY FUNCTION AND SURVIVAL IN MOTOR NEURONE DISEASE

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Introduction: In motor neuron disease (MND) respiratory compromise is often recognised late and most patients die from respiratory failure. In patients with relatively preserved bulbar function, non-invasive ventilation improves survival and quality of life. However, some patients die within one month of the onset of orthopnoea, leaving little time to initiate NIV. Vialional tests of respiratory muscle strength can be performed quickly and easily in the clinic setting but the prognostic value of such tests is unclear. We examined the relations between six month survival and (1) vital capacity (VC), (2) maximum inspiratory (Pimax) and expiratory (Pemax) pressures and (3) sniff nasal inspiratory pressure (SNIP) in 41 subjects with MND and normal or only moderately impaired bulbar function who did not receive NIV.

Methods: ROC curve analysis was used to assess the prognostic value of each index of respiratory muscle strength. Threshold values, expressed
as % predicted, were chosen to (1) maximise sensitivity and (2) optimise both sensitivity and specificity.

Results: Fifteen subjects died within six months. One subject was unable to perform Pimax. The sensitivity and specificity of different cut-off values for each index are shown in the table.

Conclusions: All indices of respiratory muscle strength, but particularly VC and SNIP, proved useful in identifying subjects at risk of death within six months. In patients with MND, surveillance of respiratory muscle function should be performed routinely.

## S151 COMPARATIVE PULMONARY MECHANICS IN CHILDREN AND ADULTS WITH NEUROMUSCULAR DISEASE

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Increasing numbers of physicians are establishing younger neuromuscular patients on non-invasive ventilation. As life expectancy increases, there is a growing need to understand the changes in pulmonary mechanics that occur with increasing age. We measured respiratory rate (fR), tidal volume (VT), inspiratory time (Ti), dynamic lung compliance (CLdyn), total pulmonary resistance (Rdyn), total WOBexp, elastic WOBexp and resistive (WOBres) work of breathing in 27 adults (40 (18) years) and 22 children (11 (4) years) with neuromuscular disease (see table).

Although the vital capacity (VC) was reduced in the children, as expected, the percent predicted VC for the adults and children were similar. Even corrected for weight the VT/Ti ratio and VT/Ti were markedly increased in the children, reflected as a higher WOBres. Interestingly, the WOBexp per kg and WOBres per kg were also increased as a result of the higher CLdyn and Rdyn respectively. These data suggest that different ventilatory strategies may be required when managing children and adults with neuromuscular disease.

Nicholas Hart was funded by Scadding-Morriston Davies Joint Fellowship in Respiratory Medicine and the Association Francaise Contre Les Myopathies.

## Physiology of obstructive sleep apnoea

### S152 THE EFFECT OF CPAP ON INSULIN RESISTANCE AND HBA1C IN PEOPLE WITH OBSTRUCTIVE SLEEP APNOEA AND TYPE 2 DIABETES: A RANDOMISED CONTROLLED TRIAL

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Background: Obstructive sleep apnoea (OSA) has been found to be associated with glucose intolerance and insulin resistance, independent of obesity. The severity of the insulin resistance is proportional to the severity of the OSA. It is hypothesised that the disordered glucose metabolism and insulin resistance are due to increased sympathetic nervous system activation caused by the frequent arousals and fragmented sleep; also the sleep deprivation itself and the hypoxia associated with OSA may cause insulin resistance. The effects of continuous positive airway pressure (CPAP) treatment for obstructive sleep apnoea (OSA) on insulin resistance are not clear; trials have found conflicting results and none have used control groups.

Methods: Forty two men with known type 2 diabetes and newly diagnosed OSA (≥10 ≥5% SaO2 dips/hour) were randomised to receive therapeutic (n = 20) or placebo CPAP (n = 22) for 3 months. Baseline tests, including glycaemic clamp, glycosylated haemoglobin, homeostatic model assessment, adiponectin, anthropometric measures, bioimpedance and actigraphy were performed and repeated after 3 months. The study was double blind.

Results: Results are expressed as mean (SD). CPAP improved the ESS significantly more in the therapeutic group than the placebo group (−6.6 (4.5) v −2.6 (4.9), p = 0.01). The maintenance of wakefulness test improved significantly in the therapeutic group, but not in the placebo group (−10.6 (13.9) v −4.7 (11.8), p = 0.001). Glycaemic control and insulin resistance did not significantly change in either the therapeutic or placebo groups: HbA1c (−0.02 (1.5) v +0.1 (0.7), p = 0.7, 95% CI −0.6% to +0.9%), euglycaemic clamp (W/I: −1.7 (14.1) v −5.7 (14.8), p = 0.2, 95% CI −1.8 to −0.3 l/kg/min1000), HOMA-%S (−1.5 (2.3) v −1.1 (1.7), p = 0.4, 95% CI −0.3 to +0.08%) and adiponectin (−1.2 v −1.1 (1.3), p = 0.2, 95% CI −0.7 to +0.6 µg/ml). Body mass index, bioimpedance and anthropometric measurements did not significantly change in either group. Activity measured by actigraphy increased overall in the group receiving therapeutic CPAP, but the results were variable and did not reach statistical significance. Hours of CPAP use per night were: therapeutic 3.6 (2.8) v placebo 3.3 (3.0), p = 0.8. There was no correlation of CPAP use with any of the measures of glycaemic control or insulin resistance.

Conclusion: Therapeutic CPAP does not improve measures of glycaemic control or insulin resistance in men with type 2 diabetes and OSA.

This study was presented at the ATS in 2006.

## S153 CHANGES IN HEALTH STATUS AFTER A TRIAL OF CONTINUOUS POSITIVE AIRWAY PRESSURE IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA: 2 WEEK V 4 WEEK TRIAL

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Introduction: The recommended treatment for patients with obstructive sleep apnoea (OSA) is continuous positive airway pressure (CPAP), which can improve hypersomnolence, cognitive function, vigilance and quality of life. Current guidelines (SIGN, 2003), however, do not provide recommendations on the necessary duration of a trial of CPAP. The aim of this study was to compare the changes in health status following either a 2 or a 4 week trial of CPAP using the Epworth Sleepiness Scale (ESS) and the Quebec Sleep Questionnaire (QSQ) (Lacasse et al. Thorax 2004;59:494–9).

Methods: Thirty patients with OSA (27 male; median age 46 years, IQR 25–67) were randomised to receive therapeutic (n = 20) or placebo CPAP (n = 22) for 3 months. The study was double blind.

Results: Results are expressed as mean (SD). CPAP improved the ESS significantly more in the therapeutic group than the placebo group (−6.6 (4.5) v −2.6 (4.9), p = 0.01). The maintenance of wakefulness test improved significantly in the therapeutic group, but not in the placebo group (−10.6 (13.9) v −4.7 (11.8), p = 0.001). Glycaemic control and insulin resistance did not significantly change in either the therapeutic or placebo groups: HbA1c (−0.02 (1.5) v +0.1 (0.7), p = 0.7, 95% CI −0.6% to +0.9%), euglycaemic clamp (W/I: −1.7 (14.1) v −5.7 (14.8), p = 0.2, 95% CI −1.8 to −0.3 l/kg/min1000), HOMA-%S (−1.5 (2.3) v −1.1 (1.7), p = 0.4, 95% CI −0.3 to +0.08%) and adiponectin (−1.2 v −1.1 (1.3), p = 0.2, 95% CI −0.7 to +0.6 µg/ml). Body mass index, bioimpedance and anthropometric measurements did not significantly change in either group. Activity measured by actigraphy increased overall in the group receiving therapeutic CPAP, but the results were variable and did not reach statistical significance. Hours of CPAP use per night were: therapeutic 3.6 (2.8) v placebo 3.3 (3.0), p = 0.8. There was no correlation of CPAP use with any of the measures of glycaemic control or insulin resistance.

Conclusion: Therapeutic CPAP does not improve measures of glycaemic control or insulin resistance in men with type 2 diabetes and OSA.

## Abstract S151

<table>
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10% may be more appropriate when risk calculator is required to assess patients with obstructive sleep apnoea (OSA), currently used risk calculator may underestimate the need for higher mean 10-year CVD risk compared with similar patients without OSA. 

**Conclusion:** Changes in health status were similar between patients undergoing a 2 or 4 week CPAP trial and could not be predicted by baseline severity of OSA. Changes in QSQ scores after the trial were correlated with changes in the ESS.

**S154 CARdiovascular Risk Assessment in Patients with Obstructive Sleep Apnoea: Clinical Utility of the Joint British Societies Cardiac Risk Assessor Program**


**Background:** Epidemiological evidence suggests a strong link between obstructive sleep apnoea (OSA) and cardiovascular diseases (CVD). Statins are highly effective in reducing cardiovascular events in a wide range of patients. The recent Joint British Societies (JBS)-2 guideline recommends that statins should be initiated for primary CV prevention in non-diabetic patients whose 10-year CVD risk is estimated to be >20%. Because the accuracy of risk prediction using a Framingham based risk tool is less clear in high risk patient groups, we sought to determine its clinical utility when applied to OSA patients.

**Methods:** A total of 79 patients (41 OSA, 38 non-OSA) referred with clinical suspicion of OSA, who are not taking lipid or glucose lowering drugs and with no previous history of CVD were included. Fasting lipids, insulin, glucose and blood pressure (BP) were measured after an overnight fast. 10 year CVD risk was calculated using the JBS Cardiac Risk Assessor Program.

**Results:** Subjects with OSA were more obese, more insulin resistant, more hyperglycaemic and higher systolic blood pressure levels. Based on the JBS risk calculator, mean 10 year CVD risk was significantly higher in the OSA group compared with the non-OSA group (11.74% vs 6.97, p = 0.003). Using stepwise multiple regression model, after adjusting for age, BMI and smoking history, increased 10 year CVD risk score did not significantly predict OSA status (p = 0.054). To determine a 10 year CVD risk levels that would distinguish between the OSA and non-OSA groups, we used 20%, 15%, and 10%, 10 year CVD risk cut offs to arbitrarily defined patients that require statin treatment. No significant difference was found in the proportion of patients who qualifies for statins between OSA and non-OSA patients when 15% or 20% 10 year CVD risk were used as cut off levels (p = 0.07 and p = 0.15 respectively). However, by lowering the cut off level to 10%, the proportion of patients that qualifies for statins was significantly higher in the OSA group compared with the non-OSA groups (55.2% vs 29.2%; Pearson’s χ²= 5.484, p = 0.02).

**Conclusion:** This finding suggests that whilst patients with OSA have a higher mean 10-year CVD risk compared with similar patients without OSA, currently used risk calculator may underestimate the need for statins in patients with OSA. Using a lower 10-year CVD risk value of 10% may be more appropriate when risk calculator is required to determine the need for statins in this high risk patient group.

<table>
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<tr>
<th>Group</th>
<th>DS</th>
<th>DSY</th>
<th>NS</th>
<th>EMOT</th>
<th>SI</th>
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<td>12.5 (4.8–19.0)</td>
<td>22.0 (9.3–35.8)</td>
<td>17.0 (7.0–24.5)</td>
<td>9.0 (2.8–13.5)</td>
<td>11.0 (4.0–14.5)</td>
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<tr>
<td>2</td>
<td>18.0 (3.3–22.5)</td>
<td>4.5 (3.3–17.0)</td>
<td>9.0 (1.5–18.0)</td>
<td>15.5 (2.0–26.3)</td>
<td>18.5 (3.3–37.8)</td>
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**S155 HIGH PREVALENCE OF SLEEP APNOEA AND NOCTURNAL HYPOVENTILATION IN PATIENTS ASSESSED FOR BARIATRIC SURGERY**

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**Introduction:** Obesity is increasing in the UK. Bariatric surgery is offered to individuals who have a BMI > 40 or BMI > 35 with another risk factor. Obese patients undergoing assessment for bariatric surgery often complain of tiredness and are at high risk of obstructive sleep apnoea (OSA). At present there are no clear guidelines on appropriate assessment and peri-operative ventilatory support. We aimed to define the prevalence of daytime sleepiness, OSA and nocturnal hyperventilation in patients considered for bariatric surgery.

**Methods:** Between November 2005 and June 2006 patients considered for surgery were referred for assessment. Daytime sleepiness was recorded using the Epworth Sleepiness Score (ESS). Due to bed weight restrictions, patients <150 kg were offered inpatient multi-channel sleep study (Win Visi 3, Stowwood Scientific Instruments, Oxon, UK). Heavier patients were offered overnight oximetry at home.

**Results:** Of the 35 patients (25 females) referred, three were above 150 kg and were offered overnight oximetry only. Of these one had hyperventilation (mean overnight oxygen saturation <92%) one had less than 10 4% dips in oxygen saturation per hour and one did not attend. Three patients did not attend the sleep study, leaving 29 patients (21 females) with full sleep study data. Patients anthropometric data at baseline was mean (SD) age 46.8 (10.7), BMI 45.0 (14.2). Mean Epworth score was median 11.3 (5.0) but 17 patients (58%) rated themselves as sleepy scoring >10. All patients had more than 6 hours of data on sleep study. Mean overnight saturation was 93.1 (4.0). Six patients (21%) had nocturnal hyperventilation (mean saturation <92%). Mean saturation was weakly negatively correlated with BMI R² = 0.25. The mean number of 4% dips in oxygen saturation per hour (dip rate) was high 24.9 (36.4) due to a non-normal distribution (median dip rate 7.45 range 0.13–117). Eleven patients had a dip rate more than 10 per hour of sleep. 8 patients more than 20/h and 6 patients more than 30/h. Daytime sleepiness poorly predicted either sleep apnoea or hyperventilation with a very weak correlation between either ESS and dip rate r² = 0.13, or between ESS and mean saturation r² = 0.1. Four patients (14%) had a normal <10 ESS and dip rate <10/h. Twelve patients (41%) reported sleepiness but had dip rate >10/h. Six patients (28%) reported little sleepiness but had a dip rate >10/h, and in some cases severe OSA. Seven patients (24%) reported sleepiness and dip rate >10/h.

**Conclusion:** Sleep apnoea and nocturnal hyperventilation are very common in the obese and severely obese considering bariatric surgery and should be considered prior to surgery. The Epworth sleepiness score poorly predicts OSA in these patients.

**S156 SNORING, SLEEPINESS AND BEHAVIOURAL CORRELATES IN CHILDREN AND ADULTS WITH DOWN’S SYNDROME**

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**Aim:** Children and adults with Down’s syndrome (DS) are predisposed to sleep disordered breathing (SDB). Sleepiness can manifest as behavioural and emotional disturbances in this group. We aimed to measure the prevalence of SDB, sleepiness and behavioural and emotional disturbances in DS.

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Method: A sleep questionnaire, including the Epworth Sleepiness Score (ESS) and modified subscales of the Developmental Behaviour Checklist-P and A were sent to 699 people with DS and their families/carers in Scotland.

Results: Of 329 responses (47%), 290 were valid for analysis (subjects aged ≥4 years). 158 children had a mean age of 11.4 (SD 4) years and 75 (47%) were snorers. Snoring children were more obese BMI kg/m²: 22 (SD 5) v 20 (SD 4) p = 0.02) and more depressed (p = 0.012) than non-snorers. Higher BMI was significantly associated with snoring in children (p = 0.034). Male children scored higher than females on the anxiety and antisocial behaviour scales (p < 0.05). Of 132 adults, median age was 28 (IQR 22–34) years and median ESS 4 (IQR 2–7.25); 53 (40%) snored. Snoring was associated with younger age (p = 0.006), higher BMI (p = 0.05) and trended to an association with hayfever (p = 0.055). The ESS correlated with snoring (p = 0.001). Snorers were more depressed (p = 0.003) and more sleepy (p = 0.016) than non-snorers. The ESS correlated significantly with all three behavioural subscales (p < 0.006).

Conclusion: This is the first population survey of SDB in both children and adults with DS. Only BMI predicted snoring status in children. Both children and adult snorers were significantly more depressed than non-snorers. ESS is useful in the adult DS population and correlated with behavioural disturbances and snoring.

Acknowledgements: Lou Marsden; Down’s Syndrome Scotland.