Spoken sessions

TB epidemiology

**S1** THE OUTCOME OF A COHORT OF TUBERCULIN POSITIVE, PREDOMINANTLY SOUTH ASIAN, NEW ENTRANTS AGED 16–34 TO THE UK: BLACKBURN 1989–2001

I. W. Chaudry1, L. P. Ormerod2,3, I. Central Lancs PCT; 2Royal Blackburn Hospital; 3University of Central Lancs, UK

**Background:** The incidence of TB in new entrants aged 16–34 with positive tuberculin tests but normal chest x ray/examination after initial entry is uncertain and has been estimated for the NICE economic appraisal of new entrant screening.

**Methods:** New entrants aged 16–34 years predominantly from South Asia with tuberculin tests inappropriately positive for BCG history from 1989–2001 were studied and matched to the local notification database to July 2006.

**Results:** 479 entrants with normal chest x rays were identified. Median age was 24.0 years, 19% had prior BCG. The observation time was 4668.5 years. 49 developed clinical TB up to July 2006. The median detection of TB was 47 months, 75% by 79 months and none after 156 months. The incidence density of cases was 1050/100 000 person years (95% CI 756 to 1344), an annual risk of 1.05% (10.5% at 10 years; 15.8% at 15 years). 5% of individuals mainly students had moved out of the area. Of the remainder 29% were definitely shown still to be locally GP registered. Efforts are continuing to assess the remaining 312 individuals.

**Conclusion:** These patient-derived data show a minimum risk of TB disease of 10.5% at 10 years. The true rate could be even higher because (a) some persons may have moved/not been notified locally and (b) gamma-interferon test would now remove false positives. The NICE Guidelines section 12.2.8 (p 168) states “The health economic model shows cost-effectiveness when risk over 15 years after entry in the UK exceeds 12%”. These data show that this cohort of South Asian entrants have TB levels of a minimum of 10.5% suggesting it would be cost effective to screen such entrants (currently excluded) for latent TB infection.

**S3** INCREASING ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE UK


**Background:** The incidence of tuberculosis is increasing in England, Wales and Northern Ireland. This study examines the recent trends in, and factors associated with, anti-tuberculosis drug resistance in these three countries.

**Methods:** Information on drug susceptibility for Mycobacterium tuberculosis complex isolates was obtained from UK reference laboratories. Isolates; matched to tuberculosis cases reported to the enhanced tuberculosis surveillance system, which contains clinical and demographic information. Trends in drug resistance and associated factors were analysed using logistic regression. Strain typing information for cases with multi-drug resistant tuberculosis (MDR-TB) were obtained from the reference laboratories.

**Results:** The proportion of culture-confirmed cases with MDR-TB remained stable between 1998 and 2005 at around 1%. Resistance to isoniazid increased from 5% to 7% in the first five years of this period. Rifampicin, ethambutol and pyrazinamide resistance remained stable at around 1.2%, 0.4% and 0.6% respectively. The increase in isoniazid resistance outside London was a result of changes in place of birth and ethnicity of cases. In London, the rise was related to an outbreak. For cases with MDR-TB susceptibility to second line drugs was available for cases reported in 2002 (84% of cases), 2003 (86%), 2004 (95%) and 2005 (100%). One case was identified as extensively drug resistant (XDR). This case was reported in 2003. Strain typing information was available for 42% of MDR-TB cases reported in 2004–5. The proportion clustered was 20%. Resistance to rifampicin, clofazimine and amikacin were associated with isoniazid resistance. Strain typing data suggest that some transmission of MDR-TB may be occurring, but the data are limited and most cases for which data were available were unclustered. The increase in isoniazid resistance reflects changes in the characteristics of cases and inadequate control of transmission in London. The observed increase highlight the need for early case detection, rapid drug susceptibility testing and improving treatment completion. Universal strain typing will facilitate the investigation of these trends.

Advice was taken from King’s College Paediatric TB Team regarding treatment. Neither patient became culture negative and treatment was abandoned. Out of the ‘slow-growers’ (MAI, Xenopi, Kanssavi and Malmoense) antibiotics consistent with the guidelines were prescribed 94% of the time and the intended duration of treatment was consistent with the guidelines in 83% of patients. However, the intended duration of treatment was only met in 50% of cases and only 33% were culture negative at the end of treatment. 33% of patients did not tolerate the treatment. Reasons given included diarrhoea with lethargy, peripheral neuropathy, renal and liver toxicity and decreased visual acuity. Of the 70% of patients not treated, the commonest reason cited was that the organism was felt to be a contaminant (60%). Other reasons included death and concomitant treatment for mycobacterium tuberculosis.

**Discussion:** Environmental mycobacteria are widely distributed in nature and are often found without evidence of disease. There is much debate as to which patients require treatment, with which drugs and for how long. The current guidelines are complex and do not include evidence from recent trials and hence clinicians have been uncertain or reluctant to follow them. Our survey found that MAI was the commonest organism identified. Although the antibiotics and intended duration of treatment stated at the start were usually consistent with the guidelines, we found that only 50% of cases completed with this, with about 1/3 being culture negative at the end of treatment. It should be noted that 1/3 of our patient remained on their treatment at the time of the survey, which may therefore underestimate this cure rate. Up to date guidelines are needed for management of these patients, and management by physicians with experience and expertise in this field is essential in order to provide the best service for these complex patients who frequently have significant other co-morbidities.
Hospitals, London, UK; 3Murambinda Mission Hospital, Buhera, Zimbabwe
decreasing trend in the USA: a matter of migration. PDO. Increasing tuberculosis in England and Wales compared with a
decreasing trend in USA. (Duraira, Davies

Introduction:

Spoken sessions A5

Abstract S4.

S4 A COMPARISON OF TUBERCULOSIS CASE RATES IN THE HOME-BORN WHITE POPULATIONS OF THE UK AND USA: AN INCREASING DISPARITY

S. Durariaj, N. Schluger, M. Asim, N. Sinnott, P. D. O. Davies. Cardio-thoracic Centre, Liverpool, UK

Introduction: In 2005 we presented data regarding the increasing TB rates in England compared with a decreasing trend in USA. (Durariaj, Davies PDO. Increasing tuberculosis in England and Wales compared with a decreasing trend in USA: a matter of migration. Thorax 2005;60:i20.) We have now carried out a further analysis to compare case rates in the home-born White populations of the UK and USA.

Methods: Data were compared using government based websites www.cdc.gov for USA statistics and www.hpa.org.uk for the UK.

Results: We compared the rate of TB in the home-born White populations of the UK and USA over the most recent 12-year period for which data are available. The data show that in 1993, the rates/100 000 for the US born White population was 3.6, compared with 4.78 for the equivalent population in UK. By 2001 the rate in the White home-born US population was 1.5 compared with the equivalent UK figure of 3.6. The latest available data are for 2005. In this year the rate in US White home-born population had declined further to 1.3 compared with the UK figure which had remained static at 3.6 (see fig). The difference in the rates in similar population groups are therefore nearly three times higher in UK compared with the USA. As seen in the figure the US rates continue to decline in the home born White population compared with rates in UK.

Conclusion: There is a widening disparity between rates of TB in the White home-born US population compared with the equivalent UK population. Rates in the UK group seem to have stopped declining. The reasons for the disparity is not yet clear. It is possible that the more aggressive policy of giving preventive therapy to individuals with latent tuberculosis in the US may be making some contribution. One possible explanation could be that there may be unidentified transmission from immigrants to the White population within the UK where TB among some ethnic minority groups is rising, whereas rates among all groups in the US continue to fall (Durariaj et al, 2005).

S5 ACCURATE DATA COLLECTION: IMPACT ON TREATMENT OUTCOMES AT A RURAL TB PROJECT IN ZIMBABWE

R. M. Smith1, K. M. Scott2, R. D. Barker2, F. J. C. Millard1, M. Glenshaw2, E. Manonamao1. 1Department of Respiratory Medicine, King’s College Hospital; 2King’s College, London School of Medicine at Guy’s, King’s and St Thomas’s Hospitals, London, UK; 3Mushamba Mission Hospital, Buhera, Zimbabwe

Introduction: Our first attempts to determine treatment outcomes for the rural TB project in Buhera district, Zimbabwe showed poor case detection; during 2004 the TB detection rate was 422/100 000/year (64% of WHO estimate).

However, treatment outcomes for those registered appeared suspiciously good considering the high HIV prevalence (see table). We wished to improve the accuracy of data collection to determine “true” outcomes.

Methods: Two data managers have been employed. They have made concerted efforts to establish accurate treatment outcomes by regularly visiting the district’s primary healthcare clinics and supporting the home-based care team with defaulter follow-up.

Results: Treatment outcomes reported for 2005 were worse than for 2004; only 44% achieved treatment success in 2005 and 46% defaulted. We believe this apparent deterioration in outcomes is a reflection of increasingly accurate data recording. Patients had been recorded as treatment complete when their outcomes were unknown. Revised results following intensive activities to gain true outcomes for those treated in 2005, and data from 2006 will be presented.

Conclusions: TB notifications in the district remain below WHO estimates. The data are likely to be more accurate than previously reported. It is essential that true outcomes are recorded in order that the problems can be defined and appropriate strategies for improving TB control implemented. These “truer” TB treatment outcomes are far from meeting the Stop TB Partnership Targets. Treatment success rates are low, and very few patients achieve “cure”. Follow-up of defaulters is difficult in such rural settings but essential in order to avoid emergence of drug-resistant TB. Systems previously in place for follow-up of defaulters have largely disintegrated owing to the political and economic situation. Further research is necessary. However, a picture is emerging of poor access to chronically under-resourced healthcare services leading to poor case detection and case holding. Local and national initiatives are needed, including improved access to diagnosis by decentralisation of sputum collection, support of the national laboratory in provision of culture and DST, collaboration with the HIV service and continued strengthening of patient follow-up at the sub-district level. We in the UK can help by providing financial and technical support for these interventions.

S6 INCREASING TREND OF NON-TUBERCULOUS MYCOBACTERIA IN ENGLAND, WALES AND NORTHERN IRELAND 1995–2006: REAL OR ARTEFACT?

J. Moore, C. Anderson, M. Kuijshaar, I. Abubakar. Health Protection Agency, UK

Introduction: Since the late 1980s, the number of cases of tuberculosis has increased in England, Wales and Northern Ireland. In light of this, reports of infections with non-tuberculous mycobacteria were investigated to see whether such infections showed similar trends.

Methods: Hospital laboratories in England, Wales and Northern Ireland voluntarily report mycobacterial infections to the Health Protection Agency Centre for Infections. Details routinely reported include age and sex of the patient, species and specimen type. All records of non-tuberculous mycobacterial infections were investigated to see whether such infections showed similar trends.

Results: The number of reported infections rose from 460 in 1995 to 1609 in 2006, an increase of 350%. Nine out of fourteen species reported increased in England, Wales and Northern Ireland. In light of this, reports of infections with non-tuberculous mycobacteria were investigated to see whether such infections showed similar trends.

Conclusions: Non-tuberculous mycobacterial infections reported has increased considerably since 1995. This may be due to changes in diagnostic and reporting practices and the rise in HIV infection and other causes of immunsuppression in the population. An investigation into possible contributions to this increase will be presented.

Asthma: clinical aspects

S7 THE EFFECT OF MECHANICAL HEAT RECOVERY VENTILATION ON THE CONTROL OF ASTHMA: A RANDOMISED CONTROLLED TRIAL

G. R. Wright1, S. G. Howieson2, C. Mcharry3, A. D. Mcmahon1, R. Chaudhuri1, J. Thompson1, I. Fraser1, L. Mcalpine2, S. Wood1, N. C. Thomson3. 1University of Glasgow; 2University of Strathclyde; 3Monklands General Hospital, Lanarkshire, UK

Background: Sensitivity to the dust mite allergen Dermatophagoides pteronyssinus 1(Der p 1) is commonly associated with asthma in the UK. The

Abstract S5  Treatment outcomes reported for 2004

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>75%</td>
</tr>
<tr>
<td>Defaulted</td>
<td>12%</td>
</tr>
<tr>
<td>Transferred out</td>
<td>6%</td>
</tr>
<tr>
<td>Failed</td>
<td>0%</td>
</tr>
<tr>
<td>Died</td>
<td>7%</td>
</tr>
</tbody>
</table>

www.thoraxjnl.com

Thorax: first published as on 19 November 2007. Downloaded from http://thorax.bmj.com/ on 14 July 2021 by guest. Protected by copyright.
warm, humid environment of modern homes favours the house dust mite population, but the effect of improved domestic ventilation on the control of asthma is uncertain.

Methods: We conducted a randomised double-blind placebo-controlled trial of the installation of mechanical heat recovery ventilation in the homes of 120 adults with asthma who were sensitive to Der p1. Activation of the unit was concealed from the subjects; half were activated at randomisation, the others after 6 months of the study. All subjects had conventional allergen avoidance at baseline. The primary outcome measure was morning peak expiratory flow at 12 months. Secondary outcome measures included evening peak expiratory flow rate, asthma control questionnaire score, St George's Respiratory Questionnaire score, courses of oral corticosteroids, hospitalisation, rhinitis visual analogue scores, relative humidity, Der p1 levels, and specific IgE to dust mite. 

Results: At 12 months, the change in mean morning peak expiratory flow as compared with baseline, did not differ between the mechanical ventilation group and the control group (mean difference 13.59 l/min, 95% CI -2.66 to 29.85, p=0.100). However, evening mean peak expiratory flow was significantly improved in the mechanical ventilation group (mean difference 24.56 l/min, 95% CI 8.97 to 40.15, p=0.002) and there were fewer hospitalisations for asthma. (0 vs 4, p=0.029). Values for other clinical outcome measures did not differ between the two groups at 12 months. Nasal symptoms significantly improved in the MHRV group compared to the control group at 6 months (nasal discharge mean difference -1.36, 95% CI -2.30 to -0.42, p=0.005), but not at 12 months (mean difference 0.46, CI -0.47 to 0.55, p=0.371). Indoor relative humidity was reduced more effectively in the bedrooms of mechanically ventilated homes in winter months. Der p1 analysis is awaited. 

Conclusion: Installation of mechanical ventilation in the homes of adults with chronic asthma and sensitivity to house dust mite results in an improvement in some indices of asthma control.

S8 EXAMINING THE RELATION BETWEEN ASTHMA AND RHINITIS RESPONSE FOLLOWING OMAZILUMAB THERAPY

L. P. Boulet1, R. Niven2. 1Institut de Cardiologie et de Pneumologie de l’Université Laval, Québec, Canada; 2North West Lung Centre, Manchester, UK

Background: Omalizumab, an anti-IgE antibody, has proven efficacy as add-on therapy in the treatment of severe persistent allergic (IgE-mediated) asthma, reducing exacerbations, emergency visits, and improving quality of life. Additionally, improvements in rhinitis control have been seen in patients with persistent allergic rhinitis. We investigated the relationship between efficacy of omalizumab on lung and nasal outcomes in patients with co-existing allergic (IgE-mediated) asthma and rhinitis.

Methods: This post hoc analysis of the SOLAR study2 examined whether a response to omalizumab in terms of asthma control predicted a higher likelihood of a large rhinitis response. Patients were classified as asthma responders if they were judged by the physician to have achieved complete or marked improvement in asthma control according to a five-level evaluation (complete control; marked improvement in control; discernable but limited control; no appreciable change; worsening in control), based on multiple aspects of response including patient interviews, review of medical notes, spirometry and diaries of symptoms, rescue medication use and peak expiratory flow. Patients were classified as having a large rhinitis response if they achieved a >1.5-point improvement in Rhinitis Quality of Life Questionnaire (RQLQ) overall score. The RQLQ self-administered questionnaire contains 28 items covering eight domains (overall, activity limitation, sleep impairment, non-nasal or non-ocular symptoms, practical problems, nasal symptoms, eye symptoms, emotional function), and assesses the previous seven days.

Results: Data were available for 207 omalizumab patients (123 (59.4%) asthma responders, 84 (40.6%) asthma non-responders) and 192 placebo patients. Overall, 90% of patients had severe persistent asthma according to GINA 2002 classification. The likelihood of a large rhinitis response (>1.5-point improvement in RQLQ) was significantly greater in omalizumab-treated asthma responders than in the placebo group (64.2% vs 36.4%, p<0.001). In patients who did not respond to omalizumab treatment, the percentage of patients who responded in terms of their rhinitis (32.1%) was similar to placebo. The odds ratio for a large rhinitis response in omalizumab-treated asthma responders vs asthma non-responders was 3.79 (95% CI 2.11 to 6.82).

Conclusions: Response to omalizumab therapy in terms of improvement in asthma control is associated with a significantly increased probability of improvement in quality of life associated with rhinitis symptoms. Omalizumab-treated asthma responders are 3.8 times more likely to experience a large (>1.5-point) improvement in rhinitis related quality of life scores than omalizumab-treated asthma non-responders.

S9 EFFECT OF INHALED CORTICOSTEROIDS ON SMALL AIRWAY DYSFUNCTION IN MILD TO MODERATE PERSISTENT ASTHMASM

D. Menzies, S. Ismail, P. Hopkinson, A. Nair, B. Lipworth. University of Dundee, Dundee, UK

Background: Small airway dysfunction in asthma is poorly characterised. We have investigated the effect of inhaled corticosteroids (ICS) on small airway inflammation and calibre in adult asthmatics.

Methods: After withdrawal of usual treatment and a steroid free run-in, mild to moderate persistent asthmatics underwent four weeks of prospective treatment with 800 μg per day of inhaled beclometasone. Healthy volunteers acted as a control group. Airway inflammation was quantified using tidal (FeNO) and alveolar (CALV) nitric oxide, and bronchial flux (JNO). Impulse oscillometry was used to determine total, central and peripheral airway resistance.

Results: Compared with healthy volunteers (n = 27), asthmatics (n = 21) after withdrawal of usual ICS treatment had significantly different values for FEV1 (median 10.7 ppp; IQR 17.9 to 17.7 vs 33.8 ppp; 16.8 to 52.5, p<0.001); JNO (0.48 n/s; 0.37 to 0.89 vs 1.71 n/s; 0.67 to 2.55, p<0.001); CALV (1.27 ppb; -1.00 to 2.07 vs 1.24 ppb; 1.49 to 3.95, p=0.009); total resistance (0.49 kPa/s); 0.36 to 0.64 vs 0.36 kPa/s; 0.30 to 0.41, p=0.002); and peripheral resistance (0.09 kPa/s; 0.02 to 0.16 vs 0.01 kPa/s; -0.01 to 0.03, p<0.001); but not central resistance (0.38 kPa/s; 0.25 to 0.47 vs 0.36 kPa/s; 0.29 to 0.39, p<0.009). ICS attenuated both FeNO (p<0.001), JNO (p<0.001), and CALV (p<0.002), such that values were no longer significantly different from HV (p=0.59, 0.79 and 0.66 respectively). There were no commensurate changes in peripheral airway resistance or spirometry indices.

Conclusion: Treatment with ICS suppresses peripheral inflammation in mild to moderate asthmatics, but has no effect on airway calibre.

S10 THE LONGITUDINAL CORRELATION BETWEEN FRACTIONAL EXHALED NITRIC OXIDE AND SPUTUM EOSINOPHIL COUNTS IN REFRACTORY ASTHMA

P. Haldar, S. Birring, M. Berry, C. Brightling, P. Bradding, A. Wardlaw, I. Pavord, R. Green. Institute for Lung Health, Leicester, UK

Introduction: Fractional exhaled nitric oxide (FeNO) concentrations correlate significantly with sputum eosinophil counts in cross-sectional studies of asthma and have been proposed as a simple clinical tool for monitoring eosinophilic airway inflammation. However, little is known of
the longitudinal correlation between these parameters. We investigated this relation in 88 patients with refractory asthma who are current non-smokers regularly attending the Glenfield Hospital Difficult Asthma Clinic. Methods: All patients had 3 or more paired measurements of FeNO at 50 ml/s and induced sputum eosinophil counts over time. Longitudinal correlation coefficients (Lc) were calculated from within subject analysis of covariance of log transformed FeNO and % sputum eosinophil counts. Results: 504 paired measurements were obtained (median 5/subject (range 3–12)). Baseline correlation between the parameters was weak but significant (r = 0.39, p < 0.001). The overall within subject longitudinal correlation was weaker (Lc = 0.28, p < 0.001). After stratifying the cohort according to concordance between FeNO and sputum eosinophils at baseline, subjects that exhibited concordance had superior longitudinal correlation (concordant group Lc = 0.34 vs discordant group Lc = 0.19). Within the discordant group, subjects expressing sputum eosinophilia without elevation of FeNO showed the poorest longitudinal correlation between the variables (Lc = 0.08, p = 0.48). We also explored the longitudinal correlation in measurements performed when subjects had concomitant symptoms (Juniper asthma control score >1.57). No significant longitudinal correlation was seen between the parameters during expression of symptoms (Lc = 0.05 calculated from 240 measurements in 68 patients, p = 0.471). This dissociation was mainly due to persistent elevation of FeNO in the absence of sputum eosinophilia (seen with 47.7% of measurements). Compared with the entire cohort, the subgroup of patients expressing this pattern (n = 16) were predominantly female (87% vs 44%, p = 0.002), younger (mean age 39 vs 49.8 yrs, p = 0.002) with minimal eosinophilic inflammation (GM Eos 0.67% vs 4.5%, p = 0.001).

Conclusion: Although a significant longitudinal correlation exists between FeNO and sputum eosinophil counts this is of weaker magnitude than cross-sectional measurements. In a subgroup of patients with uncontrolled asthma symptoms there is no longitudinal correlation between FeNO and sputum eosinophils. The clinical applicability of FeNO guided therapy for refractory asthma may therefore be limited.

S11 A QUALITATIVE ANALYSIS OF HRCT SCANS IN DIFFICULT ASTHMA

S. Gupta1, S. Siddiqui1, P. Haldar1, M. Berry1, R. Green1, J. Entwisle2, I. Pavord1, A. Wardlaw1, C. Brightling1. 1Institute for Lung Health, Glenfield Hospital, 2Glenfield Hospital, University Hospitals of Leicester, UK

Aim: Bronchial wall thickening (BWT) and bronchiectasis (BE) are familiar radiological features in asthma. We sought to identify the prevalence of these airway geometry changes in a large difficult asthma cohort and to explore the association between BWT, BE and clinical characteristics.

Materials and Methods: Patients attending our “Difficult Asthma Clinic” are extensively characterised in terms of history, lung function, health status and airway inflammation. Out of 463 patients attending our clinic between February 2000 and November 2006, 185 had HRCT scans and were included in the study. Thoracic radiologists determined the presence of BWT or BE. Patients were categorised into those with neither BWT or BE (BWT-/BE-), BE only (BWT-/BE+), BWT only (BWT+/BE-) or both (BWT+/BE+).

Results: The difficult asthma cohort (n = 185) had a mean (SEM) age 49.75 (1.76) years, male:female ratio 72:112, disease duration 26.2 (1.4) years and smoking history of 6.77 (1.0) pack years. Other clinical characteristics for the whole cohort were: FEV1/FVC ratio 69.69 (1.11), FEVI % predicted 72.38 (2.0), bronchodilator response (BDR) 8.59 (1.0%), BDP equivalent 2289 (237.5), sputum neutrophils 61.76 (2.1) %, sputum eosinophils (geometric mean 2.06 (95% CI 1.6–2.7)). Four distinct groups were formed based on presence or absence of bronchiectasis and bronchial wall thickening. Clinical characteristics of each group were as shown in the table.

Conclusion: Bronchiectasis independent of bronchial wall thickening is associated with airflow limitation, longer disease duration and higher age in difficult asthma. Further quantitative and longitudinal studies are required to assess airway calibre in this disease cohort.

S12 THE RELATIONSHIP BETWEEN GASTRO-OESOPHAGEAL REFLUX AND VOCAL CORD DYSPHONIA IN A CLINICAL SETTING

N. J. Pargeter, A. H. Mansur. Severe Asthma Unit, Birmingham Heartlands Hospital, UK

Introduction: Vocal cord dysfunction (VCD) represents paradoxical inspiratory vocal cord adduction and is commonly misdiagnosed as asthma. Various case reports have implicated gastro-oesophageal reflux disease (GORD) in triggering VCD. However, the exact prevalence of GORD in VCD has not been previously reported, which is the subject of this study.

Method: Eighty patients (66 females, 14 males, mean age 47.7, age range 16–79) consecutively referred to a VCD clinic were studied using a pre-designed protocol that included in-depth interviews and flow volume loops. Diagnosis of VCD was made via nasendoscopy. The cohort comprised three groups: confirmed VCD (by nasendoscopy); suspected VCD (not seen on nasendoscopy but suggestive from flow volume loops and/or classical symptoms); excluded VCD. Diagnosis of GORD was made by barium swallow and/or 24-h pH monitoring. GORD positive patients (60/80, 75%) received at least eight weeks of twice-daily, high-dose proton pump inhibitor (PPI) therapy. Due to poor GORD symptom control 6/60 (10%) went on to have anti-reflux fundoplication surgery, in line with their physicians’ recommendations. Patients were asked for feedback on their throat symptoms pre and post GORD treatment.

Results: VCD diagnosis was confirmed in 34 patients (42.5%), of which, 28 (82%) had physician diagnosed asthma and 27 (79%) had GORD. In the

**Abstract S12** Prevalence of asthma and GORD within the three subject groups.

<table>
<thead>
<tr>
<th></th>
<th>VCD &lt;span class=&quot;namenumber&quot;&gt;n=34&lt;/span&gt;</th>
<th>Suspect VCD &lt;span class=&quot;namenumber&quot;&gt;n=31&lt;/span&gt;</th>
<th>VCD excluded &lt;span class=&quot;namenumber&quot;&gt;n=15&lt;/span&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>57 (17%)</td>
<td>52 (17%)</td>
<td>49 (33%)</td>
</tr>
<tr>
<td>GORD</td>
<td>27 (8%)</td>
<td>25 (8%)</td>
<td>21 (14%)</td>
</tr>
</tbody>
</table>

Mean (SEM); #GEM (95%CI); ^ANOVA, p = 0.0381; *p<0.01, A&B; **p<0.05, A&C; ***p<0.01, A&B; ***p<0.001, A&B.

Mean (SEM); #GEM (95%CI); ^ANOVA, p = 0.0381; *p<0.01, A&B; **p<0.05, A&C; ***p<0.01, A&B; ***p<0.001, A&B.

www.thoraxjnl.com
Clinical trials in NIV

S13 NON-INVASIVE VENTILATION IN PATIENTS WITH ACUTE CARDIOGENIC PULMONARY OEDEMA: THE 3PCO TRIAL (A MULTICENTRE RANDOMISED CONTROLLED TRIAL)

A. Gray1, M. W. Elliott2, S. Goodacre3, D. E. Newby4, F. Sampson5, J. Nicholl6, M. Masson1. 1Royal Infirmary of Edinburgh; 2University of Edinburgh; 3University of Sheffield; 4St James’s University Hospital, Leeds, UK

Introduction: This open prospective randomised trial of the early management of acute cardiogenic pulmonary oedema (ACPO), aimed to determine (a) the clinical effectiveness of non-invasive ventilation (CPAP or NIPPV) and standard therapy against standard therapy alone, and (b) the comparative effectiveness of CPAP and NIPPV.

Setting: Emergency Departments of 26 centres between July 2003 and April 2007. Entry criteria: Clinical/radiological characteristics of ACPO, respiratory rate >20/min, arterial hydrogen ion 45 mmol/l (pH 7.35). Intervention: standard therapy, non-invasive positive pressure ventilation (NIPPV; inspiratory pressure 20–30 cmH2O, expiratory pressure 4–10 cmH2O) or (CPAP; 5–15 cmH2O). All patients received standard medical treatment at discretion of treating physician. Oxygen was titrated to a maximum of 60%.

Outcomes: Primary: 2-day mortality for standard therapy versus non-invasive ventilation. Secondary: 30-day mortality and intubation rate. Ancillary: Improvement in physiology, symptoms, myocardial infarction and intubation rates. Power calculation: Sample size 1,200 to detect 6% mortality difference with 80% power.

Results: 1,069 patients (mean age 78 years; 43% male) were recruited and randomised to standard therapy (n = 367), CPAP (n = 346; 10±4 cmH2O) or NIPPV (356; 14±5.7 cmH2O). At entry patients were tachycardic (heart rate 113 (22)/min), acidic (pH 7.25 (0.11)), tachypnoeic (respiratory rate 32 (7)/min) and hypoxic (oxygen saturation 90 (8)%). Compared to standard therapy, non-invasive ventilation was associated with greater improvements in tachycardia (102 (23) vs 96 (22)/min; p = 0.001), acidosis (pH 7.33 (0.11) vs 7.36 (0.11); p = 0.002) and tachypnoea (26 (6) vs 25 (6); p = 0.023) at one hour. The 7-day and 30-day mortality was similar for both forms of non-invasive ventilation (11.7% vs 11.1%, CPAP vs NIPPV; p = 0.806).

Conclusions: In patients with ACPO, non-invasive ventilation induces a faster improvement in respiratory distress and metabolic disturbance, but has no effect on short-term mortality. CPAP and NIPPV appear to be equally efficacious.

Funding: This project was funded by the NIHR Health Technology Assessment Programme (project number 01/43/01). The views and opinions expressed are those of the authors and do not necessarily reflect those of the Department of Health.
NON-INVASIVE VENTILATION IN MOTOR NEURON DISEASE: AN AUDIT OF CURRENT PRACTICE

B. Green, K. Adeniji, J. Wilkinson. Southampton General Hospital, UK

Background: The use of non-invasive ventilation (NIV) for symptom palliation in motor neuron disease (MND) is now well recognised, however uptake and access to NIV services shows significant regional variation. An MND NIV service was established in Southampton in 2004 for patients with respiratory symptoms or declining lung function. The possible benefits of NIV use in MND are discussed at initial assessment. Patients are offered a trial of NIV to assess the possible benefits of NIV in patients with hypercapnia. Objective: To evaluate referral outcome and degree of respiratory compromise at the time of referral by retrospective notes audit.

Results: Fifty two referrals were identified over a three-year period. 22 (42.3%) received a trial of NIV. 16 (72.7%) tolerated NIV trial. 10 died before the trial, 2 were inappropriate for, and 5 declined an NIV trial. 13 received active follow-up. 15 (28.8%) accepted long-term NIV. 52.8% declined NIV trial. Median survival from time of diagnosis for patients who accepted home NIV was 26 months contrasted to just 13 months for patients who failed to tolerate NIV (p = 0.03). There was no significant correlation between time to referral, BMI, bicarbonate, PaCO2, forced vital capacity (FVC)% predicted, bulbar score, orthopnoea or symptoms of hypercapnia, and overall outcome of the referral. Patients tolerating NIV had higher mean arterial bicarbonate (28.1 vs 25.1 mmol/l, p = 0.04) and higher PaCO2 (5.85 vs 5.12 kPa, p = 0.05) than patients that failed NIV trials. Patients who failed an NIV trial had a mean FVC% predicted of 51% compared to 62% in patients who accepted NIV (p = 0.014). No significant correlation between toleration of NIV and bulbar dysfunction score was seen (r = 0.25).

Conclusions: When an NIV service is available to MND patients its use is widely applicable and well tolerated. We observed a significant survival advantage in patients who accept home NIV although the aim of the treatment is symptom palliation. Although severity of bulbar dysfunction has previously been cited as a limitation to the use of NIV our findings do not support this. NIV was better tolerated in patients with worse respiratory function as measured by lower FVC% predicted, higher bicarbonate and higher PaCO2.

LONG-TERM OUTCOME OF VENTILATORY SUPPORT IN PATIENTS WITH RESPIRATORY FAILURE DUE TO DUCHENNE MUSCULAR DYSTrophy

M. Ali, I. E. Smith, T. Quinellin, J. M. Shneerson. 1Papworth Hospital NHS Trust, Cambridge, UK

Introduction: Duchenne muscular dystrophy (DMD) is an X-linked recessive disease characterised by progressive muscle weakness. Respiratory muscle weakness is inevitable and often leads to hypercapnic respiratory failure. Non-invasive ventilation (NIV) has been shown to improve quality of life and survival of patients with DMD who develop respiratory failure. One previous study from the UK has reported a five-year survival of 85% for hypercapnic DMD patients who were treated with NIV. Aim: To evaluate the characteristics and long-term outcomes of patients with DMD referred to a specialist service.

Method: Patients were included if they were referred for ventilatory support (between March 1985 and March 2007) were available for a retrospective review. Patients with Becker muscular dystrophy were excluded.

Results: All were males (mean age of 20 yrs at the time of referral). All were unable to walk. Eighteen (56%) had scoliosis. Median FEV1/FVC at the time of referral was 0.51/0.61 (n = 14). Mean peak inspiratory and expiratory pressures were 35 and 32 cm H2O (n = 7 and 10 respectively). Eighteen (56%) had abnormalities detected on ECG or echocardiogram. Twenty two (69%) were given NIV over the period of study (including 19 who were given NIV at their first assessment)—13 had daytime hypercapnia, 3 had already been trialled on NIV, 2 had only nocturnal hypoventilation and 4 were weaned to long-term NIV after prolonged invasive ventilation. One failed to be weaned and required long-term tracheostomy ventilation. Median survival following NIV was 7 years (95% CI 1 to 12). Following NIV, one survived for 12 years and another was still alive 22 years later. Mean age at death for NIV users was 27 years. Among 22 NIV users, 10 reported pressure sores from the mask or nasal symptoms but all continued to use NIV.

Conclusion: This study reports the survival of DMD patients following NIV over a longer period than previously reported from the UK. Following NIV, median survival was 7 years whereas 2 patients were still alive at 10 years. Following prolonged invasive ventilation, 4 of 5 were weaned successfully to long-term NIV.
Abstract S18

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>2003–6, n (%)</th>
<th>2006–7, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domiciliary NIV initiated</td>
<td>86</td>
<td>98</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55.9 (range 13–85)</td>
<td>54.2 (range 17–83)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (46.5)</td>
<td>45 (45.9)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (53.5)</td>
<td>53 (54.1)</td>
</tr>
<tr>
<td>Elective admission</td>
<td>43 (50.6)</td>
<td>53 (54.1)</td>
</tr>
<tr>
<td>Emergency admission</td>
<td>42 (49.4)</td>
<td>45 (45.9)</td>
</tr>
<tr>
<td>NIV initiated post weaning</td>
<td>6 (7.0)</td>
<td>3 (3.0)</td>
</tr>
</tbody>
</table>

*Includes in order of frequency DMD, post polio syndrome, MND, myotonic dystrophy, idiopathic diaphragm paralysis, LGMD, SMA, acid maltase deficiency, FSH, HSMN, CDP, inclusion body myositis and myasthenia gravis.

Abstract S19

Figure 1 Comparison of FTIR spectra for sputum collected from lung cancer cases (grey lines) and non-cancer cases (black lines).

Abstract S19

Figure 2 Discriminant function analysis of FTIR spectra. The plot shows how the differences between spectra can be explained by two variables (DF1 and DF2). Two subgroups of cancer cases are circled. The non-cancer cases effectively group together. There is a further grouping between these two clusters that may represent high-risk or pre-malignant lesions.

Lung cancer: basic mechanisms

S19

FOURIER TRANSFORM INFRARED SPECTROSCOPY MEASURING METABOLIC MARKERS IN SPUTUM IN PATIENTS WITH AND WITHOUT LUNG CANCER

R. Ghosal1, K. E. Lewis2, P. Kloer2, R. Mehta3, D. Parry3, C. Llewellyn-Jones1, S. L. Prior1, L. A. J. Mur4, P. D. Lewis5. 1Respiratory Unit, Carmarthenshire NHS Trust; 2School of Medicine, ILS, University of Swansea; 3Bro Morganwg NHS Trust, Brigid; 4Institute of Biological Sciences, University of Wales, Aberystwyth, UK

Introduction: There are 1.3 million worldwide and over 37,000 new cases of lung cancer diagnosed in the UK each year. The incidence of lung cancer is higher in Wales than in the UK average. MEDLUNG is a long-term study measuring different combinations of metabolic biomarkers for early detection of lung cancer. Biofluids, including sputum and serum, and biopsy tissue are being collected prospectively from people undergoing bronchoscopy for suspected lung cancer. A key objective of this project is to evaluate Fourier transform infrared (FTIR) spectroscopy for metabolic markers in sputum. FTIR is an established, cost-effective technique that enables rapid, high-throughput analysis of different sample types. FTIR has great potential as a metabolic fingerprinting technique and has been applied in a wide variety of clinical settings. We have carried out a preliminary study to evaluate: (1) suitability of sputum as a biofluid for easy/cost effective processing for FTIR and (2) ability of FTIR to distinguish between primary lung cancer and non-cancer cases from sputum.

Method: Patients: Five (biopsy proven) non-small cell lung cancer (cases) and 26 non-cancer controls (mixture of stable COPD patients, "healthy" smoking and non-smoking members of staff). Procedure: sputa was collected prior to bronchoscopy (cases) or in clinic (controls) and were frozen within 2–3 h. Sputum cells were isolated by centrifugation and freeze-dried. Bronchial cell presence in sputum was confirmed by microscopy. Freeze-dried cell extracts were processed in triplicate for FTIR. FTIR spectra data processing and multivariate analysis were performed using Matlab software.

Results: All sputum samples contained bronchial cells and lung cancer patients did not have more bronchial component. This suggests the difference in metabolites is due to different expression rather than cases just producing more sputum (cells).

Conclusion: This pilot suggests that (1) sputum is suitable as a biofluid for easy/cost effective processing for FTIR and (2) FTIR can potentially distinguish between cancer and non-cancer cases in sputum. Greater recruitment and longer term (10-year) follow-up is now assessing combinations of biomarkers in not only diagnosing lung cancer, but also in detecting pre-cancerous lesions and monitoring response to treatment.


www.thoraxjnl.com
DEGRANULATION OF STROMAL MAST CELLS OF THE TRYPOTASE-ONLY PHENOTYPE IS ASSOCIATED WITH IMPROVED PROGNOSIS IN NON-SMALL CELL LUNG CANCER

C. M. Ohri, A. Shikotra, T. Welsh, D. Waller, P. Bradding. Institute for Lung Health, Glenfield Hospital, Leicester, UK

Introduction: It is unclear whether mast cells play a role in preventing cancer formation. We have previously identified a survival advantage for patients with non-small cell lung cancer (NSCLC) who have mast cell infiltration of tumour islets compared to patients who do not.

Methods: The aim of this study was to identify the phenotype of mast cells (either MC<sub>TC</sub>, expressing both chymase and tryptase, or MC<sub>T</sub>, expressing tryptase only) and their state of degranulation in the tumour stroma and islets in NSCLC, using immunohistochemical analysis. The degree of each mast cell degranulation was evaluated using a degranulation index (DI) as follows: 0 = no degranulation, 1 = less than one third degranulation, 2 = one to two thirds degranulation, 3 = more than two thirds degranulation. We compared 20 patients with above median survival (mean survival = 1452 days) versus 20 patients with below median survival (mean survival = 256 days), (p<0.0001).

Results: The mean densities of MC<sub>TC</sub> and MC<sub>T</sub> in tumour islets were higher in patients with a survival above the median (1.2 (0.48) and 2.58 (0.40) cells/mm<sup>2</sup> respectively) compared to those below the median (0.05 (0.02) and 0.19 (0.08) cells/mm<sup>2</sup> respectively) (p=0.003 for both MC<sub>TC</sub> and MC<sub>T</sub>). In patients with above median survival, the MC<sub>T</sub> phenotype in the stroma were degranulated to a greater degree than in those with below median survival (mean DI = 2.29 (0.073) versus 1.89 (0.112) respectively) (p=0.007), as seen in figure 1. In figure 2, a ROC curve demonstrates five-year survival with regards to MC<sub>T</sub> DI in the stroma (area under curve = 0.798, 95% CI 0.661 to 0.934).

Conclusions: Both MC<sub>TC</sub> and MC<sub>T</sub> mast cells infiltrate the tumour islets in patients with NSCLC and good prognosis. While increasing islet infiltration by mast cells also predicts good prognosis, this is accompanied by a higher degree of MC<sub>T</sub> degranulation in the NSCLC stroma. Taken together, degranulating mast cells in the tumour stroma, when accompanied by mast cells infiltrating the tumour islets, contribute to an immune response which protects against tumour dissemination.

PROTEOMIC ANALYSIS OF RESECTABLE NON-SMALL CELL LUNG CANCER: IMPACT OF SMOKING, HISTOLOGICAL TYPE AND STAGE OF DISEASE

S. Rathinam<sup>1</sup>, S. Nyangoma<sup>2</sup>, D. Ward<sup>2</sup>, A. Alzetani<sup>1</sup>, J. Starczynski<sup>1</sup>, A. Martin<sup>2</sup>, P. Johnson<sup>2</sup>, N. D. James<sup>2</sup>, P. B. Rajesh<sup>1</sup>. <sup>1</sup>Birmingham Heartlands Hospital, Foundation Trust; <sup>2</sup>Cancer Research UK Institute for Cancer Studies, University of Birmingham, UK

Background: Surface Enhanced Laser Desorption Ionisation Time of flight Mass Spectrometry (SELDI-TOF-MS) is a mass spectrometry method used to generate “proteomic profiles” of body fluids such as serum. We have used this technique to produce serum proteomic profiles of non small cell lung cancer (NSCLC).

Aim: To determine the impact of smoking, histopathology of the tumour and staging on the proteomic profiles in NSCLC.

Methods: This analysis was performed as a part of the carcinoma of the lung biomarker (CLuB) Study, a prospective observational study with LREC, R&D Approval and NCRN support. The target group were patients undergoing surgery for lung cancer and the controls were from matched non-cancer subjects. Serum samples were analysed using SELDI-TOF-MS. Peak intensities were extracted from the proteomic profiles and a multiple linear regression model was used to evaluate how smoking, cancer type and stage affects the proteome. The p values from t tests of the significance based on the corresponding parameter estimates were used to identify their associated effects on peak intensities. These changes were further evaluated using two-sample t test.

<table>
<thead>
<tr>
<th>Abstract S21 Table 1 Smoking status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Status</td>
</tr>
<tr>
<td>Non-smoker</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Ex-smoker</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abstract S21 Table 2 Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abstract S21 Table 3 Stage distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>Early</td>
</tr>
<tr>
<td>Stage Ia</td>
</tr>
<tr>
<td>Stage Ib</td>
</tr>
<tr>
<td>Stage IIb</td>
</tr>
<tr>
<td>Late</td>
</tr>
<tr>
<td>Stage IIIa</td>
</tr>
<tr>
<td>Stage IIIb</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
</tbody>
</table>
Results: Between January 2005 - September 2006, 70 patients (66% male, median age 65.5 (SD 10.0)) and 75 control subjects (70% male, median age 62.9 (SD 12.5)) were recruited. 131 peaks were detected in the SELDI analysis, of which 40 showed significant differences between cancer patients and controls (p < 0.01). The smoking status is in table 1. The histology and stage distribution is shown in tables 2 and 3. There was a correlation between the stage of NSCLC and the intensity of certain peaks in the serum proteomic profiles. The differences between adenocarcinoma and squamous carcinoma were modest. Smoking also had a clearly detectable influence on the profiles. Some peaks were found to be influenced by cancer alone, some by smoking alone and some by both cancer and smoking.

Conclusions: There was a correlation between the stage of the disease and the intensity of certain peaks in the serum proteomic profiles of patients with NSCLC; however the differences between adenocarcinoma and squamous carcinoma were modest. Smoking also had a clearly detectable influence on the profiles.

Abstract S22.


M. H. Lawson1, D. Ross2, J. Brenton1, J. Hadfield1, M. Goddard2, N. Scroen3, G. Murphy4, R. C. Rintoul2. 1CRUK Cambridge Research Institute; 2Papworth Hospital NHS Foundation Trust; 3University of Cambridge, UK

Introduction: Analysis of RNA using high throughput methods offers a powerful tool for research. However the gene expression profiles generated by such methods are influenced by the quality of the starting RNA which can be influenced by the collection procedure, storage and method used for extraction as well as the type of tissue. At Papworth prospective banking of lung cancer biopsy specimens for use in future research projects has recently begun. This project aims to compare the quality and yield of RNA extracted using a standard method, from non-small cell lung cancer (NSCLC) biopsy specimens collected by different techniques.

Methods: NSCLC biopsy specimens were collected by fibre-optic bronchoscopy (FOB), endobronchial ultrasound guided biopsy (EBUS) or CT-guided needle biopsy. The specimens were snap frozen in liquid nitrogen and stored at -80°C until analysis. RNA was extracted using an RNeasy Mini kit (Qiagen) according to the manufacturer’s instructions. Yield and quality were assessed using a Nanodrop spectrophotometer and by capillary electrophoresis using an Agilent Bioanalyzer.

Results: Yield and quality of extracted RNA was dependent on both the type of biopsy analysed and the quality of each biopsy. Needle biopsy provided the smallest samples and the least RNA. FOB provided the highest yield of RNA and the best quality RNA. The EBUS samples were the largest but did not yield more RNA than FOB samples.

Discussion: It is accepted that the quality of RNA analysed can significantly influence the results of gene expression analysis. Therefore ensuring uniform RNA quality is important in any investigation of comparative gene expression. We have demonstrated that different methods of biopsy collection for lung cancer specimens can result in differences in the quality of RNA when using a standardised extraction protocol. The tissue disruption and homogenisation step of the extraction may need to be optimised for each biopsy type to improve RNA quality. However much of the RNA degradation may be a result of unavoidable tissue crushing during collection activating RNases. The implication is that the most robust design would ensure uniform RNA quality by matching biopsy types for comparison.

Abstract S23.


P. A. J. Crosbie1, G. Magrown2, M. Thormcroft2, P. N. S. O’Donnell1, S. Lewis3, K. Harrison3, R. Agius2, M. Santibanez-Koref4, G. Margisson2, A. Povey2, P. V. Barber1. 1Wythenshawe Hospital; 2Carcinogenesis Group, Paterson Institute for Cancer Research; 3Centre for Occupational and Environmental Health, University of Manchester; 4Institute of Human Genetics, University of Newcastle, UK

Introduction: Chronic exposure to tobacco smoke is associated with over 90% of lung cancer cases in the UK. Interindividual differences in the ability
to repair DNA damage, caused by carcinogens in tobacco smoke, may be a factor in determining the risk of developing lung cancer. One important component of the bodies defence against a subgroup of carcinogens, known as alkylating agents, is the DNA repair protein O6-alkylguanine-DNA alkyltransferase (MGMT). Previous work has shown that two single nucleotide polymorphisms (SNP) are significantly associated with MGMT DNA repair activity: within intron 1 (rs12268840) and in codon K178R (rs2308327). The association with lung cancer risk and these SNPs were investigated using three hospital case control studies.

Methods: Genotyping was undertaken on 617 subjects of whom 255 had lung cancer. All subjects were recruited from the Bronchoscropy Unit, Wythenshawe Hospital over a ten year period. All subjects were aged 40 or older; cases were defined as having an incident diagnosis of lung cancer and controls were cancer free. The majority of the population had a smoking history (89%) and were male (62%). Cases (n = 255) were older than controls (p = 0.001) and had smoked significantly more than controls (52.4 (32.7) vs 46.6 (33.3) pack-years).

Results: The presence of the 178R allele was associated with a reduced risk of lung cancer in two of the three studies (p < 0.05). In a meta-analysis, the odds ratio (95% CI) associated with the 178R allele relative to the 178K allele was 0.64 (0.45 to 0.92) and 0.51 (0.24 to 1.1) in fixed effects and random effects models respectively. A pooled analysis, which was adjusted for age, gender, smoking exposure (pack-years) and case-control series, revealed a reduced odds ratio (OR, 95% CI) for codon 178R heterozygotes (0.67, 0.45 to 1.01) and homozygotes (0.10, 0.01 to 0.96); the trend for a decreased risk with the number of R alleles was significant (p = 0.008). This trend was especially significant in subjects with above median smoking exposure (trend test p = 0.003) but not in those with below median exposure (p = 0.73). There was no evidence of an association between the intronic polymorphism and lung cancer risk.

Conclusions: These results provide evidence of a protective effect of the codon 178R allele with respect to lung cancer risk, especially in heavy smokers. This effect may be due to the polymorphism affecting the function of the MGMT protein and/or levels in MGMT activity.

Improving outcomes in smoking cessation

**S24 IMPORTANT FACTORS IN SMOKING CESSATION IN OLDER PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE VERSUS CRITICAL LIMB ISCHAEMIA**

P. Gleeson, A. Johnson. 1 Kent & Canterbury Hospital; 2Guy’s & St Thomas’ NHS Foundation Trust, London, UK

Introduction: Smoking cessation is a most important part of management for patients with COPD and peripheral vascular disease (PVD). Little is known about the effectiveness of various smoking cessation interventions in older patients (60 years and above) with these conditions and whether there is any correlation between smoking cessation and diagnosis. Aim: To assess the effectiveness of smoking cessation interventions in older patients with COPD or critical limb ischaemia; to ascertain if the diagnosis was a factor in giving up smoking and if not, to understand the reasons behind starting and stopping nicotine use.

Patients and Methods: Forty patients admitted to hospital with either an acute exacerbation of COPD (n = 20) or critical leg ischaemia (n = 20) manifested as ischaemic rest pain, ulceration or gangrene with/without amputation were recruited from SE London (St Thomas’ Hospital (STH)) and Kent (Kent & Canterbury Hospital, K&CH). Only those of 60 years of age or older who had stopped smoking before admission were included in the study. Patients were asked a series of 25 questions focussing on demographics, smoking history, reasons for starting smoking and age at starting, reasons for stopping, when and how, and knowledge and attendance (if any) at a smoking cessation clinic. Patients were also asked if they regretted smoking. The questionnaire was a mixture of specific closed questions and broad open questions allowing participants to express their views.

Results: 80% of vascular and 75% of respiratory patients were male and the median age was 70 years. 67.5% had been manual labourers but 27.5% had been in either office or professional employment. 16/40 patients had smoked 16–20 cigarettes per day, one had smoked <5 and four >30 per day. All patients had started smoking before the age of 20 years, two were under 10. All patients gave similar reasons for starting—peer pressure, part of the job, cheap cigarettes, advertising, the War. Most patients had stopped smoking in the last few weeks to 10 years but two had stopped 30 years before. 13/40 patients had stopped within the previous six months. Both vascular and respiratory patients reported stopping because of episodes of shortness of breath and in addition, half of the vascular patients stopped because of fear of immobility due to amputation. Hospitalisation was a potent trigger to quit (the sheer size of STH making it difficult to smoke) while patients at K&CH were afraid they would not be treated if they continued to smoke. Of those who had stopped years before, respiratory symptoms of breathlessness and coughing in public were important in 44% of COPD and 18% of vascular patients. Financial hardship was important for some patients in Kent while family support helped patients in both areas to stop. 60% of all patients had tried to quit more than once. Only 9/40 had tried nicotine patches, three regarding them as key to success. Only three had used other products without success. Most patients had not used anything to help them give up and relied on willpower. Only three had attended a smoking cessation clinic and two found it helpful. 75% of patients were not aware of any smoking cessation clinic in their area. 52.5% of patients regretted smoking but the remainder had no regrets.

Conclusions: Shortness of breath frightened people most and was a strong motivating force to quit, but the threat of amputation along with other medical conditions were also important. Most patients in this age group had made use of aid to stop smoking. Most patients had smoked >20 cigarettes per day and more than once. Only 9/40 had tried nicotine patches, three regarding them as key to success. Only three had used other products without success. Most patients had not used anything to help them give up and relied on willpower. Only three had attended a smoking cessation clinic and two found it helpful. 75% of patients were not aware of any smoking cessation clinic in their area. 52.5% of patients regretted smoking but the remainder had no regrets.

**S25 SMOKING CESSATION ADVICE FOR HOSPITAL IN-PATIENTS: ROOM FOR IMPROVEMENT**


Introduction: The widely publicised Thorax smoking cessation guidelines state that “all health professionals should give brief advice on smoking cessation” to all patients who smoke, and hospital admission is an ideal opportunity for health professionals, including doctors, to advise patients to give up smoking and provide practical support in the form of nicotine replacement therapy and referral to specialist services.

Methods: We conducted a snapshot survey of all medical, surgical and obstetric/gynaecology inpatients at our medium-sized district general hospital located in a deprived ex-mining area of the East Midlands. The authors visited all medical, surgical and obstetric/gynaecology wards and...
undertook a short questionnaire with those patients who were willing and able to participate. We asked about smoking status, whether smokers had been advised to quit on this admission and if so by whom, whether they had been offered nicotine replacement therapy and where they obtained their cigarettes. All responses were anonymous.

Results: Many of those questioned were ex-smokers, particularly on cardiac and respiratory wards, although we did not collect specific data on this. Some smokers had been offered NRT which was not then prescribed, and many smokers who had not been advised to quit commented that they felt they should have been, particularly in surgery. Most patients who had been advised to quit had been advised by doctors, and some by specialist nurses.

Conclusion: These ‘real-life’ results show that despite guidelines, and the wide availability of nicotine replacement therapy, many smokers especially in non-medical specialties are still not being given adequate help and support to quit during inpatient attendances. They also show that smuggled cigarettes remain widely available, which may be related to the deprived area that the hospital is situated in. More work needs to be done to educate health professionals from all specialties to advise and assist patients to quit smoking in hospital.


Abstract S27

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Smokers, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

S26 A QUESTIONNAIRE SURVEY ON SMOKING POLICY AND SMOKING CESSATION TOOLS IN UK SECONDARY SCHOOLS

J. T. Samuel1, K. E. Lewis1, L. G. Micalpine2. 'Basildon University Hospital, Essex, UK; 1Monklands Hospital, Airdrie, UK

Introduction: 70–80% of smokers start when they are of school age. Smoking cessation (SC) is part of health education in schools but its delivery and implementation is variable. On behalf of the British Thoracic Society (BTS) Tobacco Committee (TC), we surveyed schools across the UK regarding their policies on smoking and what services/teaching they employ.

Methods: A cross-sectional survey of secondary schools local to members of the TC between October and December 2006. Following initial telephone contact, anonymous self-addressed questionnaires were posted to the lead for Professional, Social and Health Education in each school.

Results: Sixty questionnaires were sent out and 49 replies were received (response rate of 82%). All responders said they had a complete smoking policy. 88% had a policy for staff smokers. 61% reported policy breach by students and 16% by staff. 82% reported time specifically dedicated to SC in the curriculum. 37% reported that staff were not comfortable with their level of knowledge of tobacco smoking and SC and only 41% had access to any training in SC education. Although 45% said their available education tools were of a high standard, only 27% reported they had the appropriate skills to motivate and assist pupils who smoke to quit. 92% of schools felt that the BTS could help them educate on the effects of smoking on health and deliver SC advice.

Conclusion: Individual school policies on smoking do exist but are frequently breached, mainly by pupils but also by staff. A significant proportion of responding schools did not feel comfortable with their level of knowledge and skills with less than half saying they had access to appropriate training. Three in four responders felt they did not have the skills to assist pupils who smoke to quit. Help from the BTS was welcome by a majority of schools.


Abstract S28

ACHIEVING A SMOKE-FREE SITE IN A DISTRICT GENERAL HOSPITAL: A SURVEY OF PERCEPTIONS OF HEALTHCARE WORKERS

M. D. Shipley, R. Alcock. Gateshead Health NHS Trust, UK

Background: In December 2006 all UK NHS trusts introduced smoke-free regulations prohibiting smoking on all NHS sites. These rules are to be implemented by all NHS trust staff. We have investigated barriers to the implementation and enforcement of these regulations.

Methods: Study participants were 85 medical and nursing staff working in acute medicine at the Queen Elizabeth Hospital, Gateshead. They completed a questionnaire reporting their behaviour when exposed to smokers on NHS hospital sites.

Figure 1 Summary response data as percentage of sample.
Abstract S28  Figure 2 Reasons for not challenging smokers on hospital site to stop smoking.

Results: Over 50% of medical and nursing staff reported that they would not challenge patients, staff or visitors smoking on NHS trust sites. Employees appeared more likely to challenge patients than visitors, and were more likely to challenge visitors than other staff. Fear of aggression was the most commonly reported reason for not challenging smokers.

Conclusions: This study has highlighted perceived barriers to the implementation of a smoke free NHS in a district general hospital medical unit. Most medical and nursing staff do not enforce NHS policy. Most medical and nursing staff would not challenge patients, staff, and visitors to stop smoking on a hospital site. There are perceived barriers to the implementation of NHS smoke free regulation by medical and nursing staff working in medical units at District General Hospitals in the North East of England. Many staff report non-compliance with NHS and local policies for enforcement of smoke free hospitals. There is scope to improve this through training in NHS policy and how to avoid aggression.

Abstract S29  Is the ban a good idea?

Abstract S30  BOSENTAN FOR INOPERABLE CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION: A RANDOMISED, PLACEBO-CONTROLLED TRIAL—BENEFIT

Abstract S30  Pulmonary circulation: assessment and treatment

Abstract S30  Cardiac index (l/min/m²) 0.30 (0.14 to 0.46)
TPR (dyn × sec/cm²) 193 (283 to 104)
mPAP (mmHg) 2.5 (5.0 to 0.0)
mRAP (mmHg) 0.8 (0.6 to 0.1)
SVO₂ (%) 1.2 (1.8 to 4.3)
NT-pro-BNP (ng/l) 622 (1018 to 225)

www.thoraxjnl.com

Thorax: first published as on 19 November 2007. Downloaded from http://thorax.bmj.com/ on July 14, 2021 by guest. Protected by copyright.
baseline in PVR at rest at week 16 OR change from baseline to week 16 in 6MWD. Other endpoints included: change from baseline to week 16 in WHO functional class (FC), haemodynamics, time to clinical worsening, SVO2, change from baseline in NT-pro-BNP and Borg dyspnea index.

Results: 157 patients were randomised to bosentan or placebo. The PVR analysis set excluded 20 patients (9 placebo, 11 bosentan) and the 6MWD analysis 17 patients (7 placebo, 10 bosentan) because they were considered “inoperable” post-randomisation or due to a missing baseline or post-baseline assessment. Co-primary endpoints: change in PVR from baseline to week 16 was +30 dyn × sec/cm² in the placebo group compared to −1.46 dyn × sec/cm² in the bosentan group, a significant treatment effect of 24.1% (95% CI: −31.5 to −16.0; p = 0.0001). No change in treatment effect was observed in 6MWD at 16 weeks, which increased in the placebo group by 0.8 m compared to 2.9 m in the bosentan group. Other endpoints are shown in table 1. Safety results were consistent with the established safety profile for bosentan from other trials.

Conclusions: These results suggest that bosentan improves haemodynamics in patients with inoperable CTEPH or with persistent or recurrent PH after PEA.

S31 PULMONARY ARTERY OCCLUSION PRESSURE ANALYSIS IN CHRONIC THROMBOEMBOLIC AND IDIOPATHIC PULMONARY HYPERTENSION

M. Toshner1, J. Suntharalingam2, E. Soon1, K. K. Sheares1, P. White1, R. Hughes1, P. Fesler3, R. Naeije4, J. Pepke-Zaba1.

1Papworth Hospital, Cambridge, UK; 2Royal United Hospital, Bath, UK; 3Montpellier University Hospital, France; 4Erasme University Hospital, Brussels, Belgium

Introduction: Pulmonary artery occlusion pressure (PAOP) waveform analysis is emerging as a useful tool for partitioning pulmonary vascular resistance. Previous work in chronic thrombo-embolic pulmonary hypertension (CTEPH) has suggested that it can identify patients at high risk of operative mortality and residual distal disease. The selection of patients suitable for pulmonary endarterectomy (PEA) is critical given that small vessel disease and arteriopathy account for over one third of operative deaths. To determine if PAOP analysis could discern between predominantly proximal and distal disease we examined patients with operable proximal CTEPH, inoperable distal CTEPH, and idiopathic pulmonary arterial hypertension (IPAH) including connective tissue associated PAH where the vascular obstruction is distal in nature.

Methods: All subjects were diagnosed using standard Venice classification criteria and assessed by the surgical team. PAOP were performed at right heart catheter and analysis of waveforms were undertaken blinded using a computer model as previously described and expressed as an upstream % (Rup). Statistical analysis between groups was by ANOVA.

Results: Of 35 patients recruited 14 were proximal operable CTEPH, 7 distal inoperable CTEPH and 13 IPAH/CTD. Mean Rup was significantly higher in operable, mean 86% (SD 7.6), versus inoperable disease mean 69.9% SD (8.7) p = 0.001. Postoperatively two patients died. These two patients were the lowest flow directed Rups in the operative group. IPAH mean Rup 77% (SD 8.6) was also significantly lower than proximal disease p = 0.008.

Conclusions: PAOP analysis continues to show potential for discriminating between surgically operable predominantly proximal and inoperable distally distributed disease and we confirm the observation that a low Rup is a risk factor for mortality post PEA. In IPAH as hypothesised the Rup was lower than proximal disease but not with sufficient sensitivity to distinguish between the two groups.


S32 A RANDOMISED CONTROLLED TRIAL TO INVESTIGATE THE EFFECTS OF A PHYSIOTHERAPIST-LED REHABILITATION PROGRAMME ON EXERCISE CAPACITY AND QUALITY OF LIFE MEASURES IN PATIENTS WITH PULMONARY HYPERTENSION

1Department of Physiotherapy, Royal Hallamshire Hospital; 2Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK

Introduction: Pulmonary rehabilitation has been demonstrated to be an effective intervention in a number of cardiopulmonary diseases. In pulmonary hypertension a recent study has demonstrated an improvement in exercise capacity following a period of intensive in-patient rehabilitation.

Methods: In a randomised-controlled trial we examined the effects of an out-patient based physiotherapist led rehabilitation programme. 40 patients with pulmonary hypertension were recruited. All patients had been stable for at least six weeks. Patients were excluded if on continuous oxygen, in NYHA Class IV, or with severe mobility or balance problems. Patients were randomised into two groups; control group receiving standard best practice and a rehabilitation group receiving best practice plus a physiotherapist-led rehabilitation programme. Patients were seen by the physiotherapist in a single one to one class and given a prescribed set of exercises tailored to the individual needs of the patient. The patient was followed up with telephone support during the 3-month period and the
CONCLUSIONS: This study provides evidence of the feasibility of the intervention in home settings and suggests that it is a potentially promising approach for improving exercise capacity and health-related quality of life in patients with pulmonary hypertension. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and to determine the long-term efficacy of this approach.

ACKNOWLEDGEMENT: This study was supported by a grant from the PHA-UK.
available than RHC. The relation between BNP levels and echocardiographic indices of PH is unknown in ILD patients.

**Methods:** All patients with ILD referred for BNP levels during 2005–7 were included. (n = 91, 51 male, mean age 64 (16) years). All patients had concurrent pulmonary function, 54 patients had six-minute walk testing (6MWT) and 16 had concurrent RHC. Echocardiography tapes were reviewed by an independent cardiologist blinded to patients’ other results. Relationships between BNP levels and echocardiographic measures PH were studied.

**Results:** Forty two patients had PH on echocardiography as defined by right ventricular systolic pressure (RVSP) > 40 mmHg. Median tricuspid peak gradient (TRPG; n = 70) was 36 mmHg (14 to 129) n = 68, and mean pulmonary acceleration time (PAT; n = 90) 100 (29) ms. Median BNP level was 10 pmol/l (1.4 to 377). Diagnoses included idiopathic pulmonary fibrosis (n = 15), non-specific interstitial pneumonitis (n = 31), sarcoidosis (n = 10), chronic hypersensitivity pneumonitis (n = 10), organising pneumonia (n = 2), histiocytosis X (n = 2), and other ILD (n = 22). Patients had significant functional impairment, DLco 37.8 (16.1%), 6MWT end Spo2 83 (9%), BNP levels correlated with the following echocardiographic parameters: TRPG (r = 0.4, p < 0.001), PAT (r = 0.35, p < 0.01), right atrial pressure (r = 0.3, p < 0.01), right atrial area (0.4, p = 0.001), and right ventricular inlet diameter (r = 0.4, p < 0.01), but did not correlate with indices denoting left heart function. BNP also correlated with DLco (r = 0.38, p < 0.001), DLco/V/A (r = 0.33, p < 0.01), WHO functional class (r = 0.33, p < 0.01) and 6MW distance (r = 0.34, p < 0.01). In the subgroup of patients with RHC, BNP correlated with mPAP (r = 0.56, p < 0.001).

**Conclusion:** BNP correlates with echocardiographic indices of right heart dysfunction in ILD. The role of BNP in the diagnosis and monitoring of PH in ILD merits further study.

**Approaching educational needs in professionals and patients**

---

**S36 SUCCESSFUL IMPLEMENTATION OF A NEW ACUTE OXYGEN GUIDELINE USING A TARGET DRIVEN OXYGEN SATURATION SYSTEM (THE BASIS OF THE NEW BTS GUIDELINE) WITH OXYGEN CHAMPIONS AND DROP-IN TEACHING**


**Introduction:** The BTS will soon introduce a new guideline for acute oxygen therapy in adults. Oxygen will be prescribed by circling and signing for a target saturation on the drug card (94–98% aged below 70, 92–98% aged 70 and above, 88–92% for COPD). Nurses then administer oxygen using the appropriate delivery devices and flow rate to maintain the target saturation. Southend University Hospital was one of the two pilot sites for this scheme. An audit before the scheme showed that 10% of adult inpatients were given oxygen. 66% of these did not have their saturations checked before starting oxygen. Oxygen was prescribed in only 8% of patients. 93% had oxygen saturation monitored.

**Methods and Results:** Introducing a new policy involved training all doctors and nurses. There were lectures for all medical staff and ward managers. In addition groups of 8–12 nursing staff were instructed in a ward office using a novel 20 minute drop-in teaching sessions (within their shifts) conducted by two Respiratory CNS (oxygen champions) with sessions three times a day for 2 months. This involved a short PowerPoint presentation and verbal test at the end. A record was kept of all staff attending. After 2 months an average of 40% of the trained ward staff had attended. The new oxygen policy, a clinical oxygen guideline, and a PowerPoint training package for nurses were posted on the Southend University Hospital intranet. There were 3357 hits to these sites in the 5 months after introducing the policy. Six months after the introduction of the new policy a repeat audit showed that oxygen had been prescribed in 87% of those receiving it. Oxygen saturation was monitored in 98% of cases.

**Conclusions:** An acute oxygen policy based on a target saturation range can be successfully introduced using a high level implementation plan with formal lectures, drop-in nursing teaching and back-up information on the hospital intranet. The drop-in teaching methodology was crucial. Materials (PowerPoint lectures, teaching aids, example oxygen policy, etc) will be available with the new BTS acute oxygen guideline. Medical and nursing oxygen champions are being identified in each trust and will help introduce the guideline.

---

**S37 TRAINING OF GENERAL PRACTICE NURSES: ARE WE PREPARED FOR THE NATIONAL SERVICE FRAMEWORK FOR COPD?**

J. Upton1, H. Madoc Sutton1, A. Sheikh2, S. Walker1, M. Fletcher1. 1Education for Health, Warwick, UK; 2University of Edinburgh, Edinburgh, UK.

**Introduction:** Following the new general practitioner contract (1990), it was recognised that practice nurses with specialist training had a key role to play in asthma management (Atkin and Lunt 1996). In 1993 49% of practice nurses ran asthma clinics without medical input, yet 22% of these did not have accredited training (Barnes and Partridge 1994). Here we describe current nurse-led general practice respiratory care, and investigate the level of training nurses have received to support it.

**Methods:** Questionnaires were sent to lead asthma and COPD nurses at 500 UK practices. Interviews were selected UK general practice nurses to capture their roles and specialist training, and the organisation of respiratory care. In the 1993 survey a ‘maximum role’ was defined as a nurse running an asthma clinic without medical input. In this survey it was revised to mean that the nurse both diagnosed and gave follow-up care without medical input. Training was categorised as being accredited (a diploma or degree level module recognised by a university) or non-accredited.

**Results:** Response rates were high: 78% for asthma, and 74% for COPD nurses. The number of asthma nurses in a maximum role had increased from 49% in 1993 to 66% in 2006. Of these, 20% still did not have accredited training. In 2006 58% of COPD nurses held a maximum role. Of these nurses with a maximum role, 52% did not have accredited COPD training and 89% did not have accredited spirometry training.

**Conclusion:** The NSF will come in to force in 2008, yet the proportion of COPD nurses without accredited training is currently far higher than it was for asthma 13 years ago. We must not, in our hurry to deliver more primary based care for COPD, neglect the need for a skilled workforce to undertake the necessary roles. Primary care needs to prepare itself for the NSF now in order to ensure the provision of best possible patient care.

---

**S38 SELF-MANAGEMENT IN BRONCHIECTASIS. AN EXPLORATORY RANDOMISED CONTROLLED TRIAL OF A DISEASE SPECIFIC EXPERT PATIENT PROGRAMME COMPARED TO USUAL CARE IN PATIENTS WITH BRONCHIECTASIS**

K. Lawrey1, B. O’Neill1, S. Elborn1,2, J. Bradley1,2. 1Regional Respiratory Centre, Belfast Trust, Belfast City Hospital; 2Health and Rehabilitation Sciences Research Institute, University of Ulster; 3Department of Respiratory Medicine, Queen’s University Belfast, UK.

**Introduction:** The NHS has endorsed the expert patient programme, which is a self-management programme designed to help patients manage their long-term condition. Previous research has highlighted from the patients’ perspective elements which could be included in a disease specific component of the expert patient programme for bronchiectasis.

**Aim:** To investigate the impact of a disease specific expert patient programme compared to usual care in patients with bronchiectasis.

**Methods:** Ethical approval was obtained. Sixty four patients with a diagnosis of bronchiectasis were randomised using concealed allocation to either the intervention (n = 32) or the control (n = 32) group. The intervention group attended a hospital-based programme once a week for eight weeks (two weeks disease specific education followed by six weeks expert patient programme) in addition to usual care. The control group received only usual care. The primary outcome measure was the Chronic Disease Self-efficacy Scale (CDSS). Other outcome measures included the Revised Illness Perception Questionnaire (IPQ-R) and the St. Georges Respiratory Questionnaire (SGRQ). Data collection was conducted at baseline and after 8 weeks by an independent blinded assessor.

**Data Analysis:** The Mann-Whitney test was used to assess between group differences in the change in each of the outcome measures. A p value < 0.05 was considered statistically significant.

**Results:** There was a significant between group difference in change in 8 out of the 10 subscales (no significant difference in obtaining help and disease management subscales of the CDSS). There was no significant between group differences in change in six out of the seven subscales (significant difference in treatment control subscale) of the IPQ-R. The between group difference in change in the total score and three subscales of the SGRQ were small and not significant.

**Discussion:** This disease specific expert patient programme improved self-efficacy compared to usual care in patients with bronchiectasis. There was minimal effect on illness perception and no effect on quality of life, which is in agreement with other published studies. We will assess if these
Improvements in self-efficacy translate to improvements in other outcomes e.g. hospitalisation, antibiotic usage at a 6-month follow-up of this study.

**A SURVEY OF SPECIALIST REGISTRAR KNOWLEDGE OF RADIATION DOSES FOR VARIOUS RESPIRATORY INVESTIGATIONS**

G. T. Kyei 1, E. F. Bowen 2, C. F. J. Rayner 1. 1St George’s NHS Trust; 2Hammersmith Hospitals NHS Trust, London, UK

**Introduction:** Radiological investigations are carried out in large numbers in the UK—it has been estimated that over eight million chest X-rays and nearly 200,000 CT chests are carried out per annum. Doctors must balance the benefits of radiological investigations against risks from radiation exposure and provide patients with sufficient information to allow informed consent. We hypothesised that doctors are unaware of the radiation doses for various respiratory investigations.

**Method:** A questionnaire with a list of radiation exposures was given to 34 Respiratory Specialist Registrars (SpRs) during a teaching session. They were asked to write the dose of milliSieverts (mSv) next to each exposure. A database was used to analyse the results.

**Results:** 34/34 questionnaires were returned. The ranges of estimated radiation doses (true dose in brackets) were: Posterior-anterior chest X-ray (PA-CXR) 0.2–5000 mSv (0.02 mSv); Frequent-flyer-100 h 10–20,000 mSv (0.4 mSv); HRCT-chest-20 mm 10–500,000 mSv (0.48 mSv); Q 1–25000 mSv (0.8 mSv); HRCT-chest-10 mm 10–1,000,000 mSv (0.96 mSv); V/Q 2–50,000 mSv (1.2 mSv); CTPA 40–500,000 mSv (1.6 mSv); UK-yearly-dose 0.02–10,000 mSv (2.6 mSv); CT-chest 10–50,000 mSv (8 mSv). The results were also analysed to ascertain the estimated relative amounts of radiation from different exposures compared to radiation from a PA-CXR. The ranges of estimated relative dose (true relative dose in brackets) were: frequent-flyer-100 h <0.3–100 CXR (=20 CXR); HRCT-chest-20 mm <3–6000 CXR (=24 CXR); Q <0.3–250 CXR (=40 CXR); HRCT-chest-10 mm <3–8000 CXR (=48 CXR); V/Q <1.5–500 CXR (=60 CXR); CTPA <2.5–200 CXR (=80 CXR); UK-yearly-dose <0.06–1000 CXR (=130 CXR); CT-chest <3–5000 CXR (=400 CXR).

**Discussion:** This cohort of SpRs demonstrated a lack of knowledge regarding the radiation doses for different radiation exposures. They also failed to accurately identify the correct trend in relative doses for different exposures. Doctors need to be aware of the radiation doses of the investigations that they request, as well as the risks that such doses pose, in order to confidently request investigations in the patient’s best interests. The survey is small but we suspect that it highlights a gap in medical education. Further research is needed to see whether this knowledge gap exists within the wider population of UK doctors. If so, consideration should be given to improving medical education in this area.


**WHAT DO PATIENTS WANT TO KNOW ABOUT COPD?**

H. Bakere, J. Myers, D. Denn. Royal Cornwall Hospital, UK

**Introduction:** This study looked at patients participating in an eight-week community-hospital based pulmonary rehabilitation course to see what questions they had about their disease.

**Method:** During each 8-week pulmonary rehabilitation course, a group of 10–12 patients undertook a structured program of supervised exercise and education. During the sessions participants were encouraged to bring up concerns and issues. Questions were recorded on a flip chart for use at a question and answer session towards the end of the course. We collected the 135 questions asked by 16 groups (160 patients) in the period 2004–6.

**Results:** Questions fell into 5 areas. The largest numbers of questions concerned treatments (36%), followed by aetiology (29%), symptoms (21%), prognosis (4%), and miscellaneous. The 40 treatment-related questions concerned conventional, alternative and potential future treatments (Rg). 33 questions were about aetiology. 40% of these were about smoking and 30% about the relation between COPD and asthma. 23 questions concerned the symptomatology of COPD. Roughly half of these questions concerned specific chest symptoms. The remainder related to more global symptoms such as muscle problems and tiredness.

**Discussion:** This study provides a snapshot of patients’ self-perceived educational needs during a period of pulmonary rehabilitation. A lot of questions related to treatment. Overall there was more interest in alternative therapy, future developments and possible surgery than commonly prescribed and established treatments. The number of questions asking about an aetiological link with asthma was surprising. Perhaps this suggests a folk belief that all wheezes are asthma. Questions about symptoms were equally split between chest and systemic symptoms. This suggests that COPD is a systemic disease not only from the scientific but also from the patient’s perspective. The relative lack of questions about prognosis might reflect patients shying away from an area that they think is depressing.

**Conclusion:** Looking at what relatively well-informed patients want to know about COPD can help us assess the effectiveness of our educational interventions, as well as giving us greater insights into this large patient group’s needs, concerns and priorities.
Asthma: defining the risks and the risky in children

K. Edgcombe1, S. Latter2, G. Roberts1. 1School of Medicine, 2School of Nursing, University of Southampton, UK

Introduction: Current asthma management guidelines aim to control asthma symptoms, prevent exacerbations and normalise lung function to enable people with asthma to lead normal lives. Despite our range of therapies for asthma, a sizable minority of teenagers still experience ongoing asthma symptoms that limit their lifestyle and impair their quality of life. This gap between the available therapy and ongoing asthma symptoms is a particular problem in adolescence. Little is known about the health experiences of teenagers with uncontrolled severe asthma.

Aims and Objectives: To understand the experience of living with uncontrolled, severe asthma and to use this understanding to inform our clinical management and maximise the health experiences of these individuals.

Methods: Teenagers aged 11–18 years with uncontrolled severe asthma (ongoing symptoms despite the use of at least 800 µg/day inhaled corticosteroid) were recruited from Southampton University Hospital NHS Trust, St Mary’s Hospital, Portsmouth and St Mary’s Hospital, Newport. Semi-structured interviews were conducted with the teenagers, teenagers, parents and their paediatricians also completed confidential questionnaires quantifying the severity of their asthma, quality of life and concordance with therapy. A transcription was made from the taped interview. This was analysed using a qualitative thematic approach.

Results: Twenty teenagers were recruited into the study. They were aged 11–18 years (median 14 years), had a median of 10 hospital admissions ever, 30% had had an intensive care admission, 25% were on maintenance prednisolone and their average percent predicted FEV1 (SD) was 89% (14). Four overarching themes emerged from the data: school; close supportive relationships; healthcare professionals; medication and concordance. This abstract will focus on this last theme. Most teenagers self-administered their medication but most required reminders from their parents. Despite frequent education in clinic, some were not in control. They knew the chronic conditions and the burden of them. Additionally, many felt that only some of their medications worked but were concerned about adverse effects particularly those such as weight gain that affected their self-image. When asked about intentional non-concordance, these factors were mentioned along with simply forgetting, not being bothered or conflict with other activities. In particular, most were not utilising their spacer when using a MDI. Explanations offered were that they could not be bothered or that it took too long to use the spacer device. The above table describes how often teenagers reported that they failed to take their prophylactic medication. There was only fair agreement (kappa 0.36, p<0.01) between concordance reported by teenagers and parents; there was no agreement with their paediatricians’ report of their degree of concordance. Conversely, some teenagers were using more medication than prescribed, doubling doses if they were concerned about their asthma. Additionally half the participants lived with a pet that they were known to be sensitised to and 60% lived with a smoker.

Conclusions: Asthma affects every aspect of an adolescent’s life and this should be considered when developing a management plan. Concordance is a major issue but may be improved by understanding the patient’s view of their medications, tailoring devices to individual patients (particularly when prescribing a spacer device), minimising changes to therapy and utilising a written management plan. Although the study focuses on difficult asthma, some of the findings may be transferable to a wider patient group.

Acknowledgements: We would like to thank all the staff at the three sites who helped with the study and teenagers and their families.

www.thoraxjnl.com

Abstract S42

Reported concordance with prophylactic therapy

<table>
<thead>
<tr>
<th>How often do you forget to take your daily asthma preventative medication?</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Occasional</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Once a week</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Half the time</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Most of the time</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>19 (100)</td>
</tr>
</tbody>
</table>

Abstract S43

What are the factors that underlie paediatric asthma?

E. Neville-Smith, S. Price, K. Pike, R. Kurukularathch, H. Arshad, G. Roberts. School of Medicine, University of Southampton, UK

Introduction: Asthma is a complex disease with variable clinical features and clinical course even within the paediatric age range. This may be explained by considering asthma to be a collection of phenotypes that manifest variable airway obstruction. Classically the pathophysiology of asthma is said to
Abstract S43 Table 1 Description of the subjects

<table>
<thead>
<tr>
<th>Male</th>
<th>106 (59.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (weeks)</td>
<td>39.9 (1.6)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.3 (0.5)</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>154 (89.5%)</td>
</tr>
<tr>
<td>Any smokers at home</td>
<td>82 (53.1%)</td>
</tr>
<tr>
<td>Furry pets at home</td>
<td>148 (83.1%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.2 (2.8)</td>
</tr>
<tr>
<td>Ever treated for asthma</td>
<td>173 (97.7%)</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>124 (69.7%)</td>
</tr>
<tr>
<td>Any prophylactic medication</td>
<td>138 (77.5%)</td>
</tr>
<tr>
<td>Current eczema</td>
<td>43 (24.4%)</td>
</tr>
<tr>
<td>Current rhinitis</td>
<td>69 (39.9%)</td>
</tr>
<tr>
<td>% predicted FEV₁</td>
<td>97.6% (11.7)</td>
</tr>
<tr>
<td>Any positive skin prick test</td>
<td>91 (63.6%)</td>
</tr>
</tbody>
</table>

involve airway inflammation, airway hyperreactivity and variable airway obstruction. Other factors may be involved in the pathophysiology of some of the specific asthma phenotypes. In this study we explored the factors underlying the variability expressed by children with asthma within the Isle of White 1989 birth cohort. In doing so we aimed to determine which factors were most important in explaining this variability.

Methods: A whole population birth cohort of 1456 infants was recruited on the Isle of Wight in 1989. Subjects have been reviewed at 1, 2, 4 and 10 years of age. All subjects with doctor-diagnosed asthma and symptoms in the past year were included in the analysis. The 10-year assessment included a detailed questionnaire about their symptoms, triggers and treatment, severity, lung function using ATS guidelines, skin prick testing to the common aeroallergens (house dust mite, mixed grass pollens, mixed tree pollens, cat, dog, negative and positive control; ALK-Abello, Horsholm, Denmark) and bronchial hyperresponsiveness (expressed as PC₂₀ or inverse of the slope of the methacholine dose response curve). A factor analysis was undertaken using all the variables that were thought to be important in describing subjects’ asthma (firstly, birth weight, gestation, gender and, secondly, at age 10 years, BMI, both parents smoking, any smoke exposure, any pet exposure, furry pet, lastly, atopy (SPT, total IgE)). Where there were two factors one of which was related to atopic dermatitis, and the other related to bronchial hyperreactivity (inverse dose-response slope, log total IgE). A factor analysis was undertaken with principal components analysis to define the best model, with varimax rotation to maximise the loadings on individual variables in each factor to determine whether there were distinct groupings of variables (Stata version 9).

Results: Data presented as count (%) or mean (standard deviations). Unless otherwise stated, data relates to age 10 years. Data were available for 178 subjects with current doctor-diagnosed asthma at age 10 years. They are described in the table. The final model had four factors and explained almost all the variance. Factor one reflected atopy (SPT, total IgE) and bronchial hyperreactivity (inverse slope)—elements which seem to be interlinked. Factor two reflected birth weight and gestation—possibly a reflection of small airways. Factor three reflected social class and smoking (any exposure)—which are known to be closely linked. Factor four reflected high BMI and female gender—which again are linked. There was minimal correlation between the four factors.

Conclusions: The factor analysis has highlighted four unique factors onto which different asthma related variables are loaded. This emphasises the many independent elements underlying asthma and that possibly not all are important for each individual child’s disease. This underlines the heterogeneity of childhood asthma. These data can now be utilised as a hypothesis generating exercise to explore whether this group of children with asthma can be divided into distinct asthma phenotypes based upon these elements.

Acknowledgements: We would like to acknowledge the contribution of all those involved in the recruitment and assessments of the cohort and the help of all the children and their families.

S44 ARE YOUNG CHILDREN PRESENTING WITH COUGH IN THE ABSENCE OF WHEEZE AT INCREASED RISK FOR ASTHMA IN LATER CHILDHOOD?


Introduction: Young children often present to their general practitioner (GP) with respiratory symptoms and some are diagnosed with asthma, including those presenting with cough in the absence of wheeze. The present study tested the hypothesis that young children presenting to their GP with cough in the absence of wheeze were not at increased risk for asthma at five years of age.

Methods: 1924 pregnant women were recruited and their children followed up at 2 and 5 years of age. Attendance at the GP in the previous 12 months for cough and/or wheeze was determined from a questionnaire completed at 2 years of age. Children were categorised as “cough only” (C), “cough and wheeze” (CW), “wheeze only” (W) and “neither cough or wheeze” (N). At 5 years of age, a respiratory questionnaire was completed and a representative proportion had lung function determined.

Results: Questionnaire data were available in 1373 two year olds including 285 (21%) with C, 117 (9%) with CW and 43 (3%) with W. Data at 2 and 5 years of age were available in 1112 children. A history of doctor diagnosed asthma ever by 5 years of age was reported in 7% (39 children) with C, 48% (42 children) with CW, 47% (16 children) with W and 7% (55 children) with N, p<0.001 for trend. At 5 years of age, wheeze in the previous 12 months was reported in 13% (30 children) with C, 44% (38 children) with CW, 47% (13 children) with W and 7% (54 children) with N, p<0.001 for trend. The odds ratio for wheeze in the previous 12 months at 5 years of age in comparison to children with N was as follows: C 2.0 (95% CI 1.2 to 3.2); W 8.1 (95% CI 3.9 to 17.1); CW 10.4 (6.3 to 17.3). The mean (SD) FEV₀.₅ z scores were –0.12 (1.07) for C, –0.42 (0.96) for CW, –0.14 (1.02) for W and 0.05 (1.0) for N (ANOVA p=0.014).

Conclusions: Isolated cough may be an early asthmatic symptom in young children however, cough in association with wheeze is a much better predictor of future asthma outcome than cough alone.
T-spot test in TB

**THE ROLE OF T CELL BASED INTERFERON-γ RELEASE ASSAYS IN THE EVALUATION OF PATIENTS WITH SUSPECTED ACTIVE TUBERCULOSIS**

T. S. C. Hinks, D. P. S. Dosanjh, J. A. Innes, J. Deeks, G. Pasvol, S. Hackforth, H. Varia, K. Q. Liu, K. Millington, R. Gunathasan, V. Gayat-Revol, A. Lalvani. Tuberculosis Immunology Group, National Heart and Lung Institute, Imperial College London; Birmingham Heartlands Hospital; Department of Public Health and Epidemiology, University of Birmingham; Department of Infection and Tropical Medicine, Northwick Park Hospital, Harrow, UK

**Introduction:** Diagnostic evaluation of patients with suspected tuberculosis (TB) is challenging because existing tests lack speed and sensitivity and the role of new rapid blood tests for TB infection is unclear. As Mycobacterium tuberculosis infection is a prerequisite for TB disease, rapid determination of infection status with a test of high sensitivity could enable rapid exclusion of TB where this is clinically suspected.

**Methods:** We performed a prospective blinded study of 389 consecutive patients with suspected TB presenting to two urban hospitals in the UK. Patients underwent tuberculin skin testing (TST) and the enzyme-linked immunospot assay (ELISpot) incorporating early secretory antigenic target–lymphocytes present (+) synthetic CD4.

**Results:** 194 patients had a final diagnosis of active tuberculosis, of which 154 were culture-confirmed. Sensitivity of ELISpotPLUS was 91% (95% CI 85 to 95) for culture-confirmed active TB and 89% (84 to 93) for culture-confirmed and highly-probable cases, significantly higher than the 79% (71 to 86; p = 0.005), and 79% (72 to 85; p = 0.01) sensitivity of TST in the two groups respectively. Corresponding negative likelihood ratios were 0.15 (0.10 to 0.24) and 0.25 (0.19 to 0.35) for ELISpotPLUS and TST respectively. ELISpotPLUS had 4% higher diagnostic sensitivity than standard ELISpot (p = 0.02). Combined sensitivity of ELISpotPLUS and TST in culture-confirmed and highly-probable cases was 99% (95 to 100), conferring a negative likelihood ratio of 0.02 (0 to 0.06) when both test results were negative.

**Discussion:** In routine hospital practice, ELISpotPLUS has higher diagnostic sensitivity than TST and combined use of these tests enables rapid and reliable exclusion of tuberculosis from the differential diagnosis.

**S48** RAPID IMMUNO-DIAGNOSIS OF ACTIVE EXTRAPULMONARY TUBERCULOSIS

R. A. M. Breen, A. Dunleavy, F. Perrin, T. D. McHugh, S. Gillespie, I. Crapley, M. C. I. Lipman. The Royal Free and University College London Medical School, UK

**Introduction:** Laboratory tests are often unhelpful during the initial assessment of patients with possible extrapulmonary TB. However in many such cases, there is a strong local host response, suggesting that immune-based tests may be of some value as a rapid diagnostic method. To investigate this hypothesis, we prospectively recruited subjects who were being investigated for possible active pleural or peritoneal TB at our institution.

**Method:** The percentage of interferon-γ synthetic CD4+ lymphocytes present within either pleural fluid or ascites following overnight (16-h) stimulation with purified protein derivate of M tuberculosis (PPD) was assessed using flow-cytometry. A positive assay was defined as > 1.5%. All assays were performed prior to diagnosis or commencement of anti-TB therapy and clinical decisions were made independently of immunological data.

**Results:** Twenty eight subjects with pleural effusion and 10 with ascites were recruited. Among the pleural cases 11 were diagnosed with TB (8 of 11 culture-confirmed). Of these 0 of 11 (0%) were AFB smear positive. Our PPD assay was positive in 11 of 11 (100%) of individuals diagnosed with TB and negative in 16 of 17 (94%) of individuals not diagnosed with TB. In those with ascites, 4 were diagnosed with TB of whom all were culture confirmed but none were AFB smear positive. Of these, 4 of 4 (100%) diagnosed with TB had a positive PPD assay and 6 of 6 (0%) not diagnosed with TB had a negative assay. Combining the two groups our assay had a sensitivity of 100% and a specificity of 96% against final diagnosis of TB.

**Conclusions:** These data suggest that our rapid assay has utility in the diagnosis of pleural and peritoneal TB. Further work should be performed to assess its performance as well as that of commercial interferon-γ release assays in this diagnostically challenging group.

**S47** AN ECONOMIC EVALUATION OF THE USE OF INTERFERON-γ RELEASE ASSAYS IN THE SCREENING OF CONTACTS AND NEW ENTRANTS FOR LATENT TB

M. Gray, L. P. Ormerod, Royal Blackburn Hospital; University of Central Lancs, UK

**Background:** The NICE 2006 Guidelines recommended the use of IGRA test to assess individuals with inappropriately positive tuberculin tests found through either contact or new entrant screening. Our local PCTs were persuaded to fund IGRA testing as being a cheaper option than unscreened treatment of latent TB infection (LTBI).

**Results:** In Blackburn from 1 August 2006 to 23 July 2007 all persons with an inappropriately positive Mantoux test were screened using Quantiferon-in-tube Gold (QFT) (Celltestis Ltd), 70 contacts (36 positive, 5 indeterminate, 20 negative) and 30 new entrants (17 positive; 4 indeterminate; 8 negative) were tested. Of the 9 indeterminate results, 7 were technical (in the first month of use, inexperienced lab reception staff fruged some samples). The cost of performing the QFT test was £35/test. From the NICE economic appraisal, system costs of LTBI treatment with 6H (isoniazid 6 months) was a median of £450 (range 250–800). It is assumed for the purposes of calculation that 3 months of rifampicin (R) and isoniazid (3HR) is equivalent. 100 QFT tests cost £3500. The saving in unnecessary treatment of LTBI for those with negative QFT was £28 × 450 = £12600 (range £7000–22400).

**Conclusion:** The use of QFT as an IGRA test as per NICE Guidelines was feasible with a net saving of £9100 (range £2350–£18900). The “neutral” point for QFT use in this cohort was an 8% negative QFT rate (test cost £3500; LTBI saving £3600). Colleagues should be able to use these data that the use of IGRA testing is very likely to be more cost-effective, to help persuade PCTs to fund such testing, where they are reluctant to do so.

**S50** TB CONTACT SCREENING IN IMMUNOCOMPROMISED HIV POSITIVE PATIENTS: IS THERE A RELATION BETWEEN T-SPOT TB REACTIVITY AND EXPOSURE TO THE INDEX CASE IN OUTPATIENT CONTACTS?

L. V. Baker, J. Roya, R. Erneuiche, C. Mazludhe. University Hospital Lewisham; Lambeth, Southwark and Lewisham Community TB team, London, UK

**Introduction:** Tuberculosis contact tracing in the immunocompromised in an outpatient setting is difficult. Evidence-based guidelines are lacking. The
Spoken sessions A23

**Conclusion:**

2 patients had received Rifinah, 3 isoniazid. Patients were compliant. Tests were performed 2-3 months post completion (33%) have had follow up T-spot-TB tests. 2 tests were non-reactive, 3 CFP10 only. 2 patients had counts close to the cut off. To date 5 patients 152. 9 patients were reactive to both antigens, 3 to ESAT-6 only, 2 to median 326. Corrected antigen-specific T-spot spot counts ranged from 0–

- Rifampicin and isoniazid (Rifinah), or 6 months isoniazid. All patients were course of isoniazid; those not on HAART were offered 3 months of TB tests. Chemoprophylaxis was offered using one of 2 regimens: patients 17 patients were identified with latent TB, all of whom had reactive T-spot-

**Methods:**

- We performed contact screening in an HIV outpatient clinic following exposure to infectious pulmonary tuberculosis. We defined immunocompromised as a CD4 count <350, present on two or more occasions during the exposure period. The index was symptomatic for 3–4 months. Contacts were identified within a 5-month exposure period. Contacts with a prior history of tuberculosis were excluded. T-spot-TB testing was performed 6 weeks after the last exposure. Indeterminate or borderline T-spot-TB results were repeated after a further 6 weeks.

**Results:**

114 contacts fulfilling the screening criteria were identified. 74 attended for screening, 72 underwent T-spot-TB testing. 16 countries of birth were documented, 64% with high endemic TB incidence. Prior tuberculosis/T-spot-TB reactivity was not available. 81% had prior BCG vaccination. Attendances in common with the index ranged from 2–10 (median 4). 16 (22%) contacts were reactive on T-spot-TB testing, 1 of whom had active TB. Only 1 was indeterminate after repeat testing. There was no relation between frequency of attendance and the proportion of reactive cases, or to the elispot reactivity to the TB specific antigens, ESAT-6 or CFP10. Strain typing of the M tuberculosis isolates using MIRU typing revealed two different strain types—that is, unrelated to the index.

**Conclusion:**

The T-spot-TB reactivity identified appears unrelated to outpatient exposure and is likely to represent background latent TB infection acquired following exposure in countries of birth with high endemic TB incidence.

---

**T-SPOT-TB REACTIVITY FOLLOWING CHEMOPROPHYLAXIS FOR LATENT TUBERCULOSIS IN HIV POSITIVE PATIENTS**

L. V. Baker, R. Enuechie, C. Mazhude. University Hospital Lewisham, London, UK

**Introduction:**

Gamma interferon based assays for diagnosing tuberculosis (TB) infection are reported to measure effector T cell response to the TB specific antigens ESAT-6 and CFP-10. A reactive test reflects ongoing antigen exposure to the effector T cells, ie, current TB infection, rather than previous antigen exposure which is a memory T cell response. Logically, treatment for TB infection, whether active or latent disease, associated with antigen clearance would be expected to result in reversion to a non-reactive effector T cell response. Latent TB has a much lower bacterial and therefore antigen load, antigen clearance following treatment may be more likely.

**Methods:**

We used the T-spot-TB assay in combination with Mantoux testing (10TU) in the assessment of immunocompromised HIV positive contacts (CD4 count <350) following exposure to infectious pulmonary TB. 17 patients were identified with latent TB, all of whom had reactive T-spot-TB tests. Chemophrophaxis was offered using one of 2 regimens: patients on highly active antiretroviral treatment (HAART) received a 6 month course of isoniazid; those not on HAART were offered 3 months of rifampicin and isoniazid (Rifinah), or 6 months isoniazid. All patients were prescribed supplemental pyridoxine. Compliance was monitored by the TB nurses. Patients were offered a repeat T-spot-TB test post completion of TB chemophrophaxis.

**Results:**

- 15 patients accepted chemophrophaxis, 3 received Rifinah, 12 received isoniazid. One patient developed a rash on Rifinah but tolerated isoniazid monotherapy. Pretreatment CD4 counts ranged from 220–430, median 326. Corrected antigen-specific T-spot spots counts ranged from 0–152. 9 patients were reactive to both antigens, 3 to ESAT-6 only, 2 to CFP10. 2 patients had counts close to the cut off. To date 5 patients (33%) have had follow up T-spot-TB tests. 2 tests were non-reactive, 3 remained reactive (2 of which showed a rise in spot counts, 1 a fall). All patients were compliant. Tests were performed 2-3 months post completion of chemophrophaxis, 2 patients had received Rifinah, 3 isoniazid.

**Conclusion:**

T-spot-TB reactivity does not necessarily revert following TB chemotherapy. Positive patients. This may lack of antigen clearance viable or non-viable organisms, or detection of a mixed memory not pure effector T cell response.

---

**OXIDATIVE STRESS INCREASES TRANSFORMING GROWTH FACTOR-BETA EXPRESSION AND DRIVES EPITHELIAL TO MESENCHYMAL TRANSITION IN HUMAN LUNG EPITHELIAL CELLS**


**Introduction:**

The response of lung epithelium to injury is considered crucial to the pathophysiology of chronic lung diseases including interstitial lung disease (ILD). Change in epithelial cell phenotype to that of a (myo)fibroblast via epithelial to mesenchymal transition (EMT) may contribute to lung remodelling and excessive connective tissue deposition seen in these diseases. As increased oxidative stress is commonly present in these diseases, we hypothesised that this injury source may drive EMT in the lung.

**Methods:**

Lung epithelial cells (A549) were exposed to hydrogen peroxide H₂O₂ (concentration 50–400 μM) for 1 hour and left for 12 days. Generation of intracellular reactive oxygen species (ROS) was assessed by FACS analysis using DHR and MitoSOX staining. Change in cell morphology was monitored by phase contrast microscopy. Changes in expression of EMT markers were assessed by Western blotting and confocal microscopy. Zymography was used to assess presence of active matrix metalloproteinases (MMPs) in cell supernatants. Transforming growth factor-beta (TGF-β) mRNA level was determined using real-time PCR with GAPDH as endogenous control.

**Results:**

Untreated A549 cells show a uniform epithelial morphology with high level expression of tight junction protein, E-Cadherin, with very low levels of the mesenchymal markers collagen type III and vimentin, and no expression of alpha-SMA. Exposure to H₂O₂ 200 μM and 400 μM caused a marked change in cell morphology typical of EMT. At concentrations of
400 μM cells dramatically increased expression of collagen III (75 fold change), vimentin (5 fold change) and started to express α-SMA. Moreover, collagen type III and fibrillin, as components of extracellular matrix in mesenchymal tissue, were secreted to extracellular space in response to H2O2 treatment. E-cadherin expression was almost completely abolished. Both 200 μM and 400 μM H2O2 increased 2 fold activity of MMP-9. Furthermore H2O2 exposure markedly upregulated TGF-β mRNA (2 fold change) after 2 hours post-treatment, which was maintained up to 72 hours suggesting that oxidative stress may stimulate EMT via TGF-β signalling.

Conclusion: Oxidative stress can induce EMT in lung epithelial cells. This may occur due to increased expression of TGF-β and provides a potential mechanism for fibrogenesis in the lung microenvironment.

S54 BALF PROTEIN PERMEABILITY INDEX AND MATRIX METALLOPROTEINASES IN IDIOPATHIC PULMONARY FIBROSIS: A LINK BETWEEN ABERRANT VASCULAR PERMEABILITY AND PROGNOSIS?
S. Mckeown1, A. Richter1, D. Mcaculey2, D. R. Thickett1. 1University of Birmingham, UK; 2Queen’s University, Belfast, UK

Aberrent alveolar-capillary permeability will deliver clotting cascade factors to the alveolar space and thus promote the low grade coagulopathy that may drive fibrogenesis. We hypothesised that matrix metalloproteinases (MMP) may determine the degree of increased alveolar-capillary permeability which may relate to severity or outcome in patients with idiopathic pulmonary fibrosis (IPF).

Methods: 22 patients with newly diagnosed IPF underwent bronchoalveolar lavage (BAL). BAL-1, 2, 3, 7, 8, 9, 12 and 13 protein in lavage fluid was measured by luminex-based multiplex array. Protein permeability index was calculated from the ratio of BAL fluid protein: plasma protein. Repeat bronchoscopy was performed in 8 patients after 4-6 months of treatment with combination therapy (Predni- Aza ≥ NAC).

Results: MMP-2, 3, 7, 8, and 9 were elevated in patients with IPF compared to normal controls (all p<0.01). MMP levels did not reflect the degree of cellular inflammation. MMP-3 (r=0.35, p=0.004), MMP-7 (r=0.32, p=0.005), MMP-8 (r=0.42, p=0.001) and MMP-9 (r=0.53, p=0.000) correlated with BALF protein permeability index. There were modest negative relationships between lung function parameters and BALF MMP 3 (%FVC r2 = -0.2, p = 0.048) and MMP-7 (%Tco, r2 = -0.29, p=0.008). Protein permeability index was significantly elevated in those patients who died during the follow-up phase (died median 0.015, versus survived 0.00434, p=0.04). Similarly BALF levels of MMP-3, MMP-7, MMP-8 and MMP-9 were significantly elevated in those who died. Levels of MMPs remained elevated despite treatment in the patients who underwent repeat bronchoscopy.

Conclusion: Protein permeability index of BALF MMP levels are elevated and relate to severity and outcome in patients with IPF. Current immunosuppressive treatment regimens are ineffective at abrogating these changes. These results suggest that targeting MMP and aberrant alveolar-capillary permeability is worthy of further study in patients with IPF.

S55 LYPOSOPHATIDIC ACID INDUCES αVβ6 INTEGRIN MEDIATED TRANSFORMING GROWTH FACTOR-β1 ACTIVATION VIA Gq IN EPITHELIAL CELLS
M. Xu1, J. Porte1, A. Knox1, D. Sheppard2, G. Jenkins1. 1The University of Nottingham, UK; 2Lung Biology Center, UCSF, California, USA

Introduction: Activation of latent transforming growth factor-beta (TGFβ) by the αvβ6 integrin is a critical step in the pathogenesis of acute lung injury and pulmonary fibrosis. Activation of the seven transmembrane domain Gq-coupled receptor, PAR1, can enhance αvβ6 integrin mediated TGFβ activity via RhoA and Rho kinase. Lyposophatidic acid (LPA) is a lipid mediator released locally during the early stages of wound repair, and is a ligand for the LPA class of G-coupled receptors.

Methods and results: This study investigates the mechanism of LPA induced αvβ6 integrin mediated TGFβ1 activation. We used a transformed mink lung cell line (MLE) co-culture assay and real-time PCR to measure TGFβ activity. LPA stimulation of normal human bronchial epithelial cells (NHBE) lead to a dose and time dependent increase in TGFβ1 activity, which was blocked by an αvβ6 and pan TGFβ blocking antibodies. LPA stimulated TGFβ1 activity in NHBE was inhibited by RhoA inhibitor (C3 exoenzyme) and a Rho kinase inhibitor (H-1152) in a dose dependent manner. Chimeric signal transduction pathway from LPA receptor to RhoA we used embryonic fibroblasts derived from G12/13-/- and Gqα/-, or wild-type control mice engineered to express the αvβ6 integrin (MEF16). TGFβ1 activity was measured by co-culture assay and immuno-blotting for Smad2 phosphorylation. Stimulation of wild-type MEF16 with 10 μM LPA lead to a time dependent increase in Smad2 phosphorylation that was inhibited by an αvβ6 antibody, but not the Gqα inhibitor, pertussis toxin. G12/13-/-/MEF16 had low levels of basal TGFβ1 activity that could be increased following LPA stimulation, whereas Gqα/-/MEF16 had high levels of basal TGFβ1 activity that could not be further enhanced by LPA stimulation. To confirm the role of Gqα in LPA induced TGFβ1 activity in epithelial cells, we stimulated NHBE cells in the presence of the Gqα inhibitor GP antagonist-2A resulting in dose-dependent inhibition of TGFβ1 activity.

Conclusion: These data suggest that LPA induces αvβ6 integrin mediated TGFβ1 activation via RhoA and Gqα in epithelial cells, and this pathway may play an important role in the pathogenesis of acute lung injury and pulmonary fibrosis.

S56 DIFFERENTIAL MODULATION OF LUNG FIBROBLAST AND ALVEOLAR EPITHELIAL CELL APOPTOSIS BY CYCLO-OXYGENASE (COX)-2 AND PROSTAGLANDIN E2: AN IMPORTANT MECHANISM IN THE PATHOGENESIS OF IDIOPATHIC PULMONARY FIBROSION
T. M. Maher1, S. E. Bottoms1, P. F. Mercer2, C. J. Scotton1, A. Thorley1, A. U. Wells1, A. G. Nicholson3, G. J. Laurent1, T. D. Tetley2, R. C. Chambers1, R. J. Mcauley1. 1Centre for Respiratory Research, University College London; 2Royal Brompton Hospital; 3National Heart & Lung Institute, Imperial College, London, UK

Introduction: Idiopathic pulmonary fibrosis (IPF) patients have reduced capacity to synthesise cyclo-oxygenase (COX)-2 and the anti-fibrotic mediator Prostaglandin E2 (PGE2). Outside the lung PGE2 protects epithelial cells from, but sensitises fibroblasts to, apoptosis. We hypothesised that reduced COX-2/PGE2 expression in IPF increases alveolar epithelial cell (AEC) apoptosis while rendering fibroblasts resistant to apoptosis.

Methods: Apoptosis was assessed by annexin V and propidium iodide staining and by flow cytometry. Reduced COX-2 and PGE2 expression has previously been associated with fibrosis.

Results: Reduced COX-2/PGE2 expression may play an important role in the pathogenesis of acute lung injury and pulmonary fibrosis.
Sleep disordered breathing: beyond sleepiness

Abstract S59

**SLEEP DISORDERED BREATHING, A CAUSATIVE FACTOR IN THE DEVELOPMENT OF SEVERE DIABETIC RETINOPATHY?**

S. P. Merritt, J. Maxham, A. Wong, J. Steier, P. Carroll, A. J. Williams. Sleep Disorders Centre, St Thomas’ Hospital, London, UK

**Introduction:** Sleep disordered breathing (SDB) is common in patients with type 2 diabetes mellitus (T2DM), and both disorders are increasing as the population becomes more obese. Diabetic eye disease is the most common cause of preventable visual loss in people of working age in the UK. Its pathogenesis is not fully understood, however retinal hypoxia is considered to play an important contribution. We hypothesised that SDB is more common in T2DM patients with sight threatening (pre-proliferative and/or proliferative retinopathy) eye disease than those with non-severe retinopathy (background changes or normal).

**Method:** T2DM patients, diagnosed for more than 5 years, with a BMI of >25.1 kg/m², were randomly recruited using the Diabete 3rd database at our hospital. The subjects were divided into 2 groups depending on the severity of their retinopathy, using digital retinal photographs performed in the 6 months prior to recruitment. Weight, height and blood pressure (BP) were measured. Each patient was instructed on the use of the Minolta 2000i pulse oximeter which was taken home and used that night. The following day blood was taken for HbA1c and the data from the oximeter downloaded. The number of dips in oxygen saturation ≥4% (ODI ≥4%) and the percentage of the night spent with oxygen saturations of <90% were used as markers of severity of SDB. Each oximetry trace was also visually examined to determine as to whether the typical “saw tooth” pattern characteristic of obstructive sleep apnoea (OSA) was present. The Mann Whitney U test was used to look for significant differences between the groups with regards to the continuous variables and the χ² test to look for differences in smoking status.

**Results:** 44 adults with T2DM participated, mean age 60.5 (9.7). There was no difference, between the groups, in the variables already known to influence the development and progression of diabetic retinopathy, namely HbA1c, duration of known diabetes, BP and smoking. The sight threatening eye disease group had significantly more sleep disordered breathing (mean 4% ODI 13.6 (16.5)) than the non-sight threatening group (mean 4% ODI 3.8 (3.1)), p value 0.03. It was also evident that the sight threatening group spent significantly longer with O₂ saturations of less than 90%.

<table>
<thead>
<tr>
<th>Variable (SD)</th>
<th>Non-sight threatening eye disease (n = 23)</th>
<th>Sight threatening eye disease (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>14.9 (6)</td>
<td>16.5 (7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean age</td>
<td>61 (11.4)</td>
<td>60 (7.6)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>30.4</td>
<td>30.3 (p = 0.32)</td>
<td>0.65</td>
</tr>
<tr>
<td>No. of years diabetic</td>
<td>17.5 (8.6)</td>
<td>15.5 (6.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>7.8 (1.5)</td>
<td>8.2 (1.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean systolic BP (mm Hg)</td>
<td>147.1 (15.8)</td>
<td>147.8 (18.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>No. of smokers</td>
<td>11</td>
<td>13</td>
<td>0.89</td>
</tr>
<tr>
<td>ODI ≤4%</td>
<td>3.78 (3.1)</td>
<td>13.55 (16.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>% of the night saturation &lt;90%</td>
<td>1.8 (2.6)</td>
<td>12.6 (19.7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Both TNF-α srl (r = 0.23) and TNF-α srr (p = 0.32). (see table).

Abstract S58

**INCREASING SYSTEMIC INFLAMMATORY CYTOKINES IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS**

R. Shakespeare1, A. Schwappach1, C. E. Bolton2, G. Dunseath3, D. J. Shale2, B. D. M. Hope-Gill1. 1University of Wales College of Medicine, 2Department of Respiratory Medicine, School of Medicine, Cardiff University; 3Diabetes Research Unit, School of Medicine, Cardiff University; 4Department of Respiratory Medicine, Cardiff and Vale NHS Trust, UK

**Background:** Idiopathic pulmonary fibrosis (IPF) is characterised by chronic inflammation and fibrosis of the alveolar airspaces and pulmonary interstitium. Median survival is less than three years. In other progressive pulmonary conditions elevated serum levels of interleukin-6 (IL-6), tumour necrosis factorα (TNF-α) and its soluble receptors (TNF-α srl and TNF-α srr) are associated with altered body composition and a poor prognosis. It is not known whether patients with IPF have raised serum inflammatory cytokines compared with healthy controls.

**Methods:** 23 patients (18 male), mean age (SD) 72 (11.8) years, with well-characterised IPF were recruited and sub-divided into patients treated with combined corticosteroid/immunosuppressive therapy (4/23) and non-steroid groups (19/23). All patients underwent full pulmonary function testing and had body composition assessed using body mass index (BMI) and bioelectrical impedance for fat free mass (FFM). Serum levels of IL-6, TNFα, TNF-α srl and TNF-α srr were measured using quantitative ELISAs and compared with measurements from 20 age and gender matched healthy controls.

**Results:** Circulating IL-6 (p = 0.001) and TNF-α srl (p = 0.01) were higher in patients with IPF compared with controls with no difference in serum levels of TNF-α srr (p = 0.23) and TNF-α srr (p = 0.32). (see table). Both TNF-α srl (r = 0.425, p = 0.05) and TNF-α srr (r = 0.467, p < 0.05) in IPF patients were inversely related to six minute walk distance (6MWD). Systemic inflammation was not related to BMI, however, serum TNF-α srl was inversely related to FFM (r = -0.57, p = 0.01). There was no correlation with any lung function variable.

**Conclusion:** While previous research has revealed evidence of inflammation at a local level within the lung, this study demonstrates the existence of systemic inflammation in IPF with significantly higher serum concentrations of IL-6 and TNF-α srl in patients compared to healthy controls. The marked correlation between the systemic inflammatory mediators, FFM and 6MWD may represent muscle adaptations to the inflammatory load. This requires further review.

<table>
<thead>
<tr>
<th>Variable (SD)</th>
<th>Non-steroid IPF group (n = 19)</th>
<th>Total IPF group (n = 23)</th>
<th>Healthy controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/ml)</td>
<td>4.53 (2.0)</td>
<td>4.51 (2.0)</td>
<td>1.91 (2.1)</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>1.89 (1.32)</td>
<td>1.81 (1.3)</td>
<td>2.15 (1.8)</td>
</tr>
<tr>
<td>TNF-α srl (pg/ml)</td>
<td>1420.59 (2.1)</td>
<td>1402.27 (1.9)</td>
<td>1206.56 (1.3)</td>
</tr>
<tr>
<td>TNF-α srr (pg/ml)</td>
<td>3117.38 (1.38)</td>
<td>2919.17 (1.39)</td>
<td>2377.50 (1.29)</td>
</tr>
</tbody>
</table>

All data are expressed as geometric means (SD).

*p ≤ 0.01 compared with controls.
90%, 12.6% (19.7) of the night compared to 1.8% (2.6), p value 0.03. From the typical oximetry traces it is thought that much of this SDB is as a result of OSA.

**Conclusion:** This study suggests that SDB may play an aetiological role in the development and/or progression of diabetic retinopathy. In addition to this extra burden of hypoxia to an already ischaemic retina, the recurrent activation of the sympathetic nervous system and the fluctuating BP that are characteristic of SDB may be additional contributing factors. These results suggest that obese patients with T2DM should be screened for SDB using overnight pulse oximetry, especially if retinopathy is already present.

This research was funded by an unconditional educational grant from ResMed UK.


### S60 SLEEPO DISORDERED BREATHING IN PATIENTS WITH UNILATERAL PARALYSIS OR SEVERE WEAKNESS OF THE DIAPHRAGM

J. Steier1, C. Jolley1, S. Kaul1, K. Ward1, Y. M. Luo1, M. I. Polkey3, J. Maxham1. 1King’s College London; 2Guangzhou Medical College, Guangzhou Institute of Respiratory Diseases, China; 3Royal Brompton Hospital, London, UK

**Background:** Patients with respiratory muscle weakness can develop sleep disordered breathing (SDB), in particular during rapid-eye-movement (REM) sleep. It has been described that patients with bilateral diaphragm paralysis are at risk of SDB when there is an additional load on the respiratory muscle pump while patients with hemidiaphragm paralysis or weakness are presumed to seldom develop SDB. We hypothesised that patients with unilateral diaphragm weakness do not develop SDB.

**Patients and methods:** We studied 36 patients referred with a clinical diagnosis of hemidiaphragm paralysis. After placing balloon catheters to measure oesophageal and gastric pressures, we measured diaphragm strength (sustained and twitch transdiaphragmatic pressures (Pdi)). Twitch Pdi was measured following anterolateral magnetic stimulation of the phrenic nerves. In 16 patients we confirmed unilateral diaphragm paralysis. 10 patients agreed to undergo a polysomnography with measurement of the transoesophageal electromyogram of the diaphragm (EMGdi) and surface EMG of other respiratory muscles (sternocleidomastoid, parasternal intercostals, rectus abdominis). We compared the data to 10 normal, healthy young subjects.

**Results:** We studied 10 patients (5m, age 56 (10.4), BMI 29.0 (2.7)) with hemidiaphragm paralysis or severe weakness (twitch Pdi 3.2 (1.8) cmH2O). They had a mean (SD) respiratory disturbance index (RDI) of 7.6 (10.5) h during non-REM sleep, and an RDI of 27.0 (18.4) h (p = 0.003) during REM sleep (control group 0.2 (0.3) and 0.7 (0.9) h, respectively). EMGdi (%max) was doubled compared to the control group in NREM sleep (18.1 (8.5) %max) and increased in REM sleep (21.5 (8.9) %max), while the normal subjects had a reduction of EMGdi during REM sleep (8.5 (4.5) and 5.2 (2.8) %max; p < 0.001). Accessory muscles (parasternal intercostals) did not show REM-related atonia in the patients. All dimensions of quality of life as measured by the Saint George’s Respiratory Questionnaire and the Chronic Respiratory Disease Questionnaire were reduced compared to controls.

**Conclusion:** Some patients with unilateral diaphragm weakness are at risk of developing REM-related SDB, in particular when there is an additional load on the respiratory muscle pump like an elevated body mass. Neural drive to their diaphragm is doubled compared to normal subjects, and in REM sleep. Accessory respiratory muscles have increased activation to compensate for hypoverentilation during sleep. In those with SDB respiratory related symptoms affect the quality of life.

### S61 SLEEP DISORDERED BREATHING AND LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH STABLE MODERATE HEART FAILURE, WHO ARE ON OPTIMAL MEDICAL TREATMENT

J. A. Benjamin, C. Wynne-Williams, K. E. Lewis. Prince Phillip Hospital, Swansea, UK

**Introduction:** Sleep disordered breathing (SDB) is becoming increasingly recognised in heart failure (HF) occurring in 40–90% of patients. Central sleep apnoea and Cheyne–Stokes respiration is particularly associated with a poorer prognosis. Most of these prevalence studies were performed before the introduction of HF guidelines and particularly the widespread use of β-blockers and spiranolactone. We wanted to note the effects of current medical treatment on SDB in HF.

**Methods:** Following LREC approval, we approached 32 patients attending cardiology and heart failure (of any aetiology) clinics. All had New York Heart Association (NYHA) symptoms grade II–III. All were deemed clinically stable and on appropriate medications, prescribed at maximal tolerated doses by a cardiologist, for at least 3 months.

**Exclusions:** NYHA stage IV (deemed too unstable and bedbound to attend sleep studies/echos), known sleep apnoea (n = 0), age > 80 years, PEV < 50% predicted (n = 0), ejection fraction > 50% (or unreliable images, n = 5), cardiac hospital admission within previous 3 months (n = 3), withdrawal (n = 1). Sleepiness was assessed with the Epworth Sleepiness Score (ESS). Total apnoea hypopnoea index (AHI) was estimated using a multichannel home sleep study (Stardust II, Respirinc Inc, Monroeville USA). Updated ejection fraction was estimated with transthoracic echocardiogram according to standard guidelines. We had complete data on 23 patients (20 males), mean (SD) age 61 (12.7) years, mean BMI 31.8 (5.7) kg/m².

**Results:** From 23 (17%) had ESS > 10. 17 from 23 (74%) patients had an AHI > 10 events per hour during sleep. Correlation between AHI and ejection fraction, Spearman’s Rho = 0.25, p = 0.25. (R² linear = 0.11).

**Conclusion:** The prevalence of SDB remains high in (mobile) patients with moderate HF, despite being stable and after optimising cardiac medication, using modern prescribing regimes. There is a negative weak correlation between the AHI and ejection fraction, suggesting SDB is more severe with poorer left ventricular function. This was not statistically significant and only accounted for 10% of the variance in AHI, suggesting other factors are also important. The clinical significance of SDB in this group of patients and direction of causality needs to be addressed in interventional trials.


3. www.bsecho.org

### S62 ENDOTHELIAL FUNCTION IN PATIENTS WITH MILD–MODERATE OBSTRUCTIVE SLEEP APNEOA

M. Kohler1, S. Craig1, D. Nicoll1, P. Leeson2, J. R. Stradling1. 1Oxford Centre for Respiratory Medicine; 2Department of Cardiology, John Radcliffe Hospital, Oxford, UK

**Background:** Flow mediated dilation (FMD) of the brachial artery and augmentation index are methods to assess vascular endothelial function. Both are influenced by vascular risk factors common in patients with obstructive sleep apnoea (OSA). Which of the techniques is better suited to assess endothelial function in large scale randomised controlled trials of continuous positive airways pressure (CPAP) for OSA is controversial.

**Study objectives:** To investigate if there are relationships between the 2 measures of vascular function in an OSA population, and if they are correlated to well accepted predictors of cardiovascular risk such as blood pressure, or the Framingham index.

**Methods:** Framingham index was calculated from individual patients risk factors (BMJ 2001;323:75–81). Brachial artery diameter (AD) was measured by ultrasonography at baseline, and during reactive hyperaemia after 5 minutes of forearm ischaemia in order to determine FMD (% increase from baseline). Simultaneously blood pressure was measured and augmentation index was determined by pulse wave analysis (PWA) of the radial pulse. Both these indices are thought to measure aspects of vascular endothelial function and be early markers of cardiovascular risk.

**Results:** In 45 patients (mean (SD) age, 60.0 (6.8) years, 6 females) with mild to moderate OSA (mean (SD) oxygen desaturation index, 24.1...
Basic mechanisms in COPD

V. Kumar, C. E. Charron, P. J. Barnes, K. Ito. Airway Disease, NHLU, Imperial College London, UK

Introduction: Chronic obstructive pulmonary disease (COPD) is a major global health burden. The disease is a chronic inflammatory disorder, associated with exposure to cigarette smoke and other noxious stimuli. The pathogenesis of COPD includes destruction of the lung parenchyma, progressive inflammation of the peripheral airways, and goblet cell hyperplasia. Patients with COPD suffer from an accelerated decline in lung function, and the inflammation is largely corticosteroid resistant. Previous studies have demonstrated that inflammation of the airways, particularly upper body obesity, cause both OSA and the insulin resistance critical to the metabolic syndrome, it has been difficult to tease out whether OSA could be providing a misleading signal, in the same way vitamin C always lessens the apparent role of OSA, but in many studies it does not abolish it. However, it is always possible that all confounders have not been allowed for. There is a possibility that some confounder associated with OSA could be providing a misleading signal, in the same way vitamin C levels in cross sectional studies led to erroneous conclusions that anti-oxidant therapy might reduce vascular risk. It is possible that OSA might be a better marker of the central obesity causing insulin resistance than conventional indices such as waist/hip ratio or waist/height, which themselves only account for about 30% of the variance in visceral obesity compared to the gold standard of CT measurements. Thus OSA may indirectly be coding for the obesity pattern that causes insulin resistance better than non-invasive estimations of visceral fat.

Methods: A prospective study of 86 patients with sleep study proven OSA and sufficient daytime symptoms to warrant treatment with continuous positive airways pressure (CPAP) was carried out. A particular >4% SaO2 dip rate and Epworth Sleepiness Score (ESS) were not trial entry criteria, thus providing a spread of disease severity. Measurements were made of insulin resistance (HOMA), OSA severity (>4% SaO2 dips/hour, time below 90% SaO2 and number of pulse rate rises/hr), and obesity indices (waist, height, BMI, W/Hip, W/Ht, neck circumference).

Results: Subjects (86% male) had moderately severe OSA and decreased insulin sensitivity. Sixty-four subjects had satisfactory estimates of insulin sensitivity (HOMA) and were not receiving insulin. The best predictor of insulin sensitivity (and only independent predictor in multiple linear regression incorporating all measurements described in the Methods) was neck circumference, suggesting that this is a better correlate of visceral fat than conventional surface measurements. Neck circumference, waist and weight were also the best predictors of OSA severity.

Conclusion: Thus it is quite possible that OSA codes for upper body obesity in a way that would make it erroneously appear as an independent predictor of vascular risk in cross sectional studies.
inflammation in airways disease including COPD suggests a favourable response to corticosteroid therapy. Interleukin 5 (IL-5) is a cytokine involved in eosinophil expansion, priming, recruitment, and prolonged tissue survival. To date sputum IL-5 has not been reported in COPD and therefore its relation with eosinophilic inflammation within the COPD paradigm is currently unknown.

**Methods:** Sputum supernatants were identified from subjects with clinically stable COPD who participated in a previous study. Sputum IL-5 was measured using the Meso-Scale Discovery multi-array platform. The assay was validated by measuring % recovery of spiked standard to sputum plugs from subjects with COPD (n = 4) or to PBS and then processed as per sputum. The relation of sputum IL-5 with eosinophilia was assessed by comparing sputum IL-5 concentration in COPD subjects with (n = 19) and without (n = 29) a sputum eosinophilia (<3% non-squamous cells). Within subjects, sputum IL-5 concentration determined by measuring sputum IL-5 on 2 occasions (n = 20). To assess modulation with corticosteroid therapy, sputum IL-5 was measured before and 1 month after prednisolone 10 mg daily (n = 9).

**Results:** The mean % recovery of the exogenous spike to COPD sputum samples compared to control was 81%. The mean (SEM) sputum IL-5 concentration as increased in those COPD subjects with a sputum eosinophilia 0.70 (0.19) pg/ml compared to those without a sputum eosinophilia 0.19 (0.05) pg/ml. The sputum IL-5 within subject repeatability was good (mean (SEM) difference 2.20(1.43); r = 0.6, p = 0.01). Sputum IL-5 concentration decreased following corticosteroid treatment from 2.94 (1.2) to 0.65 (0.39) (mean difference 2.30 pg/ml; 95% CI 0.3 to 4.3; p = 0.03).

**Conclusion:** We have validated the measurement of sputum IL-5 in subjects with COPD. Sputum IL-5 concentration was increased in those COPD subjects with a sputum eosinophilia IL-5 decreased in response to treatment with systemic corticosteroids. Our findings support in those COPD subjects with a sputum eosinophilia IL-5 decreased in treatment from 2.94(1.2) to 0.65(0.39) (mean difference 2.30 pg/ml; 95% CI 0.3 to 4.3; p = 0.03).

**S67 LIGANDS FOR TLR-3 AND TLR-4 INITIATE DISTINCT CYTOKINE CASCADES IN HUMAN LUNG PARENCHYMAL TISSUE**

D. R. Howell, J. A. Warner. University of Southampton, UK

**Introduction:** Toll-like receptors (TLRs) are known to play a major role in triggering inflammation in infectious exacerbations of chronic obstructive pulmonary disease (COPD) and asthma. Poly I:C is synthetic single stranded RNA that activates TLR-3, mimicking viral infection in the lung. We have examined the inflammatory response from human lung explants following stimulation with poly I:C and have compared this to a known inflammatory stimulus, lipopolysaccharide (LPS), a ligand for TLR-4 activation. We have analysed TNFα, IL-1β, epithelial cell-derived neutrophil-activating protein-78 (CXCL5), macrophage inflammatory protein 1β (CCL4) and IL-8 (CXCL8).

**Methods:** Human lung tissue (n = 19) was obtained from patients undergoing resection for cancer at Guy’s Hospital London. Tissue fragments taken from the normal margin were stimulated with either buffer control, 100 µg/ml poly I:C or 100 ng/ml LPS. Supernatants were harvested at 1, 2, 4, 6, 24 and 48 hours and the tissue was removed and weighed. Both the tissue and supernatants were stored at −80°C until analysis. Cytokine concentrations in the supernatant were determined using ELISA.

**Results:** Release of pro-inflammatory cytokines TNFα and IL-1β was significantly elevated in LPS stimulated lung at 4 hours, peaking at 24 hours for TNFα (75.5 pg/mg tissue versus 9.5 pg/mg compared to control tissue, p < 0.05) and 48 hours for IL-1β (8.0 pg/mg tissue versus 0.66 pg/mg respectively, p < 0.05). Poly I:C, however, had no significant effects on either TNFα or IL-1β production over 48 hours. In contrast, we found that poly I:C was as effective a stimulus as LPS for chemokine production (see table). Both CXCL5 and CXCL8 production significantly increased from 24 hours and continued to rise up to 48 hours for both LPS and poly I:C respectively. The poly I:C response for CCL4 was significant from 24 hours and continued to increase up to 48 hours, though the LPS response peaked and plateaued from 24 hours.

**Conclusion:** These results demonstrate both LPS and poly I:C significantly increase chemokine production; however, poly I:C fails to stimulate the inflammatory cytokine production of TNFα and IL-1β.
Abstract S68 Chemotactic activity of GROα was assessed by measuring overall chemotaxis towards fMLP (which was used as a positive control and all chemotaxis is expressed as a percentage of neutrophil chemotaxis towards this protein), GROα with and without the GROα monoclonal antibody and sputum with and without the GROα monoclonal antibody. There was a small but significant reduction in mean chemotaxis towards sputum following the addition of the GROα antibody.

considered together, the mean (SE) contribution of GROα was 7.2% (SEM 3.04%) (95% CI 0.9 to 13.5, p = 0.027). The median (IQR) GROα concentration was 11.6 nM (4.4–18.5 nM). There was no correlation between GROα concentrations and chemotactic indices.

Conclusion: GROα contributes a small but significant chemotactic effect for neutrophils towards sputum in COPD, but this contribution is much smaller than the reported contribution of interleukin 8 and LTβ4.

Abstract S69 rs2118177 genotype in emphysema.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airflow obstruction with FEV₁ &lt; 80% predicted</td>
<td>0.278 (0.105 to 0.732)</td>
<td>0.010</td>
</tr>
<tr>
<td>Emphysema on HRCT</td>
<td>0.428 (0.156 to 1.172)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

Results: There was a trend towards a difference in rs2118177 genotype (see fig) between patients with emphysema and controls, such that the CC genotype was less common in those with emphysema (p = 0.094), but no different between AATD subjects who did not have emphysema and controls (p = 0.871). The allele frequency analysis was not significant between the groups (p = 0.276).

The CC genotype of rs2118177 was significantly associated with the airflow obstruction phenotype within AATD, showing a protective effect in the AATD regression analysis (p = 0.010). There was a trend towards protection from emphysema, though this did not reach statistical significance (p = 0.099). The odds ratios (OR) of developing airflow obstruction or emphysema in AATD with the CC genotype relative to TT genotype, after regression for smoking, are shown in the table. No other analyses were statistically significant.

Conclusion: Our results support the existence of a genetic influence upon phenotype in AATD within the haplotype block containing rs2118177, and confirm that genes shown to influence usual COPD may have similar effects in AATD. They also suggest a role for SFTPB in the pathogenesis of emphysema. Low levels of this protein have been observed in the lungs of rats with emphysema, but this finding has yet to be confirmed in humans. Replication of our results in an independent patient population would confirm their importance.

Cystic fibrosis treatment responses and consequences

**S70** UK CF GENE THERAPY CONSORTIUM TRACKING STUDY: CHANGE IN SPUTUM PROPERTIES IN RESPONSE TO IV ANTIBIOTICS

U. Griesenbach1, S. B. Jeswiet1, M. D. B. Larsen1, Y. Bakar1, N. W. G. Voase1, F. M. Gammie1, K. E. Mullard1, D. M. Geddes1, J. C. Davies1, E. W. F. W. Altan1, C. Marriott1, R. Gray2, A. Horsley1, M. Imrie1, M. Dewar1, A. P. Grayling2, A. Innes1, 1Department of Gene Therapy, Imperial College London, UK; 2Department of Pharmacy, Kings College, London, UK; 3Scottish Adult CF Service, Western General Hospital Edinburgh, UK; 4UK CF Gene Therapy Consortium, UK

In preparation for our gene therapy clinical trial programme we are currently assessing a number of sputum biomarkers including viscosity, elasticity, total solids, DNA content and 24 hour sputum weight. We tracked and correlated these biomarkers in CF patients (12 years and over) during a course of IV antibiotics (Ab) by collecting samples on several occasions (visit [V1]: at the start of Ab treatment, V2: at the end of Ab treatment [generally after 2 weeks] and interim periods). To ensure adequate reproducibility of the results visco-elasticity measurements were carried out in triplicate using a CSI 100 Rheometer which required a comparatively large volume (5 ml) of spontaneously expectorated sputum. Because of this requirement paired samples could only be obtained from approximately 50% of the patients. There was no change in viscosity/elasticity (n = 1.5) or DNA (n = 18) content when comparing samples at the beginning and end of IV Ab. Sample size calculations indicated that based on data generated here several hundred subjects would be required for these end points to achieve statistical significance. A paired t-test showed that there was a significant reduction in solid content and viscosity/elasticity (r = 0.8, p < 0.0001), sputum IL-1β (r = 0.52, p < 0.0001), sputum IL-8 (r = 0.42, p < 0.001) and sputum calprotectin (r = 0.51, p < 0.0001). Twenty four hour sputum weight correlated modestly with % predicted FEV1 (r = 0.37, p < 0.05), patient scored symptom severity (r = 0.42, p < 0.001) and white blood cell (WBC) (r = 0.33, p < 0.016). WBC also correlated with DNA content (r = 0.41, p < 0.0001). Sputum elasticity and viscosity correlated with IL-1β (r = 0.50, p < 0.0001), IL-8 (r = 0.37, p < 0.01) and sputum calprotectin (r = 0.54, p < 0.0001). Interestingly, 24 hour sputum weight and viscosity/elasticity were correlated with the extent of bronchiectasis as assessed by CT (r = 0.48, p < 0.001 and r = 0.32, p < 0.03, respectively). Surprisingly, sputum DNA content did not correlate with viscosity/elasticity, despite being generally thought of as a contributor to viscosity, which may in part be related to the assay not being able to discriminate between free and cell-enclosed genomic DNA. In summary, after a course of IV antibiotics which lead to significant subjective and objective (FEV1) improvement the overall quantity of expectorated sputum significantly decreased but, based on analysis available to date, none of the other parameters (viscosity, elasticity, solid and DNA content) changed significantly, but correlated with other more routinely used assays. Considering the difficulties we encountered in collecting sufficient sputum during this period of an exacerbation and sample size consideration, sputum viscosity/elasticity measurements may not be feasible parameters to measure in a gene therapy trial to which stable patients are likely to be recruited. This study was funded by the CF Trust.

**S71** UK CF GENE THERAPY CONSORTIUM TRACKING STUDY: RESPONSE OF CLINICALLY AVAILABLE ASSAYS TO INTRAVENTOUS ANTIBIOTICS

J. C. Davies1, N. Voase1, M. Dewar1, K. Mullard1, F. Gammie1, C. Saunders1, A. Horsley2, R. Gray2, K. MacLeod1, L. Somerton1, T. Higgins1, J. Donovan1, N. Cornish1, D. Ashby1, D. Geddes2, A. Greening1, S. Cunningham1, A. Innes1, E. Alton1, 1Imperial College, 2Western General Hospital, Edinburgh, UK; 3Hospital for Sick Children, London, UK; 4Queen Mary, University of London, London, UK

Introduction: In our forthcoming clinical trial of CFTR gene therapy, the UK CF Gene Therapy Consortium will use both established assays and more novel, specifically-designed measures. In this study, we examined the performance of these assays in the context of an infective exacerbation treated with IV antibiotics. This abstract will report the response of established, clinically-available assays; available data from novel assays will be reported separately.

Methods: Children (12 years and above) and adults with CF were recruited from three centres at the time of a clinician-defined infective exacerbation requiring IV antibiotic treatment. A panel of assays was performed at the start and end of treatment, which was most commonly 14 days. Data are presented as mean (SD) or median (range). Clinical assays included sputum viscosity/elasticity, sputum microorganisms, sputum cell count and differential, serum inflammatory markers (CRP, white blood cell (WBC) count). Patients also completed a symptom score chart.

Results: Forty patients (mean age 24.2 (7.5) years, 21 male) have paired data available from the start and end of the course of IVs. At baseline, 24 were infected with *Pseudomonas* and 8 with *Streptococcus* predominately and 14 with *Staphylococcus* (2 MSSA). Significant changes from baseline were observed in FEV1 (53.3 (15.1) to 62.4 (17.5)%; p < 0.001), sputum *P. aeruginosa* colony count (log10 CFU 6.3 (0.8) to 5.1 (1.3); p < 0.01), WBC (10.2 (2.5) to 8.7 (3.2) x 109/L; p < 0.05), CRP (19 (1–249) mg/L to 3.5 (1–165) mg/L; p < 0.001) and symptom score (–6.2 (2) to 2.6 (5.4); p < 0.001). In contrast, neither sputum total cell count nor sputum neutrophils changed significantly. There was a significant correlation between change in FEV1 and symptom score (R = 0.4; p < 0.05). Although baseline FEV1 correlated significantly with several inflammatory/infector markers (including CRP, WBC, *P. aeruginosa* CFU), changes in none of these parameters correlated with improvement in FEV1.

Conclusion: The clinical response to any novel intervention—for example, CFTR gene therapy—is difficult to predict. Prior testing of experimental assays in a study such as this provides data on the variability of the measurements within the disease population and the degree of change observed with an intervention known to lead to clinical benefit. This should aid the design of rational, powered clinical trials.
were scored as a percentage. In a second scoring method, observers evaluated paired CTs as a “side-by-side” comparison. Observers were blinded to the date of the scans and used a graded score (1–5) to indicate whether certain CT features were better, worse or had not changed. Differences between CT1 and CT2 were compared with either parametric or non-parametric analysis as appropriate. Observer variation was assessed using weighted kappa or the single determinant standard deviation.

Results: A significant decrease was seen in wall thickness, small mucus plugs, large mucus plugs and air trapping on the second CT. Interobserver variation for individual CT features was excellent (see table). The “side-by-side” comparison also showed a statistically significant improvement from baseline (CT1) in bronchial wall thickness, small and large mucus plugs, air trapping, consolidation and ground glass opacification. Weighted kappas ranged from 0.68–0.94 (good to excellent).

Conclusion: CT can demonstrate significant morphologic changes over a relatively short time period and in the situation of an infective exacerbation, these correspond with the expected response to treatment. Interobserver variation of both scoring methods was either good or excellent. The relatively simple and quick method of direct comparison is a useful and robust alternative to the scoring of individual CTs in studies involving large numbers of patients.

**FUNCTIONAL AND STRUCTURAL CHANGES IN THE CYSTIC FIBROSIS LUNG FOLLOWING ANTI-BACTERIAL TREATMENT FOR EXACERBATION**


1 Western General Hospital, Edinburgh, UK; 2Department of Radiology, Barts & London NHS Trust; 3Department of Child Life & Health, Royal Hospital for Sick Children; 4Department of Gene Therapy, Royal Brompton Hospital; 5Department of Radiology, Royal Brompton Hospital, London, UK

**Background:** Lung clearance index (LCI), a measure of ventilation heterogeneity, can be calculated from multiple breath washouts. The measurement is thought to be sensitive to small airways dysfunction and is a more sensitive measure of early airway disease in CF than spirometry.

**Methods:** CF patients presenting with an exacerbation were recruited as part of the UK CF Gene Therapy Consortium “Tracking Study.” Lung HRCT was performed within 24 hours of the start of intravenous antibiotics. CT features for each lobe were scored for seven independent features by two independent blinded observers. LCI was assessed in triplicate by multiple breath washout of 0.2% SF6. Both assessments were repeated at end of treatment.

**Results:** 29 patients (15 male) completed both LCI and CT assessments. Mean age (range) was 21 (11–40) years, mean FEV1% predicted was 50%. There were 24 cases of ARF (12 male, median age 10 years, range 4 months–32 years) and 43 controls (22 male, 9 years, 10 months–32 years). In the group of patients with ARF, 21/24 had received an aminoglycoside at the time of their episode of ARF or in the preceding week, compared with only 3 of the controls for the same time period (p = 0.001). In the year prior to the episode of ARF, significantly more cases than controls received gentamicin (19/24 cases vs 1/43 controls, p < 0.001). In contrast, the numbers receiving tobramycin were similar (9/24 cases and 15/43 controls). The median lifetime exposure to aminoglycosides among the cases was 11 courses (range 0–72) vs a median of 2 courses (range 0–26) in the control group. The odds ratio for ARF was 1.20 (95% CI 1.04 to 1.38) for aminoglycoside course (p = 0.011). A clear risk factor for ARF (prior renal disease, acute dehydration or long term nephrotic drug treatment) was present in 18/24 cases and B4/43 controls (OR 23.52, 95% CI 3.02 to 183.01, p = 0.003).

**Conclusion:** Cumulative, exposure to aminoglycosides, particularly gentamicin, increases the risk of CF patients developing ARF. Most patients who develop ARF have clear risk factors which indicate the need to withhold aminoglycosides or monitor them more closely.

Supported by UK Cystic Fibrosis Trust Grant PJ465 and an unrestricted educational grant from Forest Laboratories.

**Tuberculosis treatment**

**DO MICRONUTRIENTS USED AS SUPPLEMENTATION TO STANDARD TREATMENT SPEED RESOLUTION OF TUBERCULOSIS?**


1Cardiothoracic Centre, Liverpool, UK; 2Zankli Clinic, Abuja, Nigeria

**Introduction:** Several studies have suggested that the addition of zinc and vitamin A to standard treatment may speed the resolution of tuberculosis (TB). This may be of value in resource poor settings when the addition of cheap supplements may reduce the time needed for TB treatment.

**Methods:** The study was carried out in Abuja, Nigeria. A total of 350 smear positive patients were enrolled in a double blind randomised prospective placebo controlled three arm study. Group A (the placebo arm) received standard 8 months therapy: isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid and ethambutol for 6 months. Group B received the same anti-tuberculosis chemotherapy but with zinc supplement in addition; and group C, standard treatment plus zinc plus vitamin A. Assessment of a number of factors, including symptomatology, weight, sputum smear and culture conversion, radiographic improvement and biochemical results, was carried out at the start of treatment, at 2 and 6 months of therapy.

**Results:** A total of 261 patients completed the study, 91 in group A (35 HIV-ve), 89 in group B (42 HIV-ve) and 81 in group C (30 HIV-ve). Only two factors showed a statistically significant difference between the groups: sputum smear conversion on average took 1 week longer (4 weeks compared with 3 weeks) in the placebo arm compared with the two supplementation arms. Secondly the mortality was greater in the two supplementation arms: one death in group A compared with 9 deaths each in groups B and C. All patients who died during the study were HIV-ve.

**Conclusion:** This study has shown no overall benefit of giving zinc and vitamin A supplements as an adjuvant therapy for tuberculosis. Zinc might have a possible benefit in reducing mortality.

**A CASE CONTROL STUDY OF ACUTE RENAL FAILURE IN CYSTIC FIBROSIS PATIENTS IN THE UK**

A. Smyth1, C. Bentershaw1, S. Lewis2, I. Choonara1, J. Magaw1, A. Watson3.

1Division of Child Health, University of Nottingham; 2Division of Respiratory Medicine, University of Nottingham; 3Department of Paediatrics, Nottingham University Hospitals NHS Trust, UK

**Background:** There has been a recent increase in the number of reported cases of acute renal failure (ARF) in cystic fibrosis (CF). The incidence risk of ARF in CF patients is between 4.6 and 10.5 cases/10 000 CF patients/year. We conducted a case control study to determine which factors which are associated with an increased risk of ARF.

**Methods:** Case-control study using initial survey to confirm 24 cases of ARF in CF patients from 20 UK CF Centres, presenting between 1997 and 2004. Using the UK CF database, we identified sex and age matched controls. Informed consent was sought from the control patients/parents for access to the case notes. Analysis of risk factors was by conditional logistic regression, using STATA (version 9) and Mantel Haenzsel analysis.

**Results:** There were 24 cases of ARF (12 male, median age 10 years, range 4 months–32 years) and 43 controls (22 male, 9 years, 10 months–32 years). In the group of patients with ARF, 21/24 had received an aminoglycoside at the time of their episode of ARF or in the preceding week, compared with only 3 of the controls for the same time period (p = 0.001). In the year prior to the episode of ARF, significantly more cases than controls received gentamicin (19/24 cases vs 1/43 controls, p < 0.001). In contrast, the numbers receiving tobramycin were similar (9/24 cases and 15/43 controls). The median lifetime exposure to aminoglycosides among the cases was 11 courses (range 0–72) vs a median of 2 courses (range 0–26) in the control group. The odds ratio for ARF was 1.20 (95% CI 1.04 to 1.38) for aminoglycoside course (p = 0.011). A clear risk factor for ARF (prior renal disease, acute dehydration or long term nephrotic drug treatment) was present in 18/24 cases and B4/43 controls (OR 23.52, 95% CI 3.02 to 183.01, p = 0.003).

**Conclusion:** Cumulative, exposure to aminoglycosides, particularly gentamicin, increases the risk of CF patients developing ARF. Most patients who develop ARF have clear risk factors which indicate the need to withhold aminoglycosides or monitor them more closely.

Supported by UK Cystic Fibrosis Trust Grant PJ465 and an unrestricted educational grant from Forest Laboratories.

**OUTCOMES OF A TRIPLE THERAPY REGIMEN FOR NON-TUBERCULOUS MYCOBACTERIAL PULMONARY INFECTION**

M. Murray1, R. Forsythe2, A. Hill1.

1Royal Infirmary of Edinburgh; 2University of Edinburgh College of Medicine, UK

**Aims:** There are few randomised controlled trials providing evidence for efficacious treatment regimens for non-tuberculous mycobacterial
pulmonary infection (NTM) and success rates remain low. This study aimed to assess outcomes in patients receiving a standard triple therapy regimen of rifampicin and ethambutol and clarithromycin or ciprofloxacin over 24 months for NTM. End points included microbial clearance, systemic inflammation and symptomatology.

**Methods:** A retrospective review of case notes, microbiological and haematological data for all patients diagnosed with culture positive NTM and managed with rifampicin and ethambutol and clarithromycin or ciprofloxacin over 24 months between 1998–2007 was undertaken. Patients who were HIV positive, had cystic fibrosis or were receiving chemotherapy were excluded. At baseline, 6, 12, 18 and 24 months, sputum microscopy (AFB and full culture status), ESR and symptomatology were recorded.

**Results:** 38 patients (20 male, 18 female) were eligible for inclusion. The mean (SD) age was 60.5 (16.0) years. 25 patients had completed therapy, with 13 still currently receiving treatment (mean (SD)) 13.7 (8.1) months). All patients were confirmed to be sputum culture positive for NTM: *Mycobacterium malmoense* 37.5%, *M avium complex* 32.5%, *M xenopi* 10%, *M intracellulare* 5%, *M kansasi*, *M abscessus*, *M bovis*, *M interjectum* 2.5%, respectively, and as yet unidentified NTM 5%. Main adverse treatment effects were nausea (7%), visual disturbance (3.5%) and peripheral neuritis (3.5%). There were no cases of significant hepatotoxicity (>3 times the upper limit of normal ALT range). Two patients died during treatment (one at 12 months due to pulmonary embolism and one at 14 months due to respiratory failure). One patient was lost to follow up at 3 months. The table shows the effects on sputum microbiology, systemic inflammation and symptomatology.

**Conclusion:** Treatment of NTM with a standard triple therapy regimen of rifampicin and ethambutol and clarithromycin or ciprofloxacin for 24 months significantly improves microbial clearance, reduces systemic inflammation and improves reported symptomatology. These outcomes are superior to rifampicin and ethambutol + isoniazid from historical data, but randomised controlled trials are needed.

**Abstract S76**

**Treatment outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum AFB positive (%)</td>
<td>62</td>
<td>10.3*</td>
<td>4*</td>
<td>4*</td>
<td>4.5*</td>
</tr>
<tr>
<td>Sputum culture positive (%)</td>
<td>100</td>
<td></td>
<td>17.2*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (median (IQR))</td>
<td>60.5 (30.7–89)</td>
<td>14 (7–23.8)*</td>
<td>16.5 (6.5–30.8)*</td>
<td>11.5 (5.75–26)*</td>
<td>12.5 (5–24)*</td>
</tr>
<tr>
<td>Cough (%)</td>
<td>87</td>
<td>58.5*</td>
<td>44*</td>
<td>44*</td>
<td>58*</td>
</tr>
<tr>
<td>Sputum (%)</td>
<td>87</td>
<td>50*</td>
<td>53*</td>
<td>44*</td>
<td>45*</td>
</tr>
<tr>
<td>Night sweats (%)</td>
<td>40</td>
<td>18*</td>
<td>5*</td>
<td>6*</td>
<td>4*</td>
</tr>
<tr>
<td>Anorexia (%)</td>
<td>44</td>
<td>6*</td>
<td>12*</td>
<td>18*</td>
<td>14*</td>
</tr>
</tbody>
</table>

*p<0.005 compared to baseline value.

---

**Abstract S77**

<table>
<thead>
<tr>
<th>AFB density</th>
<th>Sputum non-conversion</th>
<th>Sputum conversion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB3+</td>
<td>13</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Rest</td>
<td>3</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>42</td>
<td>58</td>
</tr>
</tbody>
</table>

P value <0.01 on x² testing

The distribution is significant.

---

### S77

**IS THE WORLD HEALTH ORGANIZATION REGIMEN OF THRICT WEEKLY CATEGORY 1 (NEW SPUTUM SMER POSITIVE PATIENTS) TREATMENT SUFFICIENT FOR PATIENTS WHO HAVE A HIGH DENSITY OF ACID-FAST BACILLI IN THE SPUTUM?**

C. Tenzing1, A. Kujur1, P. D. O. Davies1. 1-Nav Jivan Hospital, Sabatwar, India; 2-TB Unit, Liverpool, UK

**Aim:** To prove that patients with more than 2+ AFBs in sputum are more likely to fail to sputum convert at the end of the intensive phase of the World Health Organization recommended thrice weekly regimen.

**Introduction and background:** The Nav-jivan Hospital is a unit of Emmanuel Hospital Association, an NGO, based in the Palaumu district of Jharkhand. It has played an important part in the provision of tuberculosis services in the region hand-in-hand with the government as per the revised national tuberculosis programme’s public–private mix initiative. This study has been made from the records of the tuberculosis register of the unit starting from the 1 January 2006 until 31 April 2007. Category 1 patients are new sputum smear positive patients. They are commenced on standard therapy of isoniazid, rifampicin, pyrazinamide and ethambutol. If they have not converted to sputum smear negative at the end of 2 months a further month of intensive therapy is given.

**Method:** The data are the analysis of the report from the TB register of Nav-jivan district microscopic centre. It was observed that a substantial number of patients were failing to sputum convert at the end of the intensive phase and most of these had had 3+ AFBs in the sputum at diagnosis. Therefore new sputum positives who failed to convert were scrutinised and found to have the following results.

**Results:** Seventy-one sputum positive patients were diagnosed during that period out of which 58 were new (category 1) sputum positives. Twenty-seven patients had 3+ AFBs in their sputum at the time of diagnosis. Sixteen patients out of the 58 new sputum positive patients failed to convert at the end of the intensive phase. Out of the 16 patients who failed to convert, 13 (81%) had 3+ AFBs at the time of diagnosis. Of the 42 who did convert at the end of the intensive phase 14 (33%) were 3+.

**Conclusion:** We can conclude that patients with 3+ AFBs in sputum at the time of diagnosis have an increased chance of failing to convert at the end of the intensive phase of the thrice weekly category 1 regimen of WHO compared with other sputum smear positive patients. Patients who do not convert from sputum smear positive to sputum smear negative after two months of intensive phase treatment are given a further month of the intensive phase necessitating an extra and usually unexpected supply of drugs. If it is assumed that at least half of category 1 3+ smear patients will require 3 months of intensive phase therapy rather than two, drug supplies can be planned and obtained well in advance. This is an important provision in a resource poor setting.

### S78

**ARE ALL PATIENTS STARTING ETHAMBULOT THERAPY RECEIVING ADEQUATE OPTIC NERVE FUNCTION SCREENING?**

D. M. Gore1, J. Forbes1, S. Tanne2, D. Creer2. 1-Royal Free Hospital, London, UK; 2- Barnett & Chase Farm NHS Trust, London, UK

**Introduction:** Ophthalmologists have traditionally performed baseline assessments for ethambutol optic neuropathy. Following an increase in TB cases, the Eye Clinic had encountered problems providing baseline checks at short notice so specialist TB nurses were trained using a specific protocol.

**Method:** A retrospective audit of newly diagnosed TB patients over 8 months was performed, including Snellen visual acuity (VA) and Ishihara colour vision. VA of less than 6/12 or reduced colour vision warranted referral to the Eye Clinic. Randomly selected “quality control” cases were subsequently seen by ophthalmologists.

**Results:** 52 newly-diagnosed patients underwent baseline screening. 43 (83%) were screened by nurses in the clinic, the remaining nine (17%) by medical staff while in-patients. Four nurse-screened patients were referred, where ophthalmologists duplicated initial abnormal findings. Of these, three red-green colour defects consistent with congenital colour blindness were identified (two of which were new diagnoses) and one old ischaemic optic neuropathy. One in-patient was confirmed to have previously diagnosed congenital colour blindness. Including randomly selected “quality controls”, a total of 9 (20%) nurse-screened patients were examined by an ophthalmologist; no inconsistencies in VA or Ishihara colour vision scores were found.

**Conclusion:** This study demonstrates nurse-led screening for optic nerve function to be robust. Current British Thoracic Society guidelines do not recommend assessment of colour vision prior to ethambutol treatment, yet colour vision defects have been found to provide a better indicator and enable early detection of ethambutol toxicity. Correlating with this study,
Spoken sessions A33

Background: Concurrent treatment for tuberculosis (TB) and HIV is complicated by overlapping toxicities, drug-drug interactions and risk of immune reconstitution inflammatory syndrome (IRIS). It has been suggested that early initiation of antiretroviral therapy (ART) reduces mortality and prevents opportunistic infection (OI) in severely immunocompromised HIV infected individuals. However, the risk of IRIS is also highest in this group.

A balance has to be struck between the risk associated with concurrent treatment of TB and HIV and the risk of HIV disease progression. Although questions still remain about the optimum time to commence ART in co-infected patients, the British HIV Association (BHIVA) has published treatment guidelines for management of HIV infected patients with tuberculosis which are based on available evidence.

Objectives: To describe factors affecting initiation of ART in patients with HIV/TB co-infection and audit our clinical practice against the BHIVA treatment guidelines.

Methods: Retrospective case note review of all co-infected, ART-naive patients attending an HIV/TB service between January 1994 and June 2007. Data collected included demographics, drug history, CD4 time of ART initiation and reason for delay. ART delay was considered to have occurred if ART was not started within the following parameters: if the CD4 count was <100 cells/µl, within 2 weeks of commencing TB treatment; if the CD4 count was 100–200 cells/µl, after the induction phase of TB treatment; if the CD4 count >200 cells/µl, after completion of TB therapy.

Results: Ninety-one patients were identified. Median CD4 count at presentation with TB = 100 cells/µl (range 10–970). In 15/91 patients, ART could not be started. Information was missing in five. Of the remaining 76, 70 initiation of ART was within BHIVA guidelines in 13/70 (19%) rising to 25/70 (36%) and 48/70 (69%) by 1 and 3 months, respectively. Reasons for delay in initiating ART were: physician concern regarding toxicity and IRIS = 6/77, patient fear of side effects = 3/57, patient refusal = 9/57, TB therapy intolerance/toxicity = 10/77, concurrent AIDS defining OI = 4/77, TB medication adherence issues = 4/77, other = 13/77, reason not documented = 14/77. Concern regarding toxicity, IRIS and side effects was highest in the group with CD4 <100 cells/µl: 7/22(31%), compared with CD4 =100–200 cells/µl group: 2/12(16%) and CD4 >200 cells/µl group: 0/13(0%). Two patients had IRIS, both in the CD4 <100 cells/µl group; neither had delayed ART initiation. There were five deaths. Four deaths occurred in the CD4 <100 cells/µl group, all had delayed ART; no deaths could be attributed to delayed ART initiation. One death occurred in the CD4 >200 cells/µl group; the patient had been treated within BHIVA guidelines.

Conclusions: Our study highlights the complexity of initiating ART in co-infected patients. Although most patients did not start ART within guidelines, the delay started within 3 months. Despite this, the outcome was good. There were no relapses of TB before initiation of ART. The four cases who had a concomitant OI were diagnosed before ART would have been initiated following HIV/TB guidelines. Common reasons for delay were concern regarding toxicity and IRIS, and intolerance/toxicity of TB medication.

survival benefit with neo-adjuvant chemotherapy at 5 years (1507 patients, HR: 0.88, 95% CI 0.76 to 1.01, p = 0.077).

Conclusion: This intergroup trial, which is the largest trial of neo-adjuvant chemotherapy in patients with resectable NSCLC, indicated that the addition of neo-adjuvant platinum-based chemotherapy did not lead to a benefit in overall survival. However, a 20% survival benefit or a 31% detriment cannot be excluded, but when this result is combined with previous neo-adjuvant trials it indicates a survival benefit similar to that seen with adjuvant chemotherapy.

S82  TWENTY-EIGHT DAYS FROM REFERRAL TO TREATMENT FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER

J. Maguire1, J. Maguire2, V. Kelly3, R. Page1, H. Bonwick3, M. Carr1, C. Smyth1, M. Ledson1, M. Walshaw1. 1Liverpool Lung Cancer Unit; 2Clatterbridge Centre for Oncology; 3Marie Curie Hospice Liverpool, UK

Introduction: NSCLC is the most common fatal lung cancer in Britain. The average survival time for patients diagnosed as having NSCLC in the UK is only between 4 and 5 months. Therefore, even if patients with lung cancer commence treatment in the present government target time of 62 days from GP referral, an average more than 40% of a lung cancer patients’ life expectancy maybe spent undergoing diagnostic tests and waiting for treatment.

Methods and results: In the Liverpool Lung Cancer Unit and Clatterbridge Centre for Oncology, using a rapid access lung cancer diagnostic system and a modernised oncology treatment pathway for patients with lung cancer we have demonstrated that in a trial 1 month period 93% (20/22) of patients can commence definitive treatment with either surgery 15.5% chemotherapy 35%, radiotherapy 35.1% or palliative care 14.4% within 28 days of initial referral from general practice. The key components in the achievement of a 28 day referral to treatment time were: utilisation of a 1 day rapid access diagnostic service, immediate review of CT scans and performance status data by an oncologist to determine the requirement for PET CT scanning, rapid access to chemotherapy facilitated by use of oral chemotherapy for day 8 treatment, redesign of the planning process for radical radiotherapy to allow patients to proceed from planning to treatment without an interposed planning verification step, and a parallel clinic arrangement with adjacent respiratory medicine, thoracic surgery, oncology and palliative care colleagues working simultaneously to allow immediate specialists with great paper referral process.

Conclusion: We believe that 28 days from referral to treatment represents a new “gold standard” of care for patients with NSCLC and we plan to maintain and review our redesigned system from September to November 2007 to demonstrate the sustainability of these improvements in service.

S83  ANALYSIS OF A LUNG CANCER COHORT FOR VARIATION IN SURVIVAL OVER A 7 YEAR PERIOD

N. Navani1, B. North2, A. Berry3, J. Brown1, F. Bowen3. 1Hammersmith Hospital; 2Imperial College; 3Charing Cross Hospital, London, UK

Background: Lung cancer is the primary cause of cancer mortality worldwide. Despite advances in treatment, survival from lung cancer remains poor. Five year survival rates are reported as 5% in the UK compared to rates of up to 15% in other European countries.

Methods: We collected data from consecutive patients diagnosed with lung cancer from 2000–3 and 2004–7. Our primary aim was to measure the 1, 3 and 5 year survival rates and compare these to national data. Our secondary aims were to determine how mortality was affected by gender, performance status, year of diagnosis and stage at presentation. Data were obtained from MDT documentation. Kaplan–Meier graphs were plotted to calculate survival. Analysis of individual clinical attributes (eg, performance status) was performed using Cox’s regression model.

Results: There were 746 patients. A histologically proven diagnosis was obtained in 679 (91%) and WHO performance status (PS) was recorded in all but 3 patients. Survival at 1 year was 42.0%, at 3 years 17.8% and 5 years 9.5%. Survival was related to performance status (p<0.001), histological type (p=0.001) and stage at presentation (p=0.001) but not to age (p=0.077). Patients with stage 1 disease at presentation have a 5 year survival rate of 49%. For an increase of 1 in performance status, the death rate multiplies by 1.73 (95% CI 1.60 to 1.87). Similarly, an increase in stage results in an increase in mortality rate by 1.85 (95% CI 1.67 to 2.05). Survival was improved in the 2004–7 cohort compared to the 2000–3 group (p=0.006).

Conclusion: Our 1, 3 and 5 year survival data exceed the national average. The data emphasise the importance of performance status as well as stage and cell type as independent variables in determining prognosis. Improved survival in 2004–7 may be due to increased access to a new cross-site expanded multidisciplinary team and consequently an increased uptake of newer generation chemo-radiotherapy regimens.

S84  SURVIVAL FOR PATIENTS WITH LUNG CANCER: THE IMPORTANCE OF PATIENTS WITH NO HISTOLOGICAL DIAGNOSIS

O. K. Kankam, B. Jayaraman, J. Kelly, R. D. Barker. Department of Respiratory Medicine, Kings College Hospital NHS Foundation Trust, London, UK

Background: There are relatively few accurate survival data for lung cancer patients, based on detailed clinical databases. Establishing key determinants of survival would help clinicians offer a prognosis and facilitate understanding of international comparisons of survival. Broad sub-categories of lung cancer have been defined but those without a histological diagnosis are not consistently included. We explored survival for lung cancer with a particular focus on those without a histological diagnosis.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Median survival, days (95% CI)</th>
<th>1 year survival</th>
<th>3 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell</td>
<td>146 (74–219)</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Non-small cell</td>
<td>200 (172–228)</td>
<td>32%</td>
<td>9%</td>
</tr>
<tr>
<td>Probable small cell*</td>
<td>164 (137–191)</td>
<td>29%</td>
<td>9%</td>
</tr>
<tr>
<td>Unconfirmed histology</td>
<td>69 (51–87)</td>
<td>22%</td>
<td>6%</td>
</tr>
<tr>
<td>All lung cancers</td>
<td>163 (137–1890)</td>
<td>29%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Includes those without histology.

Methods: All patients with lung cancer seen at a teaching hospital in south-east London between 1 July 1999 and 1 January 2007 were included in the study. Patients were separated into those with small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) and those with presumed lung cancer but without histological confirmation. For some analyses those without histological confirmation were combined with NSCLC to form a group of probable NSCLC. Performance status was recorded at diagnosis according to ECOG criteria. Survival for NSCLC was grouped into early (1a–2b), locally advanced (3a and 3b) and metastatic disease (n = 748, 101/175 = 58%) vs 261/573 (46%). Univariate survival analysis was undertaken with the Kaplan–Meier method using the log-rank test to establish statistically significant differences. Other univariate analyses used appropriate non-parametric analyses and tests of proportions. We used SPSS version 14.

Results: 944 patients were registered with lung cancer and a confirmed vital status could be established for 909 (96%). The median age was 71 years (65 years: 30%; 65–74 years: 34%; >75 years: 36%). There were 602 male patients (65%). There were 107 SCLC (12%), 604 NSCLC (66%) and 198 (22%) had no histological confirmation. There was no difference in survival between SCLC and NSCLC (p > 0.05). NSCLC and those with unconfirmed histology. There was no difference in survival between SCLC and probable NSCLC. Patients with lung cancer but without histological confirmation had worse performance status (n = 819, median 2 vs 1; p < 0.001), were older (n = 909, median 77 vs 69; p < 0.001) and had worse airway obstruction (n = 379, FEV_1 median 1.07 vs 1.61; p < 0.001). For those with NSCLC the failure to obtain a tissue diagnosis was associated with metastatic disease (n = 748, 101/175 (58%) vs 261/573 (46%)).

Conclusion: Patients without a histological diagnosis have significantly worse survival than other patients with lung cancer perhaps because they have other poor prognostic indicators. This should be taken into account when comparing lung cancer survival between diagnostic units and between countries.

Abstract 585 Multivariate analysis of risk factors for survival in 680 patients with non-small cell lung cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage: localised</td>
<td>1</td>
</tr>
<tr>
<td>Stage: locally advanced</td>
<td>2.0 (1.5 to 2.7)</td>
</tr>
<tr>
<td>Stage: advanced</td>
<td>3.2 (2.5 to 4.3)</td>
</tr>
<tr>
<td>Performance status 0</td>
<td>1</td>
</tr>
<tr>
<td>Performance status 1</td>
<td>1.1 (0.9 to 1.4)</td>
</tr>
<tr>
<td>Performance status 2</td>
<td>1.5 (1.1 to 1.9)</td>
</tr>
<tr>
<td>Performance status 3</td>
<td>2.1 (1.6 to 2.8)</td>
</tr>
<tr>
<td>Performance status 4</td>
<td>3.6</td>
</tr>
<tr>
<td>Potentially curative resection</td>
<td>0.6 (0.4 to 0.9)</td>
</tr>
<tr>
<td>Unconfirmed histology</td>
<td>1.3 (1.0 to 1.5)</td>
</tr>
</tbody>
</table>

1 January 2007. Univariate survival analysis was undertaken with the Kaplan–Meier method using the log-rank test to establish statistically significant differences. Multivariate analysis was done using forward stepwise regression and Cox’s proportional hazards model. We used SPSS version 14.

Results: 802 patients were included. There were 538 men (67%), 239 (30%) were aged <65 years, 271 (34%) 65–74 years, 292 (36%) ≥75. Of 748 with documented staging, 138 (18%) had localised disease, 248 (33%) locally advanced, and 362 (45%) advanced disease. Of 724 with a performance status 0 = 152 (22%), 1 = 226 (31%), 2 = 156 (22%), 3 = 118 (16%), 4 = 68 (9%), 80 (10%) underwent a surgical resection. 604 (25%) had confirmed histology. In univariate analysis survival was not related to sex or age. Survival was related to age group, histological confirmation, stage of disease, performance status and whether the patient underwent resection.

Conclusion: There was no evidence of an improvement in survival with time for patients with NSCLC. Age was not a predictor of survival once adjustment had been made for other relevant factors. There was evidence for a beneficial effect of surgical resection. Unconfirmed histology acted independently of resection, performance status and age and may be a surrogate for co-morbidity.


585 - NO IMPROVEMENT IN Survival for non-small cell lung cancer between 1999 and 2007: The Experience of an inner London teaching hospital

B. Jayaraman, O.K. Kankam, J. Kelly, R.D. Barker. Department of Respiratory Medicine, Kings College Hospital NHS Foundation Trust, London, UK

Background: It was hoped that with the introduction of multidisciplinary team working and greater access to potentially curative treatment, that survival for patients with lung cancer would improve. This view has been supported by colleagues from a nearby hospital who reported a significant improvement in survival in patients with histologically proven non-small cell lung cancer (NSCLC) over a 6 year period to 2004. We wanted to see whether there had been a similar improvement in survival for our patients with NSCLC.

Methods: The patients were all diagnosed with lung cancer at an inner city teaching hospital in south-east London between 1 July 1999 and 1 January 2007. Patients with histologically proven NSCLC and patients with a clinical diagnosis, but without tissue confirmation, were included, and for this study have been categorised as NSCLC. Performance status was recorded at diagnosis according to ECOG criteria. Survival for NSCLC was grouped into localised (1a–2b), locally advanced (3a and 3b) and metastatic disease (n = 748, 101/175 = 58%) vs 261/573 (46%). Patients with lung cancer but without histological confirmation had worse performance status (n = 819, median 2 vs 1; p < 0.001), were older (n = 909, median 77 vs 69; p < 0.001) and had worse airway obstruction (n = 379, FEV_1 median 1.07 vs 1.61; p < 0.001). For those with NSCLC the failure to obtain a tissue diagnosis was associated with metastatic disease (n = 748, 101/175 (58%) vs 261/573 (46%)).

Conclusion: Patients without a histological diagnosis have significantly worse survival than other patients with lung cancer perhaps because they have other poor prognostic indicators. This should be taken into account when comparing lung cancer survival between diagnostic units and between countries.

586 - Survival in 176 patients with inoperable non-small cell lung cancer treated initially with chemotherapy in a district general hospital

A. H. N. Gerratt 1, S. Ahmad 1, K. Graham 1, S. P. Patel 2, J. R. Webb 1, T. C. Stokes 1. 1Queen Elizabeth Hospital NHS Trust; 2Health & Social Care, University of Greenwich, London, UK

In advanced non-small cell lung cancer (NSCLC) platinum based chemotherapy with second generation drugs improves median survival (MS) to 8 months and 29% and 10% at 1 and 2 years. Platinum with a third generation drug can improve survival further (BMJ 1995;311:899) (Spiro et al. Thorax 2004;59:828 Big Lung Trial; N Engl J Med 2003;346:92 ECOG study). NICE now recommends chemotherapy with platinum and a third generation drug for inoperable NSCLC as the first treatment modality.

Methods: We audited survival of 176/461 consecutive patients referred for at least 3 courses of platinum and either gemcitabine or vinorelbine from July 2001 to December 2005. Minimal follow up 17 months. Chemotherapy was given on site. Radical radiotherapy for stage IIIA, palliative radiotherapy and second line drugs were given as felt appropriate.

Results: 64% were male. 30 (17%) were <55 years; 66 (37.5%) age 55–65 years; 63 (35.8%) aged 66–75 and 16 (9.1%) ≥75 years. 5 (2.8%) were stage II; 46 (26%) stage IIIA; 68 (38%) stage IIIB and 55 (30.8%) stage IV. 68 (38%) had 0–2 courses; 63 (36%) 3 courses and 44 (25%) had 4 or more.

Survival: For the 157 (89%) patients who died, median survival was 283 days. The 18 survivors had 925 days. Median overall survival (OS) was 334 days (95% CI 258 to 410). One year OS was 45.3% (95% CI 38.9 to 53.7). Two year OS was 18.9% (95% CI 13.1 to 24.7). MS in stage IIIA was 465 days (95% CI 352 to 578), stage IIIB was 307 days (95% CI 100 to 514) and MS in stage IV was 239 days (95% CI 155 to 323).
Survival for stage IV vs (IIIA and IIIB) is significant (p < 0.0005) but not between IIIA and IIIB (p = 0.658) (Cox's proportional hazard). Survival was optimal with three courses of chemotherapy. Older patients tended to survive longer but not significantly so.

Conclusion: Our results indicate that chemotherapy can be successfully and effectively given to eligible patients with NSCLC. The survival figures are comparable to published data. In the district general hospital setting there is the added benefit to patients of having treatment close to home.

Molecular mechanisms of respiratory disease

S87 THE ROLE OF ACTIVATOR PROTEIN-1 (AP-1) FAMILY MEMBERS IN THE INDUCTION OF INTERLEUKIN (IL)-8 BY CYCLIC MECHANICAL STRAIN IN LUNG EPITHELIAL CELLS

L. Pinhu, W. Yao, M. Griffiths. NHLI, Imperial College, London, UK

Rationale: Over-distension of the lung by mechanical ventilation contributes to the mortality of patients with acute lung injury. Mechanical forces enhance the release of mediators that exacerbate lung damage (ventilator-associated lung injury: VALI) and contribute to systemic inflammation and death. The neutrophil chemokine IL-8 (CXCL-8) has been implicated in the pathogenesis of ALI clinically and in animal models. Cyclic mechanical strain (CMS) applied to A549 cells (a human alveolar epithelial cell line) and primary cultures of human alveolar type 2 cells, models of alveolar over-distension, was associated with IL-8 production that was dependent on extracellular signal-related kinase (ERK1/2) activity. Furthermore, DNA binding of the AP-1 transcription factor cFos was prevented by inhibition of the ERK1/2 pathway by U0126. The induction of cFos and other immediate early response genes to mechanical stimuli is well established. IL-1β-induced IL-8 is mediated in part by cFos and inhibited by Fra-1 through displacement of cFos from the IL-8 promoter and recruitment of HDAC1. The following experiments were performed to determine the role of cFos and other AP-1 family members (Fos-related antigen-1 [Fra-1], cJun, JunB, JunD) in the induction of IL-8 by CMS.

Methods and results: The application of CMS to A549 cells for 30 minutes induced mRNA for cFos, Fra-1, cJun, and JunB, but not JunD. The induction of cFos and Fra-1 mRNA, but not cJun was abolished by the MEK1/2 inhibitor U0126. Chromatin immunoprecipitation (ChIP) analysis of the AP-1 site of the IL-8 promoter using antibodies against cFos after CMS in the presence and absence of U0126 (10 μM), U0124 (inactive: 10 μM) and AS602868 (IKK-2 inhibitor: 3 μM) confirmed ERK1/2 dependent binding of cFos (see fig 1). Finally, siRNA-mediated knockdown of cFos specifically abolished the effect of CMS on IL-8 induction in A549 cells confirming the absolute requirement for this transcription factor (see fig 2).

Conclusions: Certain AP-1 family members are rapidly induced by CMS in A549 cells and play a crucial role in regulating the induction of IL-8 by the ERK1/2 MAPK pathway.


S88 LUNG-MARGINATED MONOCYTES PLAY A CENTRAL ROLE IN A TWO-HIT LPS-ZYMOSAN MODEL OF ACUTE LUNG INJURY IN MICE

K. P. O’Dea, M. R. Wilson, J. O. Dokpessi, M. Takata. Imperial College London, UK

Introduction: Although margination and activation of neutrophils within the lungs play an important role in the development of acute lung injury (ALI), the contribution of monocytes is unknown. During subclinical endotoxonemia in mice, large numbers of the inflammatory Gr-1high monocye subset marginate to the pulmonary microcirculation and respond vigorously to secondary septic challenge, expressing high levels of membrane tumour necrosis factor-alpha. Here we assessed recruitment of Gr-1high monocytes from the bone marrow reservoir to the pulmonary...
microcirculation during subclinical endotoxaemia and their contribution to pulmonary vascular leak in a 2-hit LPS-zymosan model of ALI.

Methods: Bone marrow mobilisation of monocytes and margination to the lungs was assessed in C57BL6 mice after subclinical, low-dose i.v. LPS challenge, using flow cytometry and in vivo BrdU labelling of dividing bone marrow monocytes. The contribution of LPS ‘pre-marginated’ monocytes to i.v. zymosan-induced changes in pulmonary vascular permeability was determined by measuring extravascular leak of labelled albumin and its modulation by clodronate-liposome mediated depletion of monocytes.

Results: Early mobilisation of bone marrow Gr-1<sup>high</sup> monocytes and their margination to the lungs during subclinical endotoxaemia was evident from a reduction of their numbers in the bone marrow (3.0±0.4×10<sup>6</sup> to 1.8±0.2×10<sup>6</sup>/femur+tibia, p<0.01) and an increase in BrdU-labelled cells in the lungs at 2 h after low-dose LPS challenge. LPS priming-dependent increases in vascular permeability after zymosan challenge were attenuated by depletion of monocytes (see fig). However, this protective effect was reversed at 48 h post-clodronate treatment, when LPS-primed monocytes, especially those in the lungs at 2 h after low-dose LPS challenge, could play a crucial role in the development of sepsis-related ALI.

Conclusion: These results suggest that recruitment of bone marrow Gr-1<sup>high</sup> monocytes to the pulmonary microcirculation during subclinical endotoxaemia transforms the lungs into a ‘primed’ state. Upon further systemic septic challenge, these pre-marginated monocytes could play a crucial role in the development of sepsis-related ALI.

This study was supported by grants from Biotechnology and Biological Sciences Research Council and Medical Research Council UK.

endotoxins’ structure to biological activity may offer new therapeutic avenues.

Methods: Strains from our transplant programme were screened. We investigated and compared the structures of LPS and lipid A core regions from clinically identical Burkholderia multivorans strains isolated pre- and post-lung transplantation through compositional analysis, mass spectrometry and 2D NMR spectroscopy. Prior pulsed field gel electrophoresis data confirmed clonal identity of the strains. The pro-inflammatory activity of extracted LPS was tested as a stimulant of human myelomonocytic U937 cell cytokine (TNF) induction.

Results: In one clonal pair there were LPS migration differences on SDS gels and significant lowering in TNF induction capacity of the post transplant strain. The predominant structural differences in these strains were found in the lipid A portion. The core oligosaccharide sequence of B multivorans species investigated was quite different to that of B cenocepacia. The lipid A from B multivorans pre-transplantation had significant structural motifs associated with activity against airway immunity including the lipid A acylation status and amino-arabinooside residues conferring resistance against defensins. Interestingly the post-transplant strain demonstrated a decreased lipid A acylation status consistent with the reduction in TNF cytokine induction capacity.

Conclusion: Such structural variations may contribute to the bacterial survival and persistence of infections despite the loss of a CF milieu following lung transplantation. This phenomenon was not noted for B vietnamiensis or B cenocepacia strains tested raising the question of differential responses between genomovars.

Abstract S92

**K5, A KAPOSI SARCOMA HERPESVIRUS GENE PRODUCT, TARGETS BONE MORPHOGENETIC PROTEIN RECEPTOR II FOR UBQUITINATION AND ENDOSONAL DEGRADATION**

H. J. Durrington1, P. Upton1, N. W. Marrell1, P. Lehner2. 1Department of Medicine, Addenbrooke’s Hospital, Cambridge University; 2Cambridge Institute of Medical Research, UK.

Introduction: 70% of patients with familial pulmonary arterial hypertension (PAH) have a mutation in the gene encoding bone morphogenetic protein receptor-II (BMPR-II). Penetration of BMPR-II mutations varies from 15–50%, suggesting additional genetic/environmental events are required to cause disease. Kaposi sarcoma herpesvirus (KSHV) has been identified as a potential aetiological agent in PAH pathogenesis (Cool et al. N Engl J Med 2003). KSHV expresses a protein, K5, which acts as an E3 ubiquitin ligase, targeting cell surface receptors (MHC class I) for degradation, allowing the virus to establish latent infection. We previously demonstrated that HeLa cells stably transfected with K5 possess reduced cell surface 125I-BMP4 binding sites and reduced activation of BMP stimulated Smad1/5 signalling compared with control cells. We hypothesise that K5 targets BMPR-II at the cell surface, reducing protein stability, by causing its degradation via ubiquitination.

Methods: Expression of BMPR-II protein was determined by Western blotting in: (1) HeLa cells stably expressing K5 compared with wild type HeLa cells; and (2) in HeLa cells transiently transfected with K5 or mutant K5m, lacking ubiquitin ligase activity. We determined the subcellular localisation of BMPR-II in the stable cell lines by immunofluorescence and confocal microscopy. Concanomycin A, an inhibitor of endosomal degradation, was used to treat stable K5 HeLa cells and control cells, prior to blotting for BMPR-II.

Results: BMPR-II protein was markedly reduced in stable K5 HeLa cells compared to control cells. This effect was seen after transient transfection of K5 into HeLa cells (at 48 hours), but not after transfection with K5m.

Immunofluorescence microscopy for BMPR-II demonstrated a reduction in BMPR-II protein expression in K5 HeLa compared to wild type. Treatment of K5 HeLa cells with Concanomycin A, rescued the reduction in BMPR-II (see fig).

Conclusion: These experiments demonstrate that BMPR-II is a cellular target of KSHV K5 and suggest that K5 degrades BMPR-II by ubiquitination via an endosomal pathway.

**Paediatric asthma: bedside and bench**

**S93 CHARACTERISATION OF CHILDREN WITH DIFFICULT TO TREAT ASTHMA**

L. Fleming1, M. Bracken2, P. Hall2, N. Wilson2, A. Bush1. 1Imperial College; 2Royal Brompton Hospital, London, UK

Background: Difficult asthma (DA) is that which is poorly controlled despite maximal doses of conventional therapy. Our current DA protocol provides a systematic approach to assessment and subsequent management.

Aim: To characterise children referred for the DA protocol and evaluate underlying contributing factors following initial assessment.

Methods: All children referred to our DA protocol from March 2005–June 2007 are included. Children were reviewed during an outpatient hospital visit and a nurse led home visit. At these visits an assessment was made of atopy (skin prick tests, SPTs), inflammation (exhaled nitric oxide (FeNO50)), spirometry pre- and post-bronchodilator (BD), psychosocial background, adherence and clinical history. Following discussion at an interdisciplinary meeting, underlying contributing factors were identified and appropriate interventions made. Only those whose control did not improve following initial intervention went on to undergo further evaluation including bronchoscopy.

Results: 63 children (26 boys), median age 12.5 years (range 5.3–17 years) were assessed. 12 (19%) had a previous life threatening episode of asthma requiring ventilation. 18 were prescribed maintenance oral steroids. The median dose of inhaled corticosteroids was 960 µg/day, fluticasone equivalent (range 240–2000 µg). 86% were atopic (>1 positive SPT for common allergens). 23 had a positive SPT for house dust mite, 24 had pets of whom 46% had a positive SPT to their own pet. 31 children were referred to a psychologist. 27 children went on to have further investigations including bronchoscopy.

Conclusion: Children with DA are a heterogeneous group both in terms of contributing factors and underlying pathology. Careful evaluation will reveal potentially remedial causes for poorly controlled symptoms avoiding the necessity for further, more invasive investigations.

<table>
<thead>
<tr>
<th>Table 1: results of investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
</tr>
<tr>
<td>FEV1 pre BD (L)</td>
</tr>
<tr>
<td>FEV1 pre BD (%)</td>
</tr>
<tr>
<td>FEV1 post BD (L)</td>
</tr>
<tr>
<td>FEV1 post BD (%)</td>
</tr>
<tr>
<td>Reversibility (%)</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: contributing factors (NB: more than one could be assigned per child)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing allergen presence</td>
</tr>
<tr>
<td>Psychosocial issues</td>
</tr>
<tr>
<td>Poor adherence</td>
</tr>
<tr>
<td>Unsuitable inhaler</td>
</tr>
<tr>
<td>Poor inhaler technique</td>
</tr>
<tr>
<td>Passive smoking</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
</tr>
</tbody>
</table>

Abstract S93

A38 www.thoraxjnl.com
AIRWAY EPITHELIAL CELL MEDIATOR RELEASE IS ASSOCIATED WITH WHEEZING BUT NOT ATOPY IN CHILDREN

C. M. McDougall, M. G. Blaylock, P. J. Helms, G. M. Walsh. University of Aberdeen, UK

Introduction: Although airway epithelial cells (AEC) are key contributors to immune function in the lungs and to the inflammatory response seen in asthma in adults, little is known about their role in childhood wheezing. Having established that nasal AEC cytokine release correlates with that of bronchial AEC, we aimed to study AEC responses in different childhood wheezing phenotypes.

Methods: After ethical approval and informed consent, nasal AEC cultures were established from children (0.6–14.9 years) undergoing elective surgical procedures under general anaesthetic, categorised as atopic asthmatics (n = 12), virus-induced wheezers (n = 8) or healthy controls (n = 32) using questionnaire and serum IgE levels. All subjects were free of current respiratory symptoms. Mediator release by resting and stimulated (IL-1β + TNFα) at 10 ng/ml for 24 hours) AEC monolayers at passage 2 was determined by cytometric bead array assay (IL-8, IL-6, VEGF, G-CSF, MCP-1, RANTES) or ELISA (MMP-9, TIMP-1) of culture supernatants and corrected for cellular protein content.

Results: Successful AEC cultures were established from 81% nasal brushings and maintained to passage 2 for 41 (79%) subjects. AEC from children with a history of wheeze produced significantly less IL-8, IL-6, MCP-1 and G-CSF than AEC from healthy controls (see table). When the wheezing phenotypes were considered separately, AEC from atopic asthmatic children released significantly less IL-8, IL-6, MCP-1 and G-CSF than AEC from controls but there were no significant differences between AEC mediator release from children with virus-induced wheeze and either atopic asthmatics or controls. Similar results were found for cytokine-stimulated AEC. In non-wheezy subjects, there were no differences in AEC mediator release between atopic and non-atopic individuals. There were no differences between the study groups in the percentage increments in mediator release in response to stimulation. In multivariate analysis, taking into account age, gender, passive smoke exposure, use of inhaled corticosteroids, total serum IgE and specific IgE responses to inhaled allergens as possible confounders, wheeze was the only significant predictor of AEC mediator release.

Conclusion: An in vitro model of respiratory epithelium, suitable for functional studies, can be established from nasal brushings from children. AEC are a potent source of inflammatory mediators and are capable of responding to proinflammatory stimuli. There are intrinsic differences in AEC from children with a history of wheeze compared to healthy controls which appear to be independent of atopic status. This may reflect a defect in cytokine production by asthmatic AEC in vivo or an altered state of differentiation of cultured asthmatic AEC compared to normal AEC.

2. Thorax, 2005;60(Suppl II), B5–6.

Abstract S94

<table>
<thead>
<tr>
<th>Mediator</th>
<th>No wheeze</th>
<th>Wheeze</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>55.0 (73.3)</td>
<td>17.2 (40.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>IL-6</td>
<td>22.2 (54.4)</td>
<td>9.3 (15.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.17 (0.38)</td>
<td>0.05 (0.10)</td>
<td>0.002</td>
</tr>
<tr>
<td>G-CSF</td>
<td>6.7 (15.2)</td>
<td>1.3 (4.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>RANTES</td>
<td>0.02 (0.03)</td>
<td>0.02 (0.03)</td>
<td>0.43</td>
</tr>
<tr>
<td>VEGF</td>
<td>21.6 (22.2)</td>
<td>16.8 (5.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>MMP-9</td>
<td>29.2 (57.7)</td>
<td>42.7 (41.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>28.1 (25.9)</td>
<td>30.4 (61.4)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*Median (IQR); †Mann-Whitney test.

DO LUNG FUNCTION TESTS AT 4–6 YEARS OF AGE IN SEVERE PRESCHOOL WHEEZERS CORRELATE WITH ENDOBRONCHIAL BIOPSY IN EARLY PRESCHOOL YEARS?

S. Sonnappa1, C. Bastardo1, S. Saglani3, S. Mckenzie2, A. Bush3, P. Aurora1.
1Great Ormond Street Hospital for Children and Institute of Child Health; 2Royal London Hospital; 3Royal Brompton Hospital and Imperial College, London, UK

Background: Non-reversible conductive airways (Scond) heterogeneity has been reported in adults with asthma.1 The aim of this study was to measure specific airways resistance (sRaw) and measures of ventilation inhomogeneity, with bronchodilator reversibility, at 4–6 years of age in children who had been investigated for severe wheeze with endobronchial biopsy (EBB) at median age 2.5 years (range 3 months–5 years).2

Methods: Children between 4–6 years with a history of severe recurrent wheeze before 3 years of age, previously investigated with EBB underwent clinical and lung function assessments before and after bronchodilator. sRaw was measured by whole body plethysmography, and lung clearance index (LCI), functional residual capacity; Scond, and acinar ventilation inhomogeneity (Sacin) measured by multiple breath washout. Pre-bronchodilator measurements were compared to healthy controls and correlated with reticular basement membrane thickening (RBM), subepithelial eosiinophilic inflammation and total inflammation as previously measured on EBB. Subgroup analysis was performed by current atopic status.

Results: Children with a history of recurrent wheeze (n = 25, median age 5.1 (range 4.9–6.9) years; atopic (n = 11); persistent wheeze (n = 16) were compared to age-matched healthy controls (n = 31). Scond was significantly higher in both groups of wheezers compared to controls (0.059 vs 0.022, median diff 0.037 (95% CI 0.022 to 0.052) p = 0.0005). There was no significant difference in the other pre-bronchodilator lung function parameters. There was no correlation between lung function and previous exposure, use of inhaled corticosteroids, total serum IgE and specific IgE associated with persistent wheeze in late preschool years.

Conclusion: Conductive airways heterogeneity, only partially responsive to bronchodilator, is already present in severe preschool wheezers irrespective of resolution of symptoms, suggesting continued structural changes in the airways. RBM thickening in early preschool years is associated with persistent wheeze in late preschool years.


EVIDENCE OF PERSISTENT SMALL AIRWAYS DISEASE MEASURED BY LUNG CLEARANCE INDEX IN WELL-CONTROLLED ASTHMATIC CHILDREN WITH NORMAL FEV1

K. A. Macdonald1, A. Horosley2, J. A. Innes2, S. Cunningham1. 1Royal Hospital for Sick Children; 2Western General Hospital, Edinburgh, UK

Introduction: In asthmatic patients, conventional spirometry (FEV1, PEFR) is known to be relatively insensitive to small airways function. Lung clearance index (LCI), a simple measure of non-uniformity of ventilation, can be calculated from multiple breath inert gas washouts and is thought to be insensitive to small airways disease.

Methods: This randomised double-blind study involved asthmatic children completing 3 multiple breath washouts from SF6 before and after inhaled salbutamol (200 μg) or placebo. Standard spirometry and exhaled nitric oxide (FeNO) were performed at the same time. At the second visit subjects repeated the process with the other intervention. Healthy volunteer controls completed 3 washouts at one visit only. Well-controlled asthmatic children on regular preventer therapy (n = 31; mean age 10.6, range 5–15) were compared with healthy controls (n = 29, mean age 11.2, range 5–16).

Results: The measurement of LCI was well tolerated by all children.

Agreement was good between 3 washouts. Mean (SD) LCI at first baselinevisit was significantly higher in asthmatic children, 6.85 (0.92) vs controls, 6.38 (0.51), p = 0.02. Mean (SD) FEV1 % predicted was not significantly different between asthmatics and controls (85.6 (17.1) vs 90.8 (11.75), p = 0.17). There was no correlation between baseline LCI and FeNO or FEV1, in either asthmatics or controls (p = 0.05). After inhaled salbutamol there was no significant change in FEV1 (p = 0.31) or LCI (p = 0.46). Mean LCI post-bronchodilator was 6.81, remaining significantly higher than healthy controls (p = 0.01).

Conclusion: LCI is a simple, reproducible measure of ventilation efficiency that is easy to perform in children using the modified Innocor device. LCI was significantly higher in well controlled asthmatics compared with controls. Post-bronchodilator LCI was still higher than in baseline controls indicating that residual airways abnormality, not responsive to inhaled β2
Aim: responsiveness. as a surrogate measure of underlying airway inflammation and steroid fall in response to corticosteroids in children with asthma and can be used investigations (stages 2 and 3). Children undergoing bronchoscopy had have not been identified and symptoms improved go on to have further investigations.

Methods: FeNO50, can be detected by LCI.

Daily FeNO50 measurements in those with a good response to triamcinolone. Daily FeNO50 measurements in those with a poor/no response to triamcinolone.

agonist and not detected by routine asthma monitoring methods (FEV1, FeNO), can be detected by LCI.

L. Fleming, N. Regamey, C. Bossley, N. Wilson, A. Bush. Imperial College, Royal Brompton Hospital, London, UK

Background: Levels of exhaled nitric oxide (FeNO50) have been shown to fall in response to corticosteroids in children with asthma and can be used as a surrogate measure of underlying airway inflammation and steroid responsiveness.

Aim: To assess whether daily recordings of FeNO50 measured from the time of triamcinolone administration can predict clinical responsiveness.

Methods: Our difficult asthma protocol involves a 3 stage assessment.

Following initial assessment (stage 1) only those for whom remedial factors have not been identified and symptoms improved go on to have further investigations (stages 2 and 3). Children undergoing bronchoscopy had inflammation measured (FeNO50, sputum eosinophil counts), spirometry (pre- and post-bronchodilator (BD)) and clinical evaluation (asthma control test (ACT)) on the day of bronchoscopy (stage 2) and 1 month later (stage 3). They were issued with NIOX MINOs, a hand held device for measuring FeNO50, and were asked to record measurements daily.

Results: 10 children (3 boys), median age 14.4 years, range 8.7–16.6 years, were issued with MINOs. At stage 3, 5 reported a good clinical response to i.m. triamcinolone (subjective improvement in symptoms, no courses of oral steroids); 5 reported a partial response (improvement in symptoms for <2 weeks) or poor response (no improvement in symptoms and/or requiring oral steroids prior to review).

Conclusion: Children with difficult asthma who have an improvement in their clinical symptoms following systemic steroids appear to have an immediate fall in FeNO50 which is then sustained over a period of at least 2 weeks. This is also reflected in a fall in sputum eosinophils. In those with a poor or no response, although the FeNO50 appears to drop initially it soon rises again, and there can be day to day variability. If measurements of FeNO50 are used as a marker of inflammation and hence response to steroids, the timing of the measurements needs to be taken into account and greater information may be gained from more frequent measurements.

### Lung cancer staging and surgery

**S98 IMPACT OF FDG-PET SCAN ON THE PREVALENCE OF BENIGN LESIONS AT THORACOTOMY**

K. Mohan, J. McShane, R. Page, M. J. Ledson, M. J. Walshaw. The Cardiothoracic Centre-Liverpool, UK

Introduction: FDG-PET scan is increasingly used to diagnose malignant pulmonary lesions, and a ‘positive’ scan (standardised uptake value, SUV >2.5) has a high specificity for lung cancer. However, a number of these scans may be falsely positive, such that patients with benign lesions may be subjected to unnecessary surgery.

Method: To test the impact of FDG-PET on the (false) operative rate for benign lesions, we compared their prevalence at surgery for two consecutive two-year groups: patients undergoing surgery in 2003–5 (before FDG-PET availability) with those after its introduction (2005–7). We reviewed clinical, radiological and histological data on patients with resected benign lesions where the scan had been misleading.

Results: 1233 consecutive patients underwent focal pulmonary lesion resection: between 2003–5, 44/626 were benign (7%). 301 of 607 patients (50%) resected during 2005–7 underwent FDG-PET: in 18 (6%) the histology was benign despite a “positive” scan. There was no difference in resection rates for benign lesions pre and post commencement of the use of FDG-PET (x2= 0.358, p=0.5). The latter group of patients had a mean age 61 years (49–74), 17 (94%) were smokers (mean 42 pack-years), 6 (33%) had asbestos exposure and 11 were male. In addition to bronchoscopy, 4 had undergone a non-diagnostic CT guided biopsy and 2 a negative rigid bronchoscopy. At CT scan, the mean size of the lesion was 2.6 cm (1–5), 89% had a solid consistency and 55% had irregular margins. Mean FDG-PET SUV was 4.8 (2.6–12.7). However, following thoracotomy (9 lobectomies, 8 wedge resections and 1 open & close (biopsy)); the final pathological diagnoses were tuberculosis (3), COP (2), fibrosis (2), aspergilloma (2), rheumatoid nodule (2) hamartoma (1), chronic inflammation (1), bulla (1), infant (1), abscess (1) and ILD (1).

Conclusions: Thus, we have shown that the use of a new advanced imaging technique (FDG-PET) does not prevent unnecessary thoracotomies in patients who ultimately have benign lesions; the rate of these did not change following its introduction. This study illustrates the continuing difficulty in managing patients with suspected chest malignancy, where many patients have existing comorbidities which complicate the diagnostic process.

<table>
<thead>
<tr>
<th>Abstract S97</th>
<th>Stage 2: Median (range)</th>
<th>Stage 3: Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Results of investigations</td>
<td>Good response</td>
</tr>
<tr>
<td>FeNO50 (ppb)</td>
<td>56 (29–132)</td>
<td>87 (45–117)</td>
</tr>
<tr>
<td>FEV1 pre BD (%)</td>
<td>60 (46–90)</td>
<td>66 (36–109)</td>
</tr>
<tr>
<td>Sputum eos (%)</td>
<td>22.6 (3.2–41.6)</td>
<td>21.7 (5.2–67)</td>
</tr>
</tbody>
</table>
Background: The availability of positron emission tomography (CT-PET) in our practice has altered the strategy for the investigation and management of the solitary pulmonary nodule (SPN). There is still debate whether the additional information from CT-PET alters surgical management if an aggressive excisional biopsy strategy is already employed.

Objectives: We aimed to evaluate if basing the decision to operate on a positive preoperative CT-PET increased the yield of malignant SPN at excisional biopsy.

Methods: Patients were offered CT-PET followed by video assisted thoracoscopic (VATS) excision with intraoperative frozen section if the CT-PET was positive. Percutaneous biopsy was not performed. Over a 30-month period, 24 patients underwent excisional VATS biopsy of a SPN following a positive CT-PET scan (PET group). Outcome was compared with 24 case-matched patients who had undergone VATS excision of SPN prior to the introduction of CT-PET (NON-PET group) based on CT scan alone. Cases were matched according to age, sex and lobar position of SPN. Histological diagnosis and immediate outcome of the two groups following surgery was compared.

Results: Each group comprised 14 female and 10 males, mean age 68 (range 49–84) years. In the PET group, 87% (21/24) of resected nodules were malignant (52% adenocarcinoma, 38% squamous) which was significantly higher than the 58% (14/24) in the NON-PET group, (p = 0.02). In the NON-PET group the 10 benign SPN included: granuloma, hamartoma and an aspergilloma. In the PET group the benign SPN were all granulomas. In both groups 58% underwent VATS resection and 42% open lobectomy. There were no false-positive frozen section results and no resection was performed for benign disease. Pathological stage distribution for PET vs NON-PET was: stage I (38% vs 63%), stage II (33% vs 0%), and stage III (5% vs 37%). Five SPN (24%) in the PET group were found to be metastatic. There was no operative mortality in either group.

Conclusions: Our early results support the routine use of CT-PET in the preoperative management of SPNs and question the additional benefit of obtaining preoperative histological confirmation.

Background: Chemo-radiation is considered the gold standard for the management of limited disease small cell lung cancer (SCLC) but cumulative results from 25 North American randomised trials report median survival of 17 months and data from the Surveillance, Epidemiological and End results programme report an overall five-year survival of 10%. In general, surgery as a treatment option has been abandoned because of poor overall survival, but many small series report good results (in selected patients). Currently only patients with very limited disease are offered surgery as an option. We sought to determine survival across a spectrum of T and N stage to explore the impact of complete surgical resection for SCLC.

Methods: A retrospective review was undertaken of patients who underwent surgery between 1980 and 2006. Patients were staged according to published series. We estimated the number of mediastinoscopies and PET scans performed, and reduce time from referral to treatment. Leeds Teaching Hospitals (LTH) does not currently offer an EBUS-TBNA service. By reviewing mediastinoscopies performed as staging procedures for lung cancer during 2006, we sought to determine the implications of establishing a service from both cost and time-to-treatment perspectives.

Results: Of 47 staging mediastinoscopies performed, 27 showed malignant disease. Sensitivity of EBUS-TBNA for malignancy was 92.3%. Fixed equipment costs of EBUS-TBNA were determined. NHS tariff and unit-based costs were calculated for mediastinoscopy, PET and EBUS-TBNA. The cost implications for the local NHS and for LTH trust were estimated. Time between initial bronchoscopy and mediastinoscopy was determined for patients referred from within the trust.

Conclusions: EBUS-TBNA offers significant time reductions between referral and treatment for lung cancer patients. It is cost effective for the NHS as a whole, but the current tariff structure acts as a disincentive for trusts to establish a service. This analysis would support the introduction of an additional tariff for EBUS-TBNA to encourage greater uptake of this technique.


Techniques and outcomes in bronchoscopy and lung biopsy

M. W. Khalil, A. Boggia, S. A. Solly, D. A. Waller. Glenfield Hospital, Leicester, UK

Objective: To review the impact on clinical practice of our five-year experience with therapeutic laser bronchoscopy.

Methods: Between 2002 and 2007 a total of 120 bronchoscopic laser procedures were carried out in our centre. During the experience, the number of laser procedures done by our unit has been steadily increasing to a current rate of 28 procedures in the present year (2007). The laser diode was used in all of our cases in a standard operating theatre with the patient under general anaesthesia in conjunction with interventional radiologists where necessary. The patient population, indications for treatment and immediate results were retrospectively analysed.

Results: A total of 120 procedures were performed on 84 patients (62% male), mean age 65.9 (30–86 years). The mean energy dosage was 4264 ± 1266 J. Ablation was performed in the main bronchus in 58 procedures, the trachea in 31, combined trachea and right main bronchus in 4, and lobar bronchi in 27. The main indication for treatment was primary lung cancer with 51 procedures including: 29 for inoperable tumours to achieve symptom control; 15 for recurrence of tumour after previous lung resections and 7 in patients thought to be inoperable who subsequently went to resection. Benign inflammatory stenoses formed the next most common indication with 43 procedures, including 12 following previous lung resections and 8 following tracheostomy. A single laser bronchoscopy was successful in treating the presenting problem in 73% of cases; 36 repeat procedures were carried out on 23 patients. Benign stenosis was also the most common indication for repeat laser ablation (23 procedures). Benign tumours, including carcinoids, were removed in 12 procedures. Eight procedures included concomitant insertion of airway stents. Complications related directly to the procedure were rare: one patient bled requiring re-bronchoscopy and resuscitation, and one developed pneumothorax which resolved. The average hospital stay was three days. There were no hospital deaths.

Conclusion: Therapeutic bronchoscopy is an invaluable and integral part of modern respiratory practice. The use of the diode laser under general anaesthetic has allowed for safe treatment of virtually all indications.

Physician and Patient Perception of Tolerance to Fibreoptic Bronchoscopy

M. Thirumaran, S. Faruqi, S. P. L. Meghjee, P. Blaxill, S. E. Williams. Pinderfields General Hospital, Mid Yorkshire Hospitals NHS Trust, UK

Introduction: Fibreoptic bronchoscopy (FOB) is a commonly performed invasive diagnostic procedure. Despite the direct relevance to the patients, there is paucity of data regarding patients’ experience of FOB and the factors affecting the same. The patients’ experience of health care is recognised as a valid and significant outcome of care. The objective of this study is to assess the patient’s perception of comfort during FOB and compare that with the physician’s perception of patients’ tolerance to the procedure. Other factors which could influence tolerance were also assessed.

Methods: A structured questionnaire was used to collect data from the patients undergoing FOB and the physicians performing it. This questionnaire included tolerance score of 1–5, 5 being very comfortable. Data regarding other factors which may have a bearing on the tolerance of the procedure like dose of Midazolam, performance status, route of intubation were included on the questionnaire. Informed consent was obtained. The physician performing the FOB filled in the questionnaire immediately after the procedure.

Results: Sixty-three patients agreed to participate in the survey and 37 returned questionnaire (males, 25). The response rate was 59%. The general tolerance to the procedure was very good with the mean patient’s tolerance score being 4.2. This was not significantly different from physicians perception of patients tolerance, 4.3 being their mean score. 75% of patients who received more than 3 mg of Midazolam gave the best response and 69% of patients who received 3 mg or less only 27% rated the procedure very comfortable. Patients with better performance status found the procedure more comfortable. Age, route of intubation and person

Abstract S102

<table>
<thead>
<tr>
<th>Sample site</th>
<th>LH</th>
<th>RH</th>
<th>RP</th>
<th>SC</th>
<th>M</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>75%</td>
<td>30%</td>
<td>50%</td>
<td>80%</td>
<td>81%</td>
<td>66.6%</td>
</tr>
<tr>
<td>(6/8)</td>
<td>(3/8)</td>
<td>(1/2)</td>
<td>(12/15)</td>
<td>(9/11)</td>
<td>(2/3)</td>
<td></td>
</tr>
</tbody>
</table>

Thorax first published as on 19 November 2007. Downloaded from http://thorax.bmj.com on July 14, 2021 by guest. Protected by copyright.

www.thoraxjnl.com
performing the procedure (Specialist Registrar or Consultant) did not influence patients' comfort. Surprisingly 38% of the patients remembered most of the details of the procedure. The mean duration before the patients felt their normal self was 8 h. All the patients said if necessary they will be happy to have the procedure done again.

**Conclusion:** Contrary to general perception, FOB is a reasonably well-tolerated procedure. The perception of comfort by the patient and the physician performing the procedure are similar. Higher doses of Midazolam and better performance status had a positive correlation with patient's tolerance of the procedure.

**S106 INTRODUCING LIQUID BASED CYTOLOGY INTO ROUTINE BRONchoscopy FOR PATIENTS WITH SUSPECTED LUNG CANCER**


**Introduction:** The introduction of liquid based cytology (LBC, ThinPrep) in 1996 increased the sensitivity of cervical smear evaluation. This increase is related to a number of factors: the preservation of cellular architecture, smaller requirement of sample size immunocytochemical staining, automatic fixation and machine analysis of the sample, and reduced compromise from excessive blood. LBC has been successfully applied to other cancers such as colorectal, breast and renal. Only case reports and small studies allude to the usefulness of LBC in bronchoscopic samples.

**Methods:** In 2006 LBC was introduced into our Trust for non-gynaecological endobronchial biopsy. We undertook to apply LBC within bronchoscopy for cytological samples taken from patients with suspected lung cancer. Using LBC, cytology brushings and TBNA samples were placed directly into ThinPrep solution as opposed to staff making smears of each directly onto slides for fixing. The cytology brush was cut off and left in the vial. If a BAL was heavily blood stained an aliquot of the lavage was placed into the LBC vial. We audited the first year's results and compared them to historical data from 2003–4 when brush and TBNA samples were smeared by hand onto slides by nursing staff and fixed. All lists during both reporting periods were supervised by the same consultants and all patients underwent a CT before bronchoscopy.

**Results:** The introduction of LBC into the routine use of bronchial brushings and TBNA samples has resulted in an improved diagnostic rate by these modalities. There has been an improvement in bronchoscopist and nurse assistants' time and safety. It was time consuming to make slides and there were issues about poor slide preparation and drying artefacts. Placing the TBNA needle directly into LBC rather than over multiple slides reduces the chance of possible needle stick injury and inhalational exposure. The small additional cost of LBC (£10 per sample) is offset by the increased diagnostic rate and subsequent reduction in additional invasive procedures.

**Conclusions:** We have shown that LBC can enhance the endobronchial diagnosis of lung cancer when applied to bronchial brushings and TBNA samples. This change in practice is safe, time and cost efficient.

<table>
<thead>
<tr>
<th>Abstract S106</th>
<th>Comparison of positive cytological samples using conventional cytology (CC) vs liquid based cytology (LBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td><strong>Endo tumour?</strong></td>
</tr>
<tr>
<td>2003–4 CC</td>
<td>48</td>
</tr>
<tr>
<td>2006–7 CC</td>
<td>48</td>
</tr>
<tr>
<td>2003–4 CC</td>
<td>20</td>
</tr>
<tr>
<td>2006–7 CC</td>
<td>26</td>
</tr>
</tbody>
</table>

**S107 DIAGNOSTIC VALUE AND RISKS OF TRANSBRONCHIAL LUNG BIOPSIES**

M. Murray, A. Hill. Royal Infirmary of Edinburgh, Edinburgh, UK

**Aims:** The aim of this study was to assess the diagnostic value and risk of transbronchial lung biopsies (TBB).

**Methods:** The authors retrospectively evaluated TBB carried out in the Royal Infirmary of Edinburgh between 2001–6. Outcomes included complications (risk of pneumothorax, life-threatening haemoptysis, admission with pneumonitis or death) and the percentage of transbronchial lung biopsies that confirmed the final diagnosis.

**Results:** 75 patients had undergone investigation with transbronchial lung biopsies. The mean (SD) age was 52.7 (14.3) years and the mean number of transbronchial lung biopsies taken was 4.2 (1.9). 10.7% developed a pneumothorax within 24 h of the biopsies. Of these, 37.5% required an intercostal chest drain. All pneumonitis resolved and no patients required thoracic surgical intervention. There were no episodes of major haemoptysis, no admissions with pneumonitis and no mortality. The diagnostic accuracy of TBB is shown in the table. No patients with usual interstitial pneumonia (UIP) had TBB. A definitive diagnosis was achieved
Pulmonary fibrosis: clinical observations

S109  SIX MINUTE WALK DESATURATION AND MAXIMAL EXERCISE TEST PARAMETERS: RELATION IN PATIENTS WITH FIBROSI NG LUNG DISEASE

T. J. Corte 1, S. J. Wort 1, S. Nogrady 2, D. Ip 1, R. Ellis 1, A. U. Wells 1.
Royal Brompton Hospital, London, UK
Australian National University, Canberra, Australia

Introduction: Six-minute walk testing (6MWT) is a reproducible diagnostic marker for patients with idiopathic interstitial pneumonia (IIP). Oxygen desaturation below 89% during 6MWT is associated with a much poorer prognosis in patients with IIP. Though the reason for this finding is unclear, it has been suggested that exercise desaturation may denote the development of pulmonary vascular damage, resulting in pulmonary hypertension on exercise (PH). We examine the relation between 6MWT and other key echocardiographic and physiologic markers.

Methods: All patients (n = 92) with fibrosing lung disease who had both 6MWT and maximal exercise testing performed concurrently between 2005 and 2007 were included. All patients studied also had concurrent resting pulmonary function tests and echocardiography.

Results: Diagnoses included idiopathic pulmonary fibrosis, n = 10; non-specific interstitial pneumonitis, n = 38; organising pneumonitis, n = 6; chronic hypersensitivity, n = 8; sarcoidosis, n = 8; other, n = 22; mean DLco 53 (15–225); mean FVC 0.79 (20%). Three of 51 (6%) had PH on echocardiography (median right ventricular systolic pressure (RVSP) 29.3 mmHg (14.3–83), pulmonary acceleration time (PAT) 126 ms (70–225)). Patients who desaturated to below 89% on 6MWT had (1) higher RVSP (p = 0.03); (2) higher resting AaDO2 (p = 0.02) and Vd/Vt (p = 0.02); (3) higher exercise AaDO2 (p = 0.001), AaDO2 (p = 0.01), Vd/Vt (p = 0.02); (4) lower DLco (p = 0.0001), FVC (p = 0.003). End 6MWT oxygen saturation correlated with (1) RVSP (r = −0.49, p < 0.001); (2) resting AaDO2 (r = −0.33, p < 0.001) and Vd/Vt (r = −0.37, p < 0.001); (3) maximal exercise PaO2 (r = 0.48, p < 0.0001), AaDO2 (r = −0.43, p < 0.0001) and Vd/Vt (r = −0.28, p < 0.01) and (4) resting pulmonary function (TLC r = 0.34, p < 0.01; DLco r = 0.44, p < 0.0001; FEV1 r = 0.4, p < 0.001; FVC r = 0.35, p < 0.001). RVSP also correlated with resting Vd/Vt (r = 0.46, p < 0.001) and DLco (r = −0.44, p < 0.001), and maximal exercise variables (PaO2 (r = −0.46, p < 0.001), AaDO2 (r = 0.49, p < 0.001), Vd/Vt (r = 0.49, p < 0.001)).

Conclusion: Desaturation below 89% in a 6MWT in diffuse lung disease is associated with more severe functional impairment, higher RVSP, and greater impairment of markers of pulmonary vascular compromise at rest (Vd/Vt) and on exercise (Vd/Vt, AaDO2). These findings provide indirect support for the hypothesis that desaturation during 6MWT in diffuse lung disease is indicative of pulmonary vascular decapsulation.

S108  RANDOMISED CONTROLLED TRIAL OF THE EFFECT OF STANDARD AND DETAILED CONSENT FORMS FOR BRONCHOSCOPY ON PERI-PROCEDURE ANXIETY AND SATISFACTION

M. Uzebeck, I. Saleem, C. Quinn, P. Cotter, S. O’Keeffe, J. J. Gilmarin. Merlin Park University Hospital, Galway, ROI

Introduction: Deciding what risks to disclose prior to a procedure is often challenging for clinicians. Although patients must receive sufficient information to make a decision, undue emphasis on rare complications may lead to anxiety and discourage patients from accepting beneficial interventions. Also, a significant proportion of patients ask not to be informed of all risks. We compared the effects of using a standard and a more detailed consent form on anxiety and satisfaction levels in patients undergoing elective bronchoscopy.

Methods: Consecutive patients who agreed to participate underwent a baseline assessment consisting of the Degner Control Preferences Scale and a 100 mm anxiety visual analogue scale (VAS). They were randomised to the standard or explicit information sheet and given 30 min to read it. The VAS was then repeated. Following the procedure, they completed a post-procedure satisfaction questionnaire consisting of four questions on a five-point Likert scale.

Results: Of 132 patients asked, 120 agreed to participate and 117 (73 men, mean age 57.5 years and 35% aged 65 years or more) completed the study. At baseline, there were no significant differences between the groups in demographic data in indications for bronchoscopy or in anxiety or information preference scores. Those who received the explicit form were significantly more anxious at the second assessment (mean (SD) VAS 44.4 (27.4 mmHg) vs 41.6 (27.4 mmHg); p = 0.04) and, although satisfaction levels were described as very similar between groups, those who received the explicit consent form described themselves as significantly more anxious at the second assessment.

Conclusions: Although the goal of adequate informed consent may be considered, these findings indicate satisfaction may be a poor indicator of anxiety levels and the use of explicit consent forms may provide a feasible way of reducing the anxiety levels of patients undergoing bronchoscopy.

S110  LUNG TRANSPLANTATION FOR IDIOPATHIC PULMONARY FIBROSIS: RECIPIENT CHARACTERISTICS AND SURVIVAL OUTCOMES IN A SINGLE CENTRE 1987–2007

Cardiopulmonary Transplant Unit, Freeman Hospital, Newcastle upon Tyne, UK

Background: Lung transplantation is the only treatment modality proven to offer a survival advantage to patients with end-stage lung disease due to idiopathic pulmonary fibrosis (IPF). Donor organ shortage limits availability of transplantation for patients with IPF. The International Society of Heart and Lung Transplantation (ISHLT) registry notes a poorer outcome post-transplant in this group compared to cystic fibrosis or COPD. In this study we evaluated our centre experience of lung transplantation for IPF.

Methods: A retrospective review was performed to identify demographics, pre-transplant physiology (Spirometry, TLC, PaO2 and PASP), functional status (6 minute walk distance) and pre-transplant drug therapy. Subsequently, length of post-transplant survival for each patient was determined.

Measurements and Main Results: Between September 1987 and February 2007, 79 patients (55 males, 24 females) underwent 55 single, 19 bilateral and 2 heart-lung transplants for IPF. Median age at transplant was 56 (35–70). Survival analysis shows worse outcome for IPF lung transplant compared to cystic fibrosis or COPD. In this study we evaluated our centre experience of lung transplantation for IPF.

Conclusion: Lung transplantation is the only treatment modality proven to offer a survival advantage to patients with end-stage lung disease due to idiopathic pulmonary fibrosis (IPF). Donor organ shortage limits availability of transplantation for patients with IPF. The International Society of Heart and Lung Transplantation (ISHLT) registry notes a poorer outcome post-transplant in this group compared to cystic fibrosis or COPD. In this study we evaluated our centre experience of lung transplantation for IPF.

Abstract S110.

Kaplan-Meier Cum. survival plot for real survival
Censor variable: status censor
Grouping variable: UIP

All lung transplants

p = 0.0394

Time

0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0

0.0 0.2 0.4 0.6 0.8 1.0

Cum. survival

0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0

0.0 0.2 0.4 0.6 0.8 1.0

Cum. survival

www.thoraxjnl.com

Thorax: first published as on 19 November 2007. Downloaded from http://thorax.bmj.com/ on July 14, 2023 by guest. Protected by copyright.
THE RISK OF ACUTE CORONARY SYNDROMES, CEREBROVASCULAR ACCIDENTS AND DEEP VEIN THROMBOSES IN PEOPLE WITH IDIOPATHIC PULMONARY FIBROSIS AND THE GENERAL POPULATION

I. Le Jeune, C. Smith, J. Gribbin, A. Fogarty, R. Hubbard. University of Nottingham, Nottingham, UK

Background: People who have factor V Leiden homozygosity have an increased tendency to clot and also to have restricted lung function.1 This raises the possibility that an increased tendency to clot may be a risk factor for diseases such as IPF. To investigate this further we have quantified the risk of acute coronary syndromes (ACS), cerebrovascular accidents (CVA) and deep vein thromboses (DVT) in people with IPF in comparison to the general population.

Methods: We used The Health Improvement Network (THIN) to identify a cohort of incident cases of IPF and four controls per case matched by age, sex and general practice. We then identified all recorded diagnoses of ACS, CVA and DVT and compared the occurrence of these outcomes between cases and controls before the date of diagnosis of IPF (or appropriate matched date for controls—hereafter termed the index date). We then compared the incidence of new, first time occurrence of these outcomes in the two cohorts after the index date.

Results: The mean age of cases at diagnosis was 71 years and 62% of cases were male. In the time before the index date the risk of having either a DVT or an ACS was increased in people with IPF, but no increase in CVA was present. During the follow-up period there was a marked increase in the incidence of ACS and DVT in people with IPF and a more modest increase in the risk of CVAs.

Conclusions: People with IPF have a markedly increased risk of having an ACS or a DVT. These increases may reflect an adverse effect of IPF on these outcomes but could also reflect a common risk factor, such as hypercoagulability, which in turn may highlight a new treatment opportunity for people with IPF.

Abstract S111

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before IPF diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>72</td>
<td>192</td>
</tr>
<tr>
<td>DVT</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>CVA</td>
<td>53</td>
<td>191</td>
</tr>
<tr>
<td><strong>After IPF diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>43</td>
<td>113</td>
</tr>
<tr>
<td>DVT</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>CVA</td>
<td>25</td>
<td>125</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndromes; DVT, deep vein thrombosis; CVA, cerebrovascular accidents.

DOES BODY MASS INDEX INFLUENCE INFLAMMATION AND PLASMA LIPIDS IN PIGEON FANCERS’ ALLERGIC ALVEOLITIS

S. Brennan1, I. Fraser2, L. Jolly2, C. Lynch2, L. Urquhart2, N. Sattar3, M. R. Adamson1, C. Mccharry2, K. Anderson1.1 Crosshouse Hospital, Kilmarnock; 2 Immunology, University of Glasgow; 3 Biochemistry, University of Glasgow, UK

Background: Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial inflammatory disease. The lymphocyte and antibody responses to inhaled antigens appear necessary but not sufficient for disease, and other susceptibility factors are unidentified. The presence of "foamy" lipid-laden histiocytes and lipid clefts in the lungs suggests that lipid metabolism may contribute to disease.

Methods: We measured plasma lipids, oxidised-LDL, and body mass index (BMI, kg/m²) in non-smoking 48 pigeon fanciers (23 with symptoms of EAA), and investigated their association with symptoms of EAA and the IgG antibody to inhaled antigen. The ox-LDL (measured by enzyme-immunoassay) and C reactive protein (CRP) (µg/ml) (measured by enzyme-immunoassay) and the lipid profile by nephelometry (mmol/l).

Results: Pigeon fanciers with EAA had higher levels of IgG antibody to avian antigen (39.0 [22.2–54.7], 12.0 [2.5–46.6], p<0.01), higher CRP levels (2.8 [1.6–8.0], 1.7 [1.2–4.4], p<0.05), and a trend to higher BMI than those without (mean [SD]) 28.70 (4.97) and 25.52 (4.35), p=0.078. The BMI levels correlated with CRP (r=0.353, p=0.035), and with ox-LDL (r=0.425, p=0.010), and a trend to higher antibody (r=0.278, p=0.1). The plasma triglyceride levels correlated with CRP (r=0.31, p=0.008) and IgG antibody (r=0.32, p=0.006), and the cholesterol level correlated with the IgG antibody titer (r=0.32, p=0.006). There was no significant association between BMI and cholesterol (r=0.132, p=0.444), triglyceride (r=0.157, p=0.359) and HDL-C (r=−0.183, p=0.285).

Conclusions: Interstitial foamy histiocytes in HP suggest altered lipid metabolism in this disease. We have found significant changes in the serum lipid profile of pigeon fanciers associated with inflammation (measured by CRP) and specific antigen sensitisation (measured by IgG antibody). The results suggest that HP has a systemic inflammatory component, with factors including BMI and altered lipids which in some way contribute to the pulmonary pathology.

Abstract S112

| Age (years) | 62.8±10.3 | 61.5±10.2 |
| Gender (M/F) | 33/8 | 19/10 |
| Never smoked (smokers) | 34/7 | 19/10 |
| Ox-LDL (µmol/L) | 51.2±19.2 | 59.4±21.6 |
| DIO (µmol/L) | 27.3±9.8 | 32.4±7.8 |
| Mean O2 flow rates at baseline test (l/min) | 2.8±1.9 | No O2 |
| Mean O2 flow rates at optimal O2 walk test (l/min) | 6.1±2.2 | 4.1±1.8 |

Abstract S113
Abstract S114  
Table 1

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>ACA</th>
<th>ATA</th>
<th>ARA</th>
<th>Undefined antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF/total</td>
<td>4/27</td>
<td>39/48</td>
<td>5/15</td>
<td>71/97</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>0.022</td>
<td>0.008</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.07 (0.02 to 0.21)</td>
<td>3.20 (1.44 to 7.11)</td>
<td>0.25 (0.08 to 0.78)</td>
<td>2.39 (1.30 to 4.40)</td>
</tr>
</tbody>
</table>

Abstract S114  
Table 2

<table>
<thead>
<tr>
<th>HLA-DRB1</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF/total</td>
<td>23/48</td>
<td>85/123</td>
<td>24/29</td>
<td>84/142</td>
</tr>
<tr>
<td>p Value</td>
<td>0.016</td>
<td>0.020</td>
<td>0.41 (0.21 to 0.81)</td>
<td>3.31 (1.20 to 9.19)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All other HLA-DRB1 alleles were non-significant.*

Treatment trials in chronic obstructive pulmonary disease

S115  EFFECT OF LONG-TERM ERYTHROMYCIN IN COPD TRIAL (ELECT): EXACERBATIONS AND INFLAMMATION

T. M. A. Wilkinson, T. A. R. Seemungal, R. Sapsford, J. R. Hurst, W. Perera, J. A. Wedzicha. 1Southampton University, Southampton, UK; 2University of the West Indies, Trinidad and Tobago; 3Royal Free and University College School of Medicine, London, UK

Introduction: Chronic obstructive pulmonary disease (COPD) is characterised by heightened airway and systemic inflammation and by frequent exacerbations that are a major cause of hospital admission, mortality and contribute to disease progression. Macrolide antibiotics have been shown to have anti-inflammatory activity and their long-term use may impact upon inflammation and exacerbation risk in subjects with COPD.

Methods: We performed a one-year randomised double-blind placebo-controlled study of erythromycin 250 mg twice daily in COPD patients, with total number of treated exacerbations as the primary outcome and sequentially collected sputum and blood samples to determine effects on airway and systemic inflammation. We recruited 109 COPD outpatients: 69 males, 52 current smokers, mean (SD) age 67.2 (8.6) years, FEV1 1.32 (0.53) l, FEV1/FVC 0.50 (18%).

Results: There was no difference in any of these parameters between the two treatment groups at study start. Dropouts (n) were placebo (6) and macrolide arm (7). The total number of treated exacerbations was 233 median (IQR) 1 (0–3). Poison generalised linear modelling was used to determine the effect of treatment on exacerbation frequency with allowance for time on treatment, smoking status, disease severity, baseline exacerbation frequency, age and gender. Macrolide therapy was associated with a reduction in the incidence of exacerbations, the odds ratio (OR) for exacerbation on placebo compared to macrolide therapy was 1.48 (p=0.004). No significant effect of treatment was seen on serum CRP, interleukin 6, or on sputum interleukin 6, 8 or myeloperoxidase, at 1, 3, 6, 9 or 12 months (p>0.05). Macrolide therapy was associated with a significant reduction in exacerbations compared to placebo, however no significant effect on airway or systemic inflammation was found.

Conclusions: Further studies are required to determine the mechanism of action of this therapy as it has potential to reduce the clinical burden of exacerbations of this important disease.

Abstract S115  Baseline values for inflammatory markers for each treatment arm, p<0.05 for differences between each parameter between groups

<table>
<thead>
<tr>
<th>Baseline parameter</th>
<th>Placebo</th>
<th>Macrolide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>CRP blood (mg/l)</td>
<td>7.72</td>
<td>7.33</td>
</tr>
<tr>
<td>IL6 blood (pg/ml)</td>
<td>6.56</td>
<td>16.62</td>
</tr>
<tr>
<td>IL6 sputum (pg/ml)</td>
<td>188.34</td>
<td>169.28</td>
</tr>
<tr>
<td>IL8 sputum (pg/ml)</td>
<td>2806.00</td>
<td>1348.57</td>
</tr>
<tr>
<td>MPO sputum (ng/ml)</td>
<td>9.95</td>
<td>12.24</td>
</tr>
</tbody>
</table>

procedure continued until patients did not desaturate <90%; that is, optimal O2 flow rates were achieved (optimal O2 walk test).

Results: Patients not on O2 pre-test managed to walk a statistically and clinically significant 81.2 m (mean) further using optimal O2 therapy. Patients already on O2 walked an extra 16.9 m (mean). Borg scores at test using sequence-specific primers (SSP-PCR) in 171. Frequencies were compared clinically significant 81.2 m (mean) further using optimal O2 therapy.

Methods: AT/ERS International Multidisciplinary Consensus Classification of the benefits for these patients.

Aim: To investigate whether associations with human leukocyte antigen (HLA) genes.

Background: Systemic sclerosis (SSc) is characterised by microvascular damage, immune activation and fibrosis of the skin and various internal organs including the lung. Although antinuclear antibodies are present in up to 95% of cases the precise antigen cannot be determined in a significant minority of cases. Patients with anticentromere antibodies (ACA) and anti-RNA polymerase I/III antibodies (ARA) have a low average extent of pulmonary fibrosis (PF) while those with antithromboposerae antibodies (ATA) have a higher average extent. ACA and ATA have distinct associations with human leukocyte antigen (HLA) genes.

Aim: To investigate whether associations with PF are stronger for HLA alleles or autoantibodies.

Methods: 187 patients with SSc assessed at the Royal Brompton Hospital for the presence of PF had high resolution computed tomography (HRCT) performed. HRCTs were quantified by two independent observers for overall disease extent (to the nearest 5%). Patients with anticentromere antibodies (ACA) and anti-RNA polymerase I/III antibodies (ARA) have a low average extent of pulmonary fibrosis (PF) while those with antithromboposerae antibodies (ATA) have a higher average extent. ACA and ATA have distinct associations with human leukocyte antigen (HLA) genes.

Introduction: Chronic obstructive pulmonary disease (COPD) is characterised by heightened airway and systemic inflammation and by frequent exacerbations that are a major cause of hospital admission, mortality and contribute to disease progression. Macrolide antibiotics have been shown to have anti-inflammatory activity and their long-term use may impact upon inflammation and exacerbation risk in subjects with COPD.

Methods: We performed a one-year randomised double-blind placebo-controlled study of erythromycin 250 mg twice daily in COPD patients, with total number of treated exacerbations as the primary outcome and sequentially collected sputum and blood samples to determine effects on airway and systemic inflammation. We recruited 109 COPD outpatients: 69 males, 52 current smokers, mean (SD) age 67.2 (8.6) years, FEV1 1.32 (0.53) l, FEV1/FVC 0.50 (18%).

Results: There was no difference in any of these parameters between the two treatment groups at study start. Dropouts (n) were placebo (6) and macrolide arm (7). The total number of treated exacerbations was 233 median (IQR) 1 (0–3). Poison generalised linear modelling was used to determine the effect of treatment on exacerbation frequency with allowance for time on treatment, smoking status, disease severity, baseline exacerbation frequency, age and gender. Macrolide therapy was associated with a reduction in the incidence of exacerbations, the odds ratio (OR) for exacerbation on placebo compared to macrolide therapy was 1.48 (p=0.004). No significant effect of treatment was seen on serum CRP, interleukin 6, or on sputum interleukin 6, 8 or myeloperoxidase, at 1, 3, 6, 9 or 12 months (p>0.05). Macrolide therapy was associated with a significant reduction in exacerbations compared to placebo, however no significant affect on airway or systemic inflammation was found.

Conclusions: Further studies are required to determine the mechanism of action of this therapy as it has potential to reduce the clinical burden of exacerbations of this important disease.

Abstract S115  Baseline values for inflammatory markers for each treatment arm, p<0.05 for differences between each parameter between groups

<table>
<thead>
<tr>
<th>Baseline parameter</th>
<th>Placebo</th>
<th>Macrolide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>CRP blood (mg/l)</td>
<td>7.72</td>
<td>7.33</td>
</tr>
<tr>
<td>IL6 blood (pg/ml)</td>
<td>6.56</td>
<td>16.62</td>
</tr>
<tr>
<td>IL6 sputum (pg/ml)</td>
<td>188.34</td>
<td>169.28</td>
</tr>
<tr>
<td>IL8 sputum (pg/ml)</td>
<td>2806.00</td>
<td>1348.57</td>
</tr>
<tr>
<td>MPO sputum (ng/ml)</td>
<td>9.95</td>
<td>12.24</td>
</tr>
</tbody>
</table>

www.thoraxjnl.com
**S116**

**ERDOSTEINE IN ASSOCIATION WITH AMOXICILLIN IMPROVES THE OUTCOME OF ACUTE EXACERBATIONS COMPARED TO AMOXICillin ALONE IN COPD PATIENTS**

A. Morice1, M. Moretti2, M. Bollabio3. 1University of Hull, Castle Hill Hospital, Hull, UK; 2Polyclinic of Modena and Reggio Emilia, Modeno, Italy; 3Edmond Pharma, Milan, Italy

**Introduction:** Acute infective exacerbations represent an important cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). The European Chronic Obstructive Bronchitis Erdosteine Study trial has shown that erdosteine in association with amoxicillin can improve symptoms and clinical conditions earlier and more effectively compared to antibiotic monotherapy (Int J Clin Pharmacol Ther 1995;33:612). As entry criteria were mainly based on clinical diagnosis, a post hoc analysis has been performed to confirm efficacy of erdosteine in the subset of patients fulfilling spirometric criteria for COPD diagnosis (diagnosed by FEV1/FVC <70% pred).

**Methods:** Of 237, 175 patients fulfilled the diagnostic criteria of COPD and were randomised to erdosteine + amoxicillin (E+A) or placebo + amoxicillin (P+A) for 7–10 days. The primary efficacy endpoint was cumulative Global Clinical Assessment (GCA) composed of four-point categorical scores (3 being the worst) evaluating six items at Day 3–4 and Day 7–10: sputum appearance and viscosity, difficulty to expectorate, catarh rhinorrhea at auscultation, cough and dyspnoea. Secondary endpoints were the overall physician’s and patient’s judgement of efficacy, and pulmonary function tests (FEV1, FVC, MMFE25–75%). An entry criterion was mainly based on clinical diagnosis, a post hoc analysis has been performed to confirm efficacy of erdosteine in the subset of patients fulfilling spirometric criteria for COPD diagnosis.

**Results:** Mean GCA score at baseline was 12.38 in E+A (n = 89) and 12.99 in P+A group (n = 86). At both intermediate and final evaluation GCA was significantly lower in E+A than in P+A group (ANOVA LSMeans 9.05 vs 10.25 at Day 3–4, and 5.86 vs 7.85 at Day 7–10, respectively; p < 0.001). In the overall efficacy assessment a higher percentage of patients treated with E+A rated a return to pre-treatment baseline state (25.8% vs 9.4%) which was consistent with the physicians’ evaluations (21.3% vs 7.1%). Pulmonary function parameters improved in both groups at the end of treatment, being numerically better in patients receiving E+A (FEV1, LSMeans: 1.50 and 1.44 l in two groups, respectively).

**Conclusions:** Erdosteine plus antibiotics is more effective than antibiotic monotherapy for the treatment of acute infective exacerbations in patients with spirometric-diagnosed COPD. Early and aggressive management may reduce the length of the exacerbation. By the addition of erdosteine to usual care further resolution of symptoms may allow a more rapid recovery.

**S117**

**COST-EFFECTIVENESS OF ERDOSTEINE IN THE TREATMENT OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

J. Haughney1, M. Grishchenko2, H. A. Dakin3, M. Bollabio2, G. Caputo2. 1University of Aberdeen, Aberdeen, UK; 2Abacus International, Bicester, UK; 3Edmond Pharma, Milan, Italy

**Introduction:** Acute exacerbations of chronic obstructive pulmonary disease (COPD). The European Chronic Obstructive Bronchitis Erdosteine Study trial, which demonstrated that 25.8% of erdosteine/amoxicillin-treated patients and 11.1% of placebo/amoxicillin-treated patients returned to pre-exacerbation pulmonary state within 7–10 days (p < 0.05; number-needed-to-treat, 7). Quality-adjusted life-years (QALYs) were calculated using published utility data and assuming a logarithmic recovery function.

**Results:** Erdosteine was found to dominate UC, being both more effective and cost-saving. The total costs of erdosteine were, on average, £3.47/exacerbation lower than those of UC (£104.58 vs £108.05) due to reductions in healthcare use. Erdosteine was also associated with QALY gains over UC (£0.0293/exacerbation vs £0.02935/exacerbation) and an additional 0.74 exacerbation-free days. Scenario analyses suggest that treatment with erdosteine dominates UC alone in patients treated with/without a homecare pack, whether they had mild, moderate or severe disease. Extensive sensitivity analyses demonstrated that these conclusions are robust. All parameters were varied within their plausible ranges; none caused erdosteine to generate fewer QALYs than UC alone and only one parameter could cause erdosteine to cost more than £20,000/QALY.

**Conclusions:** Adding erdosteine to UC in the treatment of AECOPD is highly cost-effective compared with UC alone, generating additional health benefits at lower cost.

**S118**

**FAST ONSET OF ANTIOXIDANT ACTIONS OF ERDOSTEINE AND ITS POTENTIAL USE FOR ACUTE TREATMENT OF COPD EXACERBATIONS**

S. A. Kharitonov. Imperial College London, Royal Brompton NHS Trust, UK

**Introduction:** Increased frequency of exacerbations in patients with chronic obstructive pulmonary disease (COPD) is associated with increased oxidative stress. The average exacerbation recovery time of COPD patients is 10.7 days, with conventional treatment of antibiotics and corticosteroids. A significant proportion of these patients demonstrate incomplete recovery, and frequent exacerbations contribute to decline in lung function and poor health status.

**Results:** Erdosteine possesses mucolytic, antioxidant and anti-inflammatory properties that prevent the accumulation of reactive oxygen species (ROS) when their production is accelerated and increases antioxidant cellular protective mechanisms. Fast onset of antioxidant action of erdosteine has been demonstrated following acute experimental liver and renal toxicity (5–7 days of treatment), ischemia reperfusion (2 days) and hypoxia-induced patients to pre-exacerbation pulmonary state as rapidly as possible. Erdosteine is a third-generation mucolytic used in the treatment of AECOPD. Clinical trials involving more than 2,500 patients have demonstrated its efficacy and safety.

**Objectives:** To assess the cost effectiveness of erdosteine + usual care (UC) versus UC alone in the treatment of AECOPD in a primary care setting from the perspective of the UK NHS.

**Methods:** A cost-utility analysis was conducted. The cost and benefits were assessed over 14 days (a typical treatment and recovery time for AECOPD). The costs associated with treatment alternatives were calculated using a decision-tree approach. Resource use data were derived from a survey of 30 randomly-selected UK clinicians. Costs of erdosteine and primary care consultations were taken from standard UK price tariffs. Efficacy data were based on a post hoc intent-to-treat analysis of the ECORES (European Chronic Obstructive Bronchitis Erdosteine Study) trial, which demonstrated that 25.8% of erdosteine/amoxicillin-treated patients and 11.1% of placebo/amoxicillin-treated patients returned to pre-exacerbation pulmonary state within 7–10 days (p < 0.05; number-needed-to-treat, 7). Quality-adjusted life-years (QALYs) were calculated using published utility data and assuming a logarithmic recovery function.

**Results:** Erdosteine was found to dominate UC, being both more effective and cost-saving. The total costs of erdosteine were, on average, £3.47/exacerbation lower than those of UC (£104.58 vs £108.05) due to reductions in healthcare use. Erdosteine was also associated with QALY gains over UC (£0.0293/exacerbation vs £0.02935/exacerbation) and an additional 0.74 exacerbation-free days. Scenario analyses suggest that treatment with erdosteine dominates UC alone in patients treated with/without a homecare pack, whether they had mild, moderate or severe disease. Extensive sensitivity analyses demonstrated that these conclusions are robust. All parameters were varied within their plausible ranges; none caused erdosteine to generate fewer QALYs than UC alone and only one parameter could cause erdosteine to cost more than £20,000/QALY.

**Conclusions:** Adding erdosteine to UC in the treatment of AECOPD is highly cost-effective compared with UC alone, generating additional health benefits at lower cost.

---

**Abstract S118**

**Selected papers demonstrating an acute effect of erdosteine in smokers and COPD**

<table>
<thead>
<tr>
<th>Subjects/patients/treatment</th>
<th>Biomarker</th>
<th>Onset of action and effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy current smokers: 175 bid/ placebo for 30 days</td>
<td>TBARS</td>
<td>Minutes*: 5 (↓↓↓↓↓), 30 (↓↓↓↓↓)</td>
<td>Basigyi et al, 2005</td>
</tr>
<tr>
<td>(serum)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis current smokers: 300 mg bid/ placebo for 5 days (BAL)</td>
<td>GSH</td>
<td>Hours: 2 (↓↓↓), 12 (↓↓↓↓)</td>
<td>Mitrea et al, 1998</td>
</tr>
<tr>
<td>Healthy current smokers: 300mg bid for 7 days (serum)</td>
<td>GSSG</td>
<td>2 (↓↓↓), 12 (↓↓↓↓↓)</td>
<td>Mancini et al, 1998</td>
</tr>
<tr>
<td>COPD (GOLD 0–2) current smokers: 300 mg bid for 10 days/ placebo (serum)</td>
<td>MDA</td>
<td>Days: 7 (↓↓↓↓↓)</td>
<td>Dal Negro et al, 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>ROS</td>
<td>4 (↓↓↓↓), 7 (↓↓↓↓↓), 10 (↓↓↓↓↓)</td>
<td>Dal Negro et al, 2006</td>
</tr>
<tr>
<td>8-iso</td>
<td></td>
<td>4 (&lt;↓↓↓↓), 7 (&lt;↓↓↓↓↓), 10 (&lt;↓↓↓↓↓)</td>
<td>Dal Negro et al, 2006</td>
</tr>
</tbody>
</table>

TBARS, thiobarbituric acid reactive substances, including malonaldehyde (MDA); BAL, bronchoalveolar lavage; GSH, glutathione; GSSG, oxidised GSH; ROS, reactive oxygen species; IL-8, interleukin 8; 8-iso, 8 isoprostane.  
*Time after smoking.*

www.thoraxjnl.com
lungs and pulmonary vasculature damage (2 weeks). Combination of erdosteine and formoterol in COPD might be beneficial in preventing COPD exacerbations. It has been shown that when budesonide and erdosteine were administered in combination, their antioxidative effect on the release of ROS and peroxynitrite by stimulated neutrophils was higher than the effect of a single drug.

Conclusions: This analysis indicates that erdosteine given acutely minimises the impact of oxidative stress during a COPD exacerbation. The antioxidant properties of the drug, considering its fast onset of antioxidant action (table) may play an important role in COPD patients during exacerbations where the oxidant/antioxidant imbalance is higher.

S119 INITIAL EXPERIENCE WITH AN EMPHYSEMA MULTIDISCIPLINARY MEETING FOR THE MANAGEMENT OF PATIENTS FOR LUNG VOLUME REDUCTION

I. F. Oey1, D. A. Waller1, J. Entwisle2, S. J. Singh3, M. C. Steiner1, M. D. Morgan1.
1Department of Respiratory Medicine and Thoracic Surgery, Glenfield Hospital; 2Department of Radiology, Glenfield Hospital; 3Department of Pulmonary Rehabilitation, Glenfield Hospital, Leicester, UK

Objective: It has become common practice to manage lung cancer patients through a multidisciplinary meeting (MDT). We describe our 10-year experience with an emphysema MDT for lung volume reduction surgery (LVRS) and an audit of our results.

Method: We have been performing LVRS since 1995 and established an EMDT in 1997. Patients are initially referred to either a thoracic surgeon or a respiratory physician with special interest in LVRS. Subsequently these patients are discussed at a bimonthly meeting, which is attended by representatives of respiratory medicine, thoracic surgery, radiology and pulmonary rehabilitation. The prior investigations required for each patient are available and adjusted by continuously auditing our own results.

Results: To date 386 patients have been referred for LVRS. These include 126 patients from Leicestershire and 260 external referrals. So far, 144 LVRS procedures on 131 patients have been performed. Nine patients are currently on our waiting list for LVRS. The figure shows the annual distribution. Although patients for bullectomy are not normally discussed at this meeting, 11 patients on our waiting list for LVRS. The figure shows the annual distribution. Although patients for bullectomy are not normally discussed at this meeting, 11 patients currently represent respiratory medicine, thoracic surgery, radiology and pulmonary rehabilitation. The prior investigations required for each patient are available and adjusted by continuously auditing our own results.

Conclusion: Our experience of an EMDT has been favourable and we would advocate its use. It has ensured a regular throughput of patients for LVRS and has helped to refine referrals. The number of patients suitable for surgical volume reduction remains small and is not increasing.

---

Investigations and interventions in pleural disease

S120 ACCURACY OF PLEURAL FLUID PH MEASUREMENT IS CRITICALLY INFLUENCED BY SAMPLE COLLECTION AND HANDLING

E. Mishra1, N. M. Rahman1, H. E. Davies1, K. Russell1, R. J. O. Davies1, Y. C. G. Lee1.
1Oxford Centre for Respiratory Medicine; 2Norfolk and Norwich University Hospital, Norwich, UK

Background: Significant emphasis has been placed on pleural fluid pH (and glucose) measurement, especially in guiding clinical management of parapneumonic effusion and predicting outcome in malignant effusion. However, there is no standard method to collect pleural fluid for pH measurement. We hypothesise that pleural fluid pH, but not glucose, measurements are susceptible to variations in methods of collection. This study assessed the consistency of pleural fluid pH and glucose measurements in samples contaminated with likely agents from clinical practice.

Methods: Exudative pleural effusions from 63 patients (malignancy, n = 22; infection, n = 41) were included. Samples were collected in commercially available blood gas syringes (with or without residual lignocaine, air or heparin) and analysed immediately using a blood gas machine (Radiometer ABL 700 series, Copenhagen). The plain sample was analysed at 0, 1, 4 and 24 h, and pH and glucose were assayed in all samples. A further sample was sent to the laboratory for glucose analysis.

Results: Pleural fluid pH was significantly affected by leftover lignocaine in a dose-dependent fashion. 0.2 ml of residual lignocaine was sufficient to induce a clinically significant decrease in pleural fluid pH (~0.14 SD 0.08); 95% CI –0.12 to –0.17; p < 0.001). Incomplete expulsion of air from the collection syringe resulted in a significant rise in pleural pH by 0.08 (SD 0.05); 95% CI 0.09 to 0.06; p < 0.001). Retaining heparin within the blood gas syringe caused a significant reduction in pleural fluid pH (~0.02 (SD 0.05); 95% CI –0.002 to –0.04; p = 0.03). Pleural fluid pH was stable in samples left at room temperature for 1 h. Significant changes were observed at 4 h (~0.02 (SD 0.08); 95% CI –0.04 to –0.003, p = 0.03) and at 24 h (~0.06 (SD 0.13); 95% CI –0.15 to –0.02; p = 0.001). In contrast, glucose measurements as analysed by blood gas machine were not significantly affected (changes < 1 mmol/l) in the presence of lignocaine (up to 0.4 ml), air or heparin, and remained stable after 1, 4 and 24 h. There was a strong correlation between glucose measured by the machine and laboratory measured glucose.

Conclusion: Accuracy of pleural fluid pH measurement is critically dependent on the precise manner under which the sample is collected. This is the first study to show that common variations in collection of pleural fluid, for example, carried over lignocaine (even in minute volumes), presence of air, or delay in pH assay, all lead to significant changes in pH that may alter clinical management. Pleural fluid glucose, however, is more stable and less susceptible to variations in collection details. Strict
A RANDOMISED PHASE III TRIAL OF ACTIVE SYMPTOM CONTROL WITH OR WITHOUT CHEMOTHERAPY IN THE TREATMENT OF PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA. THE MEDICAL RESEARCH COUNCIL/BRITISH THORACIC SOCIETY MS01 TRIAL

M. Muers1, P. Fisher2, M. O’Brien3, M. Peake4, R. Rudd5, M. Snear6, J. Steele7, M. Nankivell8, C. Pugh2, R. J. Stephens9, 1Leeds General Infirmary, 2Weston Park Hospital, Sheffield, UK; 3Royal Marsden Hospital, 4Glenfield Hospital, Leicester, UK; 5St Bartholomew’s Hospital, London, UK; 6Cookridge Hospital, Leeds, UK; 7MRC Clinical Trials Unit, London, UK

Background: Although chemotherapy is widely used in the treatment of mesothelioma it has never been compared in a randomised trial with active symptom control (ASC) alone.

Methods: Patients with malignant pleural mesothelioma were randomised to ASC alone (including steroids, analgesics, bronchodilators, palliative radiotherapy, etc), ASC+MVP (4 x 3-weekly cycles of mitomycin 6 g/m², vinblastine 6 mg/m², and cisplatin 50 mg/m²), or ASC+V (12 weekly injections of vinorelbine 30 mg/m²). 420 patients were required to detect a 3-month improvement in median survival with ASC+CT (both chemotherapy arms combined).

Results: 409 patients were accrued (136 ASC, 137 ASC+MVP, 136 ASC+V). Median age: 65 years, male: 91%, performance status 0: 23%, epithelial histology: 73%, Stage III: 33%, Stage IV: 48%. Good symptom palliation was achieved in all three groups, and no between-group differences were observed in four pre-defined quality of life subscales. A small survival benefit was seen for ASC+CT (349 deaths, HR 0.89, 95% CI 0.72 to 1.12, p = 0.32). Median survival: ASC: 7.6 months, ASC+CT: 8.5 months. Exploratory analyses suggested a survival advantage for vinorelbine compared to ASC alone (232 deaths, HR 0.81, 95% CI 0.63 to 1.05, p = 0.11), with a median survival of 9.4 months, but no evidence of a difference in death/surgical rate when these groups were divided according to pleural fluid purulence. There were no significant differences in any secondary outcomes between chest tube bore groups.

Conclusions: This is the second largest ever randomised trial in mesothelioma and the first to compare ASC with or without chemotherapy. Although the addition of chemotherapy to ASC did not result in a conventionally significant survival benefit, there was an indication that vinorelbine should be investigated further, and that MVP probably has no role in this disease.

THE RELATION BETWEEN CHEST TUBE BORE, CLINICAL OUTCOME AND TUBE-RELATED ADVERSE EVENTS IN PLEURAL INFECTION

N. M. Rahman1, N. A. Maskell2, E. L. Hedley1, A. J. Nunn3, F. V. Gleeson1, R. J. O. Davies1. 1Oxford Centre for Respiratory Medicine, 2Southend Hospital, Bristol, UK; 3Medical Research Council, Clinical Trials Unit, London, UK

Introduction: The primary treatment modalities of pleural infection are drainage of infected fluid combined with antibiotic therapy. There is no evidence to inform clinicians as to the optimal size of chest tube for this purpose, and practice is based on expert opinion. We have previously shown that smaller bore (<14F), guide-wire inserted chest tubes are less painful than larger bore, blunt dissection tubes (Rahman et al, Thorax 2006;61(Suppl 2):191A). This study addresses whether the size of tube is associated with differential clinical outcome in patients with pleural infection. The primary outcome measure (death and surgery rate combined at one year), and secondary outcomes (FEV1, FVC and CXR abnormality at three months, length of hospital stay, adverse events) were related to the size of the initial chest tube in 405 patients with pleural infection taking part in the UK MRC MIST1 trial.

Abstract S122 The rate of surgery free survival over 12 months in patients treated with chest tubes of different bore.

The death and surgery rate at 1 year (table) did not vary with initial chest drain size, and this outcome did not evolve over time (fig). There was no difference in death/surgical rate when these groups were divided according to pleural fluid purulence. There were no significant differences in any secondary outcomes between chest tube bore groups.

The method of chest tube insertion was not associated with death and surgery rate (guide-wire, death + surgery 97/265 (37%), blunt 57/140 (41%) OR = 1.19, 95% CI 0.79 to 1.81, χ² df=0.66, p=0.42, nor with any other adverse event. Apart from the previously demonstrated greater pain with larger blunt dissection inserted chest tubes (Thorax 2006;61(Suppl 2);191A), tube insertion technique was not associated with a difference in adverse event rate. The initial choice of a small bore, guide-wire inserted, chest tube for pleural infection produces as good a clinical result as a larger, blunt dissection, inserted tube, but causes less pain for the patient.

PREDICTORS OF LONG-TERM POSTOPERATIVE SURVIVAL IN MALIGNANT PLEURAL MESOTHELIOMA: A MULTIVARIATE ANALYSIS IN 300 PATIENTS TREATED IN A SINGLE INSTITUTION

D. S. Trousse1, A. Nakas1, J. G. Edwards2, A. E. Martin-Ucar1, K. J. O’Byrne2. 1Glenfield Hospital, Leicester, UK; 2Northern General Hospital, Sheffield, UK; 3St James’s University Hospital, Dublin, ROI

Background: Current guidelines advocate surgery for malignant pleural mesothelioma (MPM) for symptom control; the role of therapeutic surgery remains controversial. There is non-randomised evidence for a multifactorial approach including extrapleural pneumonectomy (EPP) or radical pleurectomy/decortication (P/D) or non-radical by thorascopy (VATS P/D) or thoracotomy (open P/D).

Objective: To analyse our single-institution surgical experience with MPM to identify long-term survivors and factors predicting their favourable outcome.

Abstract S123 Death and surgery rate at 1 year according to drain size

<table>
<thead>
<tr>
<th>Tube size (F)</th>
<th>n (%)</th>
<th>Death + surgery combined (%)</th>
<th>Death (%)</th>
<th>Surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>58 (14)</td>
<td>21 (36)</td>
<td>10 (17)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>10–14</td>
<td>208 (51)</td>
<td>75 (36)</td>
<td>46 (22)</td>
<td>35 (17)</td>
</tr>
<tr>
<td>15–20</td>
<td>70 (17)</td>
<td>28 (40)</td>
<td>18 (25)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>69 (17)</td>
<td>30 (43)</td>
<td>17 (25)</td>
<td>13 (19)</td>
</tr>
</tbody>
</table>

χ² 3df=1.41, p=0.70  χ² 3df=1.53, p=0.67  χ² 3df=0.27, p=0.97
Methods: In a retrospective review of a prospective database of 300 consecutive patients with MPM operated on over a 10-year period long-term overall survival was analysed using the Kaplan-Meier method. Potential prognostic factors were tested in univariate and multivariate analysis.

Results: We operated upon 300 patients (89% male, mean age 61 years). Procedures included: 124 EPP, 51 radical P/D, 74 VATS P/D and 51 open P/D. Epithelial MPM was the most frequent (71%). The overall 30-day and 90-day mortality rates were 6% and 14% respectively. Postoperative complications occurred in 40%. Mean hospital stay and duration of drainage were 14.2 and 10.8 days respectively. Overall 1-year, 2-year, 3-year and median survival rates were respectively 63%, 33%, 18%, 15 months for EPP, 54%, 46%, 40%, 23 months for radical P/D, 55%, 19%, 9%, 12 months for VATS P/D, and 35%, 13%, 0%, 7 months for open P/D, (p < 0.001). On multivariate analysis, younger age (p = 0.003), epithelial type cell (p < 0.01), radical surgery in favour of radical P/D (p < 0.01), negative node staging following mediastinoscopy (p = 0.014), haemoglobin > 14 g/dl (p = 0.012), WCC < 8.3 x 10^3/l (p = 0.005) and adjuvant chemotherapy (p < 0.01) or radiotherapy (p = 0.03) were significant good prognostic factors. On multivariate analysis, age > 60 years (p = 0.006, HR 1.7), non-epithelial histology (p < 0.01) were independent predictors of poor long-term survival. Conversely, haemoglobin > 14 g/dl (p = 0.014, HR 0.57), radical P/D (p = 0.047, HR 0.53) and adjuvant chemotherapy (p = 0.002, HR 0.43) were positive predictors of outcome.

Conclusions: Long-term survival in MPM can be achieved by radical surgery in selected candidates aged 60 years, normal haemoglobin level, epithelial histology and negative mediastinoscopy. Radical debulking surgery in the form of decortication/pleurectomy followed by adjuvant chemotherapy appears to be the best therapeutic option.

**S124 PNEUMOTHORAX AND PREGNANCY**

M. Alhajji, A. G. Arnold. Castle Hill Hospital, East Yorkshire, UK

Introduction: Primary spontaneous pneumothorax (PSP) affects young female patients of childbearing age. Recurrence is a recognised feature of PSP. Several guidelines have been developed to assist the diagnosis and management of this condition, the latest being the BTS guidelines of May 2003, but they do not contain advice on the management of pneumothorax during pregnancy or parturition. PSP might be expected to occur reasonably commonly during pregnancy, but only 43 cases have been reported, with individual series consisting of between one and three patients. These studies describe an increased risk of recurrence both in pregnancy and during childbirth in patients with pneumothorax, and relatively invasive management strategies.

Methods: As the only major hospital in our area, with a stable catchment population of half a million patients, we have collected a database of 250 consecutive pneumothorax patients over the last decade. We present the largest series reported to date of the management of pneumothorax in pregnancy and during childbirth. PSP might be expected to occur reasonably commonly during pregnancy, but only 43 cases have been reported, with individual series consisting of between one and three patients. These studies describe an increased risk of recurrence both in pregnancy and during childbirth in patients with pneumothorax, and relatively invasive management strategies.

Results: See table.

**Results:** See table.

Conclusion: We have reviewed the existing medical literature of pneumothorax during pregnancy and added our own experience, the largest group of patients from a single centre, using less invasive management strategies. Current guidelines do not contain advice on the management of this situation. The potential hazards to the mother and child are such that practising chest physicians, surgeons and obstetricians need awareness of the problem and close cooperation in its management.

**S126 GALACTOMANNA DETECTION IN EXHALED BREATH CONDENSATE OF NEUTROPENIC PATIENTS WITH SUSPECTED INVASIVE PULMONARY ASPERGILLOSIS**

S. R. Doffman1, L. J. Griffiths2, G. R. Athorn1, J. S. Vinnicombe2, J. C. Moore-Gillon2, M. J. Griffiths3, S. G. Agrawal1.1 Queen Mary, University of London; 2Barts and the London Hospital; 3Royal Brompton Hospital, London, UK

Introduction: The mortality from invasive pulmonary aspergillosis (IPA) associated with treatment of haematological malignancies is high and diagnosis can be difficult due to its non-specific clinical features. Galactomannan (GM), a polysaccharide component of Aspergillus spp cell wall, is detectable in serum and bronchoalveolar lavage (BAL) fluid in IPA. The application of exhaled breath condensate (EBC) analysis, a non-invasive technique, has not been explored in this setting. We report on pilot data of the detection of GM in EBC from a subset of patients forming part of a prospective trial into the early diagnosis of IPA in haematological patients at high risk.

Methods: EBC and serum were collected once and twice weekly, respectively, throughout the study period. BAL was carried out in patients with an abnormal HRCT chest after > 96 h of persistent fever despite antibiotics. GM was measured in EBC, serum and, where appropriate, BAL fluid using a commercially available kit (Platelia Aspergillus, Bio-Rad, France). The application of exhaled breath condensate (EBC) analysis, a non-invasive technique, has not been explored in this setting. We report on pilot data of the detection of GM in EBC from a subset of patients forming part of a prospective trial into the early diagnosis of IPA in haematological patients at high risk.

Methods: EBC and serum were collected once and twice weekly, respectively, throughout the study period. BAL was carried out in patients with an abnormal HRCT chest after > 96 h of persistent fever despite antibiotics. GM was measured in EBC, serum and, where appropriate, BAL fluid using a commercially available kit (Platelia Aspergillus, Bio-Rad, France).

**Abstract S124**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age of patient</th>
<th>Gravidity of patient</th>
<th>Weeks of gestation</th>
<th>Pneumothorax treatment</th>
<th>Pulmonary outcome</th>
<th>Obstetric outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>2</td>
<td>13</td>
<td>Aspiration</td>
<td>Resolved</td>
<td>C Section</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>2</td>
<td>11</td>
<td>Aspiration x 2</td>
<td>VATS (post partum)</td>
<td>C Section</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>3</td>
<td>15</td>
<td>Aspiration</td>
<td>VATS (post partum)</td>
<td>C Section</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>1</td>
<td>11</td>
<td>Aspiration</td>
<td>Resolved</td>
<td>V Extraction</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>1</td>
<td>11</td>
<td>VATS</td>
<td>Fetal loss</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>3</td>
<td>35</td>
<td>ICD</td>
<td>VATS (post partum)</td>
<td>C Section</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>2</td>
<td>16</td>
<td>ICD x 3</td>
<td>VATS (intra partum)</td>
<td>Insufficient information</td>
</tr>
</tbody>
</table>
Spoken sessions
France. The likelihood of IPA was assigned using well-recognised criteria by two investigators blinded to clinical details.

Results: Of 33 patients studied, 7 had proven/probable IPA, 7 possible and 21 unclassified. 17 had no evidence of IPA. Of the 7 patients with proven/probable disease, four of whom had GM-positive sera, EBC and serum GM followed the same trend. In one patient the EBC GM was positive early in the infection, while BAL GM remained negative. In another who developed HRCT evidence of IPA with a positive BAL GM, the EBC GM was positive four weeks earlier. GM was negative in all but one of the serum and EBC samples of patients with possible, unclassified or no evidence of IPA.

Conclusions: GM can be detected in EBC, and follows the same trend as in serum. It may even predate GM detection in BAL fluid, thereby obviating the need for more invasive investigations. Elevated levels early in the course of neutropenia may represent infection and could be applied to the employment of pre-emptive treatment strategies.


S127 VARIATION IN COLONIAL MORPHOTYPE AND ANTIBIOTIC SUSCEPTIBILITY IN PSEUDOMONAS AERUGINOSA IN SPUTA FROM PATIENTS WITH NON-CYSTIC FIBROSIS BRONCHIECTASIS AND ITS IMPACT ON ANTIBIOTIC SUSCEPTIBILITY TESTING

M. I. Gilmour, S. Sundaram, C. R. Laughton, C. Haworth, D. Bilton, J. E. Fowler. Papworth Hospital, Cambridge, UK

Background: P. aeruginosa is a common cause of infection in bronchiectasis. In chronic P. aeruginosa infection in cystic fibrosis (CF), various colonial forms (morphotypes) and different antibiotic susceptibilities are present in single sputa. Susceptibility testing is poorly reproducible, with resistant isolates missed. There is little information on phenotypic variability in P. aeruginosa in patients with non-CF bronchiectasis.

Aim: To investigate the variability of antibiotic susceptibility and morphotype of P. aeruginosa from sputa of patients with bronchiectasis and compare this with other pseudomonal infections.

Methods: P. aeruginosa was isolated from sputa from 31 patients, mean age 63 (38-81) years with well-characterised bronchiectasis, either stable (23) or during acute exacerbation (8). The morphotype of each isolate was assessed by size, texture, colour and mucoidity. Antibiotic susceptibility testing of four examples of each morphotype to 12 antibiotics was performed using disc diffusion and the zone of inhibition was measured. This variability in susceptibility was compared with control P. aeruginosa from 9 skin swabs and 7 sputa from ventilated patients without bronchiectasis. Antibiotic susceptibility was also tested by the standard method used in a hospital diagnostic laboratory.

Results: Control P. aeruginosa isolates were all classical morphotype. The maximum difference in zone diameter between four isolates from each sample was 4 mm. A single morphotype was present in 18 bronchiectasis sputa and mixed morphotypes in 13. In six bronchiectasis sputa, maximum variation in zone diameter was up to 23 mm; others had wider variation, up to 24 mm, between isolates of the same morphotype in one sputum. There was more variability in antibiotic susceptibility where mixed morphotypes were present. Similar variability was seen in sputa from stable patients and during exacerbations. Routine laboratory methods missed resistance in 10 patients with bronchiectasis.

Conclusion: Some patients with bronchiectasis have a uniform population of P. aeruginosa; others show variation in morphotype and susceptibility, similar to CF. Routine antibiotic susceptibility testing may miss resistance once the population is so diverse. The natural epidemiology of P. aeruginosa in non-CF bronchiectasis needs further study.

S128 LUNG FUNCTION DOES NOT DECLINE IN AN EIGHT-YEAR SURVEILLANCE STUDY OF BRONCHIECTASIS PATIENTS ATTENDING A REGIONAL SPECIALIST CENTRE


Introduction: There are limited data demonstrating the long-term outcome of patients, in terms of lung function in adult non-cystic fibrosis bronchiectasis. There is debate (Evans, 1996; Davies, 2006) whether patients colonised with pseudomonas have a faster decline in lung function than non-pseudomonas colonised patients. Evans (1996) confirmed the association of chronic pseudomonas aeruginosa colonisation with poorer and faster decline in lung function. Davies (2006) concluded that infection with pseudomonas aeruginosa was a marker of disease severity but not linked with an accelerated decline in lung function.

Methods: This study evaluates the rate of decline in lung function over an 8-year period in patients attending a bronchiectasis clinic. All patients in the RCT of nurse- versus Dr-led care (Sharples, 2002) were approached. In 1998, 80 patients were recruited, 54 females and 26 males, mean age 58.76 (SD 13.9) years, and defined as having chronic infection with pseudomonas or not. At each yearly point of review lung function data were collected. At study end (2006) 12 patients had died and 11 had not been reviewed to their local primary care teams.

Results: Baseline lung function in 1998, n=80, mean FEV1%pred 69.7% (SD 20) and mean FVC%pred 82.2% (SD 16.9). 1998–2006: an average increase in FEV1%pred of 1.2% (SD 1.8%) and FVC%pred average increase of 2.1% (SD 1.4%) which was statistically significant (p<0.01).

Subanalysis of lung function of patients colonised (n=178) and non-colonised with pseudomonas aeruginosa (n=62) was undertaken. This analysis showed there a significant difference (p<0.003) in baseline lung function in the pseudomonas cohort (FEV1%pred 60% (SD 18.3) versus non-colonised patients (FEV1%pred 72.5% (SD 19.7)). There was no statistically significant difference between the groups in the rate of improvement in lung function (p=0.35). Pseudomonas cohort: an increase in FEV1%pred of 0.7% per year (SD 2.0) and FVC%pred of 1.8% per year (SD 1.7). Non-pseudomonas cohort: an increase in FEV1%pred of 1.3% (SD 1.8) and increase in FVC%pred of 2.1% per year (SD 1.4%).

Conclusions: Patient with bronchiectasis can be stabilised and decline in lung function prevented, regardless of pseudomonas colonisation, with aggressive management and education of the patient.
Management and organisation of respiratory services

[S132] POTENTIAL ADVANTAGES OF AN INITIAL TELEPHONE CONSULTATION IN THOSE REFERRED FOR A SPECIALIST RESPIRATORY OPINION

C. Darlow1, N. J. Roberts1, G. Wilson2, M. R. Partridge1. 1Imperial College London, NHLI Division at Charing Cross Hospital; 2Charing Cross Hospital, Department of Respiratory Medicine, London, UK

Background: Telephone consultations have been shown to be an efficient method of following up over 30% of respiratory outpatients. An initial telephone conversation with new patients has the potential to permit better selection and timing of investigations and reduce the number of hospital attendances by patients. This study was designed to determine how accurately necessary investigations could be determined from the GP's referral letter and to look at how often follow-up patients currently attend the hospital before receiving a diagnosis.

Methods: Sixty five sequential follow-up patients were interviewed and their notes and investigation records examined to determine how many times they had attended for a consultation or for investigations before they received a firm diagnosis. For 28 new referrals the consultants were asked to list the investigations they thought would be necessary; (1) after reading the letter from the referring GP; (2) after they had taken the history from the patient; and (3) after they had examined the patient. A significant change between (1) and (2) and no change after (3) would suggest a potential advantage to taking the patients’ history over the telephone.

Results: Patients attended the hospital a mean 2.3 times before receiving a diagnosis and management plan. 44% (94/213) of investigations were not performed on the same day as the patients’ clinic visit. With pre-planning, potentially 76% (71/94) of those investigations could have been performed during the same hospital visit. Reading the GP referral letter alone was not sufficient to predict the investigations needed. The clinical history altered the investigations ordered in 64.3% (18/28) of patients. Subsequent clinical examination only rarely led to further changes.

Conclusions: This study suggests that patients being referred to a respiratory outpatient clinic have had several attendances before receiving a diagnosis and management plan. Taking the history by telephone has the potential to permit accurate selection of the investigations that the patient may need. These investigations could then be arranged before, or synchronously with, the first face-to-face consultation and reduce the number of hospital attendances.

[S133] AN AUDIT OF PHYSIOTHERAPY AND OCCUPATIONAL THERAPY SERVICES TO MEDICAL PATIENTS IN THE EMERGENCY PORTALS AT UNIVERSITY HOSPITALS OF NORTH Staffs

E. C. Brown, S. Tudor Ansell, J. Asher. University Hospitals of North Staffordshire, Stoke on Trent, UK

Background: A process-mapping exercise of the medical patient’s journey in relation to therapies highlighted delays in the initiation of therapies on the medical wards at University Hospitals of North Staffordshire (UHNS). Data reflected an average delay in referral to Physiotherapy of 6 days and 10 days for Occupational Therapy. As a result therapies tended to run consecutive rather than in parallel to medical intervention, resulting in increased lengths of stay (LOS). This led to delayed discharge or patients being discharged without therapy interventions being complete. Adverse incident forms and complaints highlighted the resulting unsafe discharges. A Physiotherapy and Occupational Therapy service to the emergency...
portals (Accident and Emergency Dept, Emergency Assessment Unit and Medical Admissions Unit) was piloted in order to evaluate the impact of early therapy intervention on discharge planning. Respiratory, neurological and mobility patients were assessed in these admission units and therapy intervention initiated earlier. Clinicians facilitated the safe discharge home of patients from the units or referred patients to more appropriate care providers, such as intermediate care or supported early discharge services (COPD services). Admitted patients were referred directly to ward therapists following an admission, thus reducing the number of steps in the referral process, reducing the delay in therapy intervention.

The pilot data proved that the service facilitated direct patient discharge from the emergency portals and markedly improved the signposting of patients to other services for ongoing rehabilitation, as well as ensuring that there was no delay in referral to therapies once the patient is admitted to a ward area. During the pilot 52% (114/200) of patients referred to therapies in these units were discharged, that otherwise would have been admitted onto a ward with LOS for respiratory and mobility patients being reduced by three days. Service improvement (SIP) concluded that the impact of therapies with regards to preventing admissions, managing variation in discharge and increasing the reliability of therapeutic interventions through a “care bundle” approach (HIC 3, 4 and 6) had been significant.

Method: SIP and Therapies re-audited this service over a three-month period (December 2005–February 2006) to ensure that this service continued to deliver on its targets of: safe patient discharges, reduced LOS and admission avoidance. An audit tool collated data including referral date, reason for referral, therapy intervention required, reason for admission, discharge date and destination. Patients were followed up after three months to ascertain if they had required further admissions post-therapy discharge. Project controls were adopted to ensure the project collated valid data. This included signatures from doctors stating “this patient would have been admitted if it were not for the presence of therapies” in the emergency portals.

Results: During the audit 308 referrals were made with 206 (66%) admissions avoided as a direct result of therapies intervention; 39% (122/308) were discharged home and 27% (84/308) discharged to intermediate care. 83% of patients referred were assessed in 4 h. Of the 102 (34%) admissions 16 (15%) were admitted due lack of intermediate care bed (ICB) availability and 10 (10%) were awaiting social services. Average emergency portals re-admission rate pre-therapy services was four visits per patient in the three-month period post-discharge. Post-therapy intervention this dropped to an average of 1.9. A total of 13 patients required emergency respiratory physiotherapy and 62 patients overall benefited from early respiratory physiotherapy intervention. Process-mapping following implementation of the service to MAU and EAU has shown that therapy referrals are communicated more efficiently as treatment is now initiated on the day of admission for physiotherapy and day two for OT on the medical wards. Early initiation of therapy referrals has led to therapies intervention occurring alongside medical intervention, so that when a patient is medically fit for discharge they are physically safe for discharge and can be referred to a more appropriate care provider, such as ICB. This has facilitates better management of variation in discharge planning and reduced length of stay (HIC 3) while ensuring equity in therapy provision.

Conclusion: The impact of therapies in the emergency portals continues to have a significant impact upon preventing admissions, reducing LOS, managing variation in discharge and increasing the reliability of therapeutic interventions through a “care bundle” approach (HIC 3, 4 and 6). These findings support the investment in therapy services in the emergency portals as it is of financial benefit to both primary and secondary care providers while also enhancing the patient’s quality of care.

Aims: To establish baseline level of recorded severity of COPD by FEV1% predicted mapped to deprivation across the whole PCT population and by practice cluster. To establish baseline levels of maintenance treatments for COPD, specifically long-acting bronchodilators (LABAs), anticholinergics and inhaled corticosteroids (ICS).

Methods: We retrospectively analysed the baseline data collected from the COPD register: FEV1% predicted, smoking status, BMI, current medication. We are currently analysing the number of unscheduled COPD admissions from the Department of Health hospital episode statistics data for the year 2006/7. Outcomes for individual practices, aggregated to practice cluster, will be analysed using multiple regression techniques, adjusting for the demographics of the practices.

Results: Data from the preliminary analysis are reported; GOF prevalence 2.3% n = 5501, (range 0.1%–4.7% across all 59 practices). Of 38 practices with available data for analysis: 4344 COPD patients (48.5% male); mean age of 68 years; 41% current smokers, 12.5% never smoked; mean BMI 27 kg/m2; spirometry in the last 15 months recorded on 2577 (57%) patients; mean %predicted FEV1, 56%; severity by FEV1% predicted values, 50% mild, 30% moderate, 9% severe (NICE, 2004); 11% had an FEV1%predicted value >80. Of 4534 patients, 29% received ICS without LABA; 7% received LABA alone; 42% received both ICS and LABA; 42% were receiving anticholinergics (both short and/or long-acting); % patients who received both ICS and LABA 32% mild, 47% moderate, 58% severe COPD.

Conclusions: In this population prevalence of COPD is higher than the national average and more common in females. COPD is recorded in 12.5% of never smokers and in 11.1% of the population with FEV1 >80% predicted. Combined therapy with ICS/LABA is prescribed more frequently in those with moderate to severe disease. Further analysis of these data will provide valuable information for planning service delivery to meet the health needs of this population.

S134 BENCHMARKING CHRONIC OBSTRUCTIVE PULMONARY DISEASE ACROSS AN INNER CITY PCT-WIDE POPULATION

J. A. Roberts, N. Dier Bakerly. Salford Royal Foundation Trust and Salford PCT, UK

Introduction: Our primary care trust (PCT) population (n = 236 919) has high levels of social deprivation, health inequalities and COPD and comprises 59 practices, structured as eight practice-based commissioning clusters. The COPD register structures COPD consultations in line with current guidelines using a standardised template that sits within existing GP computer systems across the PCT. Anonymised data are collected remotely on three-monthly intervals. We hypothesised that practices clustered in areas of highest deprivation would have higher rates of COPD, more severe disease and a higher use of NHS resources.

Aims: To establish baseline level of recorded severity of COPD by FEV1% predicted mapped to deprivation across the whole PCT population and by practice cluster. To establish baseline levels of maintenance treatments for COPD, specifically long-acting bronchodilators (LABAs), anticholinergics and inhaled corticosteroids (ICS).

Methods: We retrospectively analysed the baseline data collected from the COPD register: FEV1% predicted, smoking status, BMI, current medication. We are currently analysing the number of unscheduled COPD admissions from the Department of Health hospital episode statistics data for the year 2006/7. Outcomes for individual practices, aggregated to practice cluster, will be analysed using multiple regression techniques, adjusting for the demographics of the practices.

Results: Data from the preliminary analysis are reported; GOF prevalence 2.3% n = 5501, (range 0.1%–4.7% across all 59 practices). Of 38 practices with available data for analysis: 4344 COPD patients (48.5% male); mean age of 68 years; 41% current smokers, 12.5% never smoked; mean BMI 27 kg/m2; spirometry in the last 15 months recorded on 2577 (57%) patients; mean %predicted FEV1, 56%; severity by FEV1% predicted values, 50% mild, 30% moderate, 9% severe (NICE, 2004); 11% had an FEV1%predicted value >80. Of 4534 patients, 29% received ICS without LABA; 7% received LABA alone; 42% received both ICS and LABA; 42% were receiving anticholinergics (both short and/or long-acting); % patients who received both ICS and LABA 32% mild, 47% moderate, 58% severe COPD.

Conclusions: In this population prevalence of COPD is higher than the national average and more common in females. COPD is recorded in 12.5% of never smokers and in 11.1% of the population with FEV1 >80% predicted. Combined therapy with ICS/LABA is prescribed more frequently in those with moderate to severe disease. Further analysis of these data will provide valuable information for planning service delivery to meet the health needs of this population.

S135 THE FIRST SIX MONTHS OF HOSPITAL AND COMMUNITY-BASED OXYGEN ASSESSMENT SERVICE FUNDED BY A PRIMARY CARE TRUST

K. Pye, C. Stevens, A. Kwok, L. Davies. University Hospital Aintree, Liverpool, UK

Background: In 1999 guidelines for domiciliary oxygen services were published; however deficiencies remained. The Clinical Component for the Home Oxygen Service 2006 recommends that assessment for home oxygen should be the responsibility of a respiratory specialist in secondary care. Funding was devolved to the primary care trusts (PCTs). At Aintree Chest Centre, Liverpool, a nurse-led oxygen assessment service taking referrals from secondary care, on an ad hoc basis, has been operational for five years. In October 2006, Sefton PCT funded an oxygen assessment service to allow assessment of all patients receiving domiciliary oxygen within that PCT.

Methods: In October 2006, with information from Air Products, Sefton PCT established a database of all patients receiving oxygen. 380 patients were identified as receiving either long-term (LTOT) or short burst (SBOT) oxygen therapy.

Results: After initial review of the 304: 81 had died since the database was received, 18 palliative care, 11 receiving O2 with IV, 8 cluster headaches, 13 are still waiting appointment, 4 repeatedly DNA’d, 4
declined appointment, 4 moved away from the area leaving 161 (68 male) assessed. All patients were reviewed by experienced respiratory nurse specialists according to accepted guidelines, and r either in a hospital or primary care outreach oxygen clinic, or at home [n = 17]. 86/161 (53%) patients, 54 female, mean (SD) 73 (10) years were outside the criteria for either long-term oxygen therapy (LTOT) or ambulatory oxygen. Of these 70 (81%) had COPD, 5 (6%) had asthma, 5 (6%) pulmonary fibrosis, 3 (3%) obstructive sleep apnoea, 3 (3%) heart disease. Following assessment, four patients on SBOT were subsequently prescribed LTOT.

Conclusions: Nurse-led oxygen assessment is deliverable in the hospital and community setting. Around half of patients receiving domiciliary oxygen are currently receiving this unnecessarily. In our practice, results of assessments were sent to all GPs and the decision to remove the oxygen equipment was left to individual practitioners. We will review whether our recommendations are acted upon and would like to move to a service in which, apart from emergencies, patients are assessed for oxygen therapy before HOOF completion.

1. RCP. Domiciliary oxygen therapy services, clinical guidelines and advice for prescribers. A report by the Royal College of Physicians.


S136 AN INTEGRATED HOME OXYGEN SERVICE SAVES £130,000 PER YEAR ON HOME OXYGEN TARIFFS

C. Deeming, L. Ward, J. Townsend, G. Lingam, S. Ansari, D. Powrie, A. Davison. Southend University Hospital, Essex, UK

In February 2006 a new home oxygen service was introduced to improve the assessment of patients on oxygen and allow access to newer technologies such as ambulatory oxygen. Oxygen is provided following completion of a home oxygen order form and is allocated a tariff according to delivery device and usage. There are 54 tariffs ranging from 34 p/day (standard portable cylinder < 2 l/min, <1 h/day) to £27.90/day (long-term oxygen therapy plus standard portables > 6–8 l/min, > 4 h/day). In South East Essex there are 554 patients receiving home oxygen with an annual cost of £668,546.

South East Essex PCT and Southend Acute Trust set up an integrated home oxygen service comprising four respiratory consultants, one respiratory physiotherapist and three respiratory nurse specialists (one community-based). The role of this service is to identify patients requiring home oxygen, to provide formalised oxygen assessments and home or outpatient monitoring once oxygen is ordered.

In order to investigate high oxygen order costs 22 patients with a tariff of more than £5/day were identified from the BOC monthly statement of December 2006 for review. Of these, four had the correct order, three no longer required home oxygen, one was unwilling to change his order and 14 were re-categorised to a lower tariff. This resulted in an annual saving of £76,993. Over the following six months during routine follow-up a further 43 patients had their home oxygen order re-categorised. Eight no longer required home oxygen and 35 were re-categorised with an annual saving of £52,819.

Re-evaluation of patients on home oxygen resulted in a cost saving of £129,812/year. A saving of £76,993 was made by targeting just 22 patients on the highest tariff.

S137 COSTS IMPLICATIONS OF OXYGEN PRESCRIPTION WITHIN A PCT, IF NOT SUPPLIED BY A SPECIALIST RESPIRATORY TEAM


Introduction: In February 2006, oxygen services changed over to a single provider system, The British Thoracic Society (BTS) working group on Home Oxygen Services published a guidance document in January 2006 on the clinical standards for assessment and prescription of oxygen therapy. Although GPs could still prescribe all forms of oxygen, long-term oxygen therapy (LTOT), short burst oxygen therapy (SBOT) and ambulatory oxygen on the HOOF (Home Oxygen Order Form), the BTS working group recommends that LTOT and ambulatory oxygen should be carried out by specialist respiratory teams, for assessment and ongoing follow-up. This paper aims to look at primary care trust (PCT) cost implications when oxygen is not even prescribed by a specialist respiratory team.

Method: Between April and May 2006, Brent PCT commissioned a small specialist team headed by the Consultant Physiotherapist, to evaluate all the oxygen prescriptions, with the aim of: (1) converting all Emergency Orders to regular tariff [n = 17]; (2) converting all patients on FP10 prescriptions to ambulatory oxygen (by local pharmacists) over to the HOOF system [n = 84]. However, at the time of reviewing the FP10 patients, 28 had been converted via HOOF forms by GPs and 23 were not appropriate for prescriptions. Consequently the final number of FP10 patients to covert to the HOOF system by the respiratory specialist team was 32. All oxygen prescriptions were not evaluated for quality of prescription, as this was a simple cost exercise. Ambulatory oxygen prescriptions were not addressed. Compiling an accurate database on patients within Brent who were receiving oxygen required the comparison of patients’ names from the previous oxygen provider, the GP practices and the Brent Prescribing Team. Emergency tariff patients’ prescription data were obtained from the provider, and this prescription was cancelled and converted into a normal tariff. The respiratory specialist team contacted the FP10 patients and also occasionally their GP to discuss their oxygen usage before completing a HOOF.

Results: Emergency orders [n = 17]; days on Emergency Tariff, 8– 129 days; FP10 patients GP completed HOOF = 28; not appropriate = 24; final number patients to convert to HOOF = 32. HOOF prescription on FP10 patients; GP prescription n = 28 LTOT = 20, SBOT (concentrators) = 5, SBOT (cylinders) = 3; Specialist Team n = 32 LTOT = 3, SBOT (concentrators) = 3, SBOT (cylinders) = 26. Cost of FP10 patients/year: SBOT (cylinders) n = 29 £4,128.15; SBOT (concentrators) n = 8 £3,533.20; LTOT n = 23 £1,18,836.95. Actual cost saving for 2006/7 by: cancelling emergency orders and replacing with normal tariff HOOF n = 17, £54,131.46; prescribing cylinders vs concentrators for SBOT (saving of £299.30/patient/year) n = 29, £8,679.70. Actual cost of oxygen prescriptions: total number of oxygen prescriptions in 2006/7 = 175. April 2007 = 280 (increase of 60%); total cost of oxygen prescription for 2006/7 = £1,753,864.09 (DH funding = £84,000).

Analysis: There is a considerable cost saving in cancelling emergency prescriptions: total number of oxygen prescriptions in 2006/7 = 175. April 2007 = 280 (increase of 60%); total cost of oxygen prescription for 2006/7 = £1,753,864.09 (DH funding = £84,000).

Conclusion: Respiratory specialist teams have the knowledge and expertise to assess the need for oxygen in chronic respiratory patients. Oxygen is costing PCTs much more than the funding supplied by the DH; therefore the need for accurate prescription is essential. Incorrect prescription of oxygen is not only costly, it also has serious implications for our patients. Commissioning respiratory specialist teams to provide assessment and follow-up of oxygen prescription within the PCT could have major impacts on cost and improve the appropriateness of prescription and subsequent management of these patients enormously.

S138 QUADRICIPES MUSCLE ENDURANCE AND ITS RELATION TO PHYSICAL ACTIVITY AND EXERCISE CAPACITY IN COPD

S. A. Sathyapala1, G. S. Marsh1, N. S. Hopkinson1, J. Maxham2, M. I. Polkey1.

1Royal Brompton Hospital; 2King’s College Hospital, London, UK

Introduction: Quadriceps muscle dysfunction appears to correlate with exercise capacity and activity in COPD. However, quadriceps endurance (Qend) has previously been assessed with volitional tests and activity with questionnaires which quantify activity poorly. We have described a non-volitional test of Qend using repetitive magnetic stimulation. Aim: To investigate, in COPD patients and healthy controls, relations between Qend and physical activity and exercise capacity in COPD.

Methods: Thirty GOLD Grade II-IV COPD patients and 13 healthy controls had lung function, arterialised capillary earlobe blood gases and right leg isometric quadriceps maximal voluntary contraction (MVC) measured. Right leg Qend was assessed with a magnetic stimulator (Magstim, UK) powered to generate 20% of MVC, delivering 50 trains of 30 Hz magnetic stimulation with a 0.4 duty cycle through a mat coil over the muscle body. Time until the force-time product (FTP) fell below 80% of the initial FTP (FTP0) was noted. Activity was measured with a tri-axial accelerometer (Dynaport, Leidschendam, The Netherlands) worn for 12 h/day for 2 days and the results averaged. Exercise capacity was assessed by symptom-limited incremental cycle ergometry with metabolic testing and a 6 minute walk test (6MW).

Analysis of group differences was performed using the unpaired Student t-test.
Abstract S138

<table>
<thead>
<tr>
<th>COPD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (9) 21M 9F</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>38 (3)**</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>58 (10)**</td>
</tr>
<tr>
<td>TLco (% predicted)</td>
<td>42 (18)**</td>
</tr>
<tr>
<td>PaO2</td>
<td>98 (1.3)**</td>
</tr>
<tr>
<td>MVC (kg)</td>
<td>27 (10)*</td>
</tr>
<tr>
<td>Qend T80 (s)</td>
<td>65 (10)**</td>
</tr>
<tr>
<td>Sitting time (min in 12 h)</td>
<td>45 (27)*</td>
</tr>
<tr>
<td>Siting time (min in 12 h)</td>
<td>330 (90)</td>
</tr>
<tr>
<td>Movement intensity (M, m/s²)</td>
<td>1.65 (0.23)*</td>
</tr>
<tr>
<td>6MW distance (% predicted)</td>
<td>71 (22)**</td>
</tr>
<tr>
<td>Peak VO2 (% predicted)</td>
<td>44 (18)**</td>
</tr>
</tbody>
</table>

Mean (SD) values (median and median absolute deviation).
***p = 0.0001; **p = 0.0004; *p<0.05 indicate significant group differences.
The date in italics are not normally distributed.

EMPHYSEMA SEVERITY IS ASSOCIATED WITH ARTERIAL STIFFNESS, A MARKER OF CARDIOVASCULAR RISK


Rationale: More patients with COPD die from cardiovascular causes than from respiratory, and patients with COPD have increased morbidity and mortality from coronary heart disease.

Objective: To identify whether the extent of arterial stiffness in patients with COPD is associated with the severity of emphysema.

Methods: We measured pulse wave velocity (a validated measure of arterial stiffness), blood pressure, smoking pack years, glucose, cholesterol and C-reactive protein and assessed emphysema using quantitative CT scanning in a subgroup of 73 patients with COPD.

Results: We found that emphysema severity was associated with arterial stiffness (r = 0.47, p<0.001, fig A), more closely than FEV1% predicted (fig B). The association was independent of smoking, age, sex, FEV1% predicted, highly sensitive C-reactive protein and glucose concentrations, cholesterol/HDL ratio, and oxygen saturations.

Conclusion: This is a similar figure to that observed in patients with chronic rheumatoid disease and chronic renal and heart failures. The suggestion is that the observed anaemia is a consequence of systemic inflammatory mediators. No studies have yet been reported from the UK and no studies have to date compared the prevalence of anaemia in COPD patients in the stable clinical state with those during an exacerbation when systemic inflammation may be significantly increased.

Method: We designed a retrospective, observational study to explore the prevalence of anaemia in a cohort of COPD patients measured both in the stable clinical state and also during a hospitalised exacerbation. A cohort of 1325 patients with a coded primary discharge diagnosis of COPD admitted to a University Hospital in London from January 2004 to December 2005 was selected. Of these, 458 patients had spirometry results available that could be used to confirm the presence of significant airflow obstruction. 147 of these patients were further excluded from...
but not statistically significant, correlation between FEV1% predicted and level and CRP in both stable and exacerbation states. However there was no significant correlation between Hb with the degree of anaemia. During stable state, haematocrit was low in 15.3% of females and 14.3% of males. During exacerbation, it was significantly lower; 21% in females and 25% of males. This has not changed significantly during exacerbations. During stable state, haematoctrit was low in 15.3% of females and 14.3% of males while during exacerbation, it was significantly lower; 21% in females and 27.4% in males. In both stable and exacerbation states we found that haematocrit, albumin and to a lesser degree creatinine correlated positively with the degree of anaemia (p<0.001, p<0.005 and p<0.031 respectively). However there was no significant correlation between Hb level and CRP in both stable and exacerbation states. We did find some, but not statistically significant, correlation between FEV1% predicted and the degree of anaemia.

Conclusion: This study has shown a significant prevalence of anaemia in our stable patients, albeit a lower level than reported in the US series. During an exacerbation the prevalence of anaemia rises, with the haematocrit dropping significantly. The fall in Hb and haematocrit were both more prominent in the men studied than the women. It is notable that we found no significant correlation between all levels of Hb and the measured FEV1% in both stable and exacerbation states.


S141 COPD IS ASSOCIATED WITH ABNORMAL VASCULAR ENDOTHELIAL FUNCTION


Introduction: Patients with COPD have increased cardiovascular morbidity and mortality, independent of traditional risk factors including smoking (Sin et al. Circulation 2003). Systemic inflammation is a well-recognised feature of COPD and inflammation plays a central role in the pathogenesis of atherosclerosis. We have previously shown that acute systemic inflammation causes impairment of vascular endothelial function (Chia et al, J Am Coll Cardiol 2003). Thus we believe that patients with COPD will have abnormal endothelial function which may contribute to their increased cardiovascular risk.

Methods: Twelve male ex-smokers with COPD and seven healthy ex-smokers were recruited for this pilot study with no history of cardiovascular disease, diabetes or inflammatory disorders, and not taking statins, ACE inhibitors or anti-inflammatory drugs. These groups were matched for age and smoking history. Living venous occlusion plethysmography, we measured change in forearm blood flow following infusion of the endothelium-dependent vasodilator acetylsalicylic acid (5–20 μg/min) and the endothelium-independent vasodilator sodium nitroprusside (2–8 μg/min) into the brachial artery.

Results: There was no difference in resting forearm blood flow between patients and controls. There was a dose dependent increase in forearm blood flow in response to both vasodilators (p<0.0001), however the response to acetylsalicylic acid was reduced in COPD patients (peak response, 5.2 (3.1) vs 7.5 (2.8) ml/100 ml of tissue/min; two-way ANOVA p=0.01). There was no difference in sodium nitroprusside mediated vasodilatation (peak response, 9.5 (1.8) vs 10.2 (2.1) ml/100 ml of tissue/min; two-way ANOVA p=0.30) see fig.

Conclusion: In this preliminary study we have shown that patients with COPD have impaired endothelial vasomotor function compared to controls matched for age, sex and smoking history. In ongoing studies, we will determine whether other aspects of vascular function including endogenous fibrinolysis are altered in COPD.
Pulmonary rehabilitation in practice

**S143** CAN SENSEWEAR ACTIVITY MONITORS DETECT SLOW SPEEDS OF WALKING IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE?

R. D. Smith¹, L. Sewell², O. Cain², S. Singh², M. Morgan². ¹Coventry University; ²University Hospitals of Leicester NHS Trust, UK

**Background:** One aim of pulmonary rehabilitation is to increase the daily physical activity for patients with COPD. The SenseWear activity monitor (BodyMedia Inc, Pittsburgh, PA, USA) is a device that measure activity in energy expenditure (kcal) and metabolic equivalents (METS). It is a small, light device worn on the back of the upper arm. The usefulness of the SenseWear activity monitor has not been established in patients with COPD at their slow walking speeds. We aimed to investigate if SenseWear activity monitors can accurately measure activity at slow walking speeds and discriminate between different speeds using the incremental shuttle walk test (ISWT) in patients with COPD.

**Method:** Twenty-six patients (18 male) mean (SD) FEV1 47.12 (26.21)% predicted, age 71 (9) years, BMI 26.03 (5.32) kg/m² and median MRC grade 3 (range of 1–5) were recruited from the pulmonary rehabilitation programme. Patients wore the activity monitor 2 min prior to completing the ISWT. 11 subjects repeated the test. Outcome measures reported are minute-by-minute METS. To explore the difference between speeds ANOVA and Tukey post hoc was employed; repeatability was examined with the intra-class correlation (ICC).

**Results:** All 37 ISWTS completed the first level (at 1.8 km/h) of the ISWT, 31 of those completed level 2 (2.44 km/h), 28, 20, 16 and 11 completed levels 3 (3.03 km/h), 4 (3.63 km/h), 5 (4.25 km/h) and 6 (4.86 km/h) respectively. Mean ISWT was 201 (127) m (range 30–560 m). An increase in activity was recorded with an increasing walking speed (fig 1). ANOVA identified a statistically significant difference between METS values between the walking speeds (p<0.005). Post hoc analysis identified that each walking speed generated a statistically significant difference for MET values compared to all of the speeds (p<0.005) except between 3.63 km/h and 4.25 km/h (p=0.019). ICC was r=0.95 (p<0.005).

**Discussion:** The SenseWear activity monitor can detect activity at slow speeds of walking and can also distinguish differences in estimated energy expenditure at different walking intensities employed in the ISWT. The SenseWear activity monitor is an acceptable method of measuring activity in patients severely disabled by COPD.

**Abstract S143**

| Speed (km/h) | Mean (95% confidence interval) of activity monitor
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.80</td>
<td>0.5 (0.3–0.8)</td>
</tr>
<tr>
<td>2.44</td>
<td>3.0 (2.8–3.2)</td>
</tr>
<tr>
<td>3.03</td>
<td>3.6 (3.4–3.8)</td>
</tr>
<tr>
<td>3.63</td>
<td>4.2 (4.0–4.4)</td>
</tr>
<tr>
<td>4.25</td>
<td>4.8 (4.6–5.0)</td>
</tr>
<tr>
<td>4.86</td>
<td>5.5 (5.3–5.7)</td>
</tr>
</tbody>
</table>

Abstract S143 Change in mean METS as speed increases.

**S144** ELIGIBILITY FOR AMBULATORY OXYGEN ASSESSMENT CHANGES FOLLOWING A PULMONARY REHABILITATION PROGRAMME

J. A. Smith¹, N. I. O’Kelly¹, E. Hill², B. J. Smith². ¹Primary Care Trust, Lincolnshire; ²Birmingham Medical School, UK

**Background:** The provision of ambulatory oxygen within the National Health Service is a relatively new option for patients with chronic respiratory disease. Consequently, there are few examples of integrated referral pathways for assessment of suitability for this therapy. National guidelines exist that define the eligibility criteria for ambulatory oxygen assessment (SpO2 drops by >4% and to below 90% from baseline), and recommend that this should occur following completion of a pulmonary rehabilitation (PR) programme. Despite this, many patients currently receive ambulatory oxygen therapy (AOT) without an assessment. This retrospective observational quantitative study investigated the impact of PR on the oxygen saturation in patients with chronic obstructive pulmonary disease (COPD).

**Method:** Patients chosen for this study had completed a PR programme between 2005 and 2007 (n = 177). To determine eligibility for AOT assessment, all patients had pulse oximetry measurements performed before and after an endurance walking test both at the start and on completion of the PR programme. Looking at the retrospective data, patients were divided into four groups depending on their eligibility at baseline and on completion of the PR programme (see table).

**Results:** See table.

**Discussion:** Nineteen patients (10.7%) who did not meet the eligibility at baseline subsequently did after the PR intervention. These patients would not have been put forward for formal AOT assessment and thus, may have lost out on the potential benefit of receiving this therapy. Also 12 patients (6.8%) who did meet the eligibility criteria at baseline subsequently did not after completion of the programme. These patients did not require referral for formalised AOT assessment. At a time when financial balance within health economies is paramount, having an efficient pathway to ensure that the correct patients are referred to formalised AOT assessment services is sensible. Incorporating baseline and final assessments of SpO2 within a PR programme may provide a cost efficient solution to this challenge.

**Conclusion:** The above findings would seem to concur with the AOT guidelines and support the recommendation that patients should be offered PR prior to AOT assessment.

<table>
<thead>
<tr>
<th>Ambulatory O2 assessment</th>
<th>n (n = 177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria met at baseline and completion</td>
<td>52</td>
</tr>
<tr>
<td>Criteria not met at baseline and completion</td>
<td>94</td>
</tr>
<tr>
<td>Criteria met at baseline but not at completion</td>
<td>12</td>
</tr>
<tr>
<td>Criteria not met at baseline but met at completion</td>
<td>19</td>
</tr>
</tbody>
</table>

**Abstract S144**

**S145** DOES PULMONARY REHABILITATION IN PATIENTS WITH ‘NON-COPD’ CHRONIC RESPIRATORY DISEASE CONFER SIMILAR BENEFITS TO THAT IN PATIENTS WITH COPD?

I. J. Benton¹, E. Hilsden¹, T. Lines¹, D. J. Shale², C. E. Bolton². ¹Llandough Hospital; ²Respiratory Medicine, Cardiff University, UK

**Background:** Improved exercise tolerance and quality of life following pulmonary rehabilitation (PR) in patients with COPD is proven through large randomised controlled trials. The gains in other chronic respiratory conditions are less clear, with reports suggesting some benefit. However, these conditions have differing pathophysiology, responses to exercise and nature of symptomatic exacerbations. We explored the effect of PR in different patient subgroups.

**Method:** We reviewed patients entering PR, comprising a standard 18 session (3/week) course including education, exercise prescription, relaxation and goal setting, over the last 16 months. At the start and completion of PR, an incremental shuttle walk test (ISWT), St George’s Respiratory Questionnaire (SGRQ) and hospital anxiety depression score (HAD) score are performed. Patients were subdivided into “COPD” or “non-COPD”.

Abstract S144
Results: Over the observation period, 171 patients were entered for PR of which 166 commenced (96 male), mean (range) age 67.6 (39–88) years. There were 144 with a primary diagnosis of COPD and 22 had “non-COPD” chronic respiratory disease; 12 ILD and 10 bronchiectasis. The two groups had similar SGRQ scores and HAD scores (Table 1). There was a trend for shorter ISWT in the non-COPD group (p = 0.06) and the non-COPD group (27%) tended to drop out more compared with COPD (14%), p = 0.1. The gain in ISWT and improvements in SGRQ domains and the total score and the HAD scores were similar in both groups (see Table 2).

Conclusion: Determining the benefit of PR in different disease populations is important both for the patient and service development and planning. The groups had similar baseline measurements and improvements were comparable. These data suggest encouraging patients with a range of chronic respiratory disease to enter PR. There is a need to determine why the drop out rate for the non-COPD patients is greater, which may be related to intercurrent infections in bronchiectasis or not meeting the expected goals.

Acknowledgement: With thanks to the Pulmonary Rehabilitation Staff.


S146 ASSESSMENT OF PULMONARY REHABILITATION PROGRAMME WITHOUT THE PHYSICAL TRAINING

S. Ives-Lappin 2, L. Visker 2, W. Mitchell 2, S. Martin 2, R. C. Butey 1. 1Hinchingbrooke Hospital NHS Trust, Huntingdon, UK; 2Cambridgeshire Primary Care Trust, UK

Introduction: Although the benefits of pulmonary rehabilitation (PR) are now well recognised, most programmes are offered as a one-off treatment (based at Papworth Hospital NHS Foundation Trust) between 6 months and 3 years previously, were invited to attend a six-week PR maintenance programme at a local health centre in Huntingdon. The programme was supported by two respiratory physiotherapy technical instructors and group size was limited to eight patients. The course was centred upon individualised, patient-targeted goals and home exercise plans; pedometers were used throughout the course, with a portable weekly pedometer count given at Week 1 and Week 6 of the following: FEV1, FVC and FEVs1, SaO2 6-minute walk, exercise capacity in an individualised exercise circuit, MRC breathlessness score and quality of life score.

Methods: All patients in Cambridgeshire Primary Care Trust Huntingdon locality, who had been through a full pulmonary rehabilitation programme (based at Papworth Hospital NHS Foundation Trust) between 6 months and 3 years previously, were invited to attend a six-week PR maintenance programme at a local health centre in Huntingdon. The programme was supported by two respiratory physiotherapy technical instructors and group size was limited to eight patients. The course was centred upon individualised, patient-targeted goals and home exercise plans; pedometers were used throughout the course, with a portable weekly pedometer count given at Week 1 and Week 6 of the following: FEV1, FVC and FEVs1, SaO2 6-minute walk, exercise capacity in an individualised exercise circuit, MRC breathlessness score and quality of life score.

Results: Two groups (A and B) have completed the course so far. A total of 8/15 (53%) invited patients have attended and completed the course. Of the seven who declined or failed to complete, 2/7 have declined long term; 4/7 failed as a result of unrelated intercurrent illness and are rebooked to attend later groups; 1/7 attends an alternative local exercise group. Of the eight who

Abstract S145 Table 1

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) COPD</th>
<th>Mean (SD) Non-COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISWT (m)</td>
<td>187 (11.4)</td>
<td>135 (9.2)</td>
</tr>
<tr>
<td>SGRQ - Symptoms</td>
<td>60.5 (18.8)</td>
<td>62.2 (21.9)</td>
</tr>
<tr>
<td>SGRQ - Activity</td>
<td>78.0 (14.7)</td>
<td>74.2 (15.6)</td>
</tr>
<tr>
<td>SGRQ - Impact</td>
<td>48.3 (16.9)</td>
<td>48.4 (16.6)</td>
</tr>
<tr>
<td>SGRQ - Total</td>
<td>59.3 (13.8)</td>
<td>58.6 (14.5)</td>
</tr>
<tr>
<td>HAD - Anxiety</td>
<td>8.2 (4.6)</td>
<td>7.5 (4.4)</td>
</tr>
<tr>
<td>HAD - Depression</td>
<td>6.8 (3.3)</td>
<td>5.5 (2.9)</td>
</tr>
</tbody>
</table>

Abstract S145 Table 2

<table>
<thead>
<tr>
<th></th>
<th>Mean (95% CI) COPD</th>
<th>Mean (95% CI) Non-COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ ISWT (m)</td>
<td>45 (34.2 to 55.8)</td>
<td>42 (6.9 to 76.4)</td>
</tr>
<tr>
<td>∆ SGRQ - Symptom</td>
<td>-8.7 (-11.9 to -5.7)</td>
<td>-3.7 (-11.1 to 2.7)</td>
</tr>
<tr>
<td>∆ SGRQ - Activity</td>
<td>-3.5 (-5.9 to -2.1)</td>
<td>-5.9 (-10.8 to -0.9)</td>
</tr>
<tr>
<td>∆ SGRQ - Impact</td>
<td>-9.1 (-11.5 to -6.7)</td>
<td>-10.4 (-16.6 to -4.3)</td>
</tr>
<tr>
<td>∆ SGRQ - Total</td>
<td>-7.4 (-9.3 to -5.5)</td>
<td>-7.9 (-12.1 to -3.8)</td>
</tr>
<tr>
<td>∆ HAD - Anxiety</td>
<td>-2 (-2.5 to -1.5)</td>
<td>-3.4 (-2.6 to -0.1)</td>
</tr>
<tr>
<td>∆ HAD - Depression</td>
<td>-1.9 (-2.4 to -1.4)</td>
<td>-0.63 (-1.9 to 0.6)</td>
</tr>
</tbody>
</table>

% predicted. Nearly half of the patients brought a carer with them. 33 patients attended all four clinics; illnesses and hospital transport problems were the reasons for attendance. The control group had a mean age of 72.9 (10) years and mean FEV1 of 33.3 (5.7) % predicted. The mean scores pre-clinic, at the end of clinic and post-clinic for depression were 8.9, 7.8 and 7.5 (p < 0.01), for anxiety 10.7, 10.3 and 9.7 (p < 0.05), for SGRQ were 72.2, 67.1 and 67.1 (p < 0.05). The total number of A&E attendances was significantly lower in the intervention group versus the control group at six months pre-clinic this was 43 and 56 respectively, and at six months post-clinic this was 32 and 81 respectively (p < 0.001). The total hospital LOS (days) was significantly lower in the intervention group versus the control group: at six months pre-clinic this was 119 and 132 respectively, and at six months post-clinic this was 114 and 199 respectively (p < 0.001). The reduction in A&E attendances and LOS gave an estimated total saving of £16,500,000 compared to £15,000,000. Pre-clinic evaluation showed over 90% of the participants “moderately to strongly agreed” the clinic was beneficial.

Conclusion: After attending our PR programme there was a significant fall in the SGRQ and depression scores, number of A&E attendances and LOS. Also when compared to the control group there was a significant fall in A&E attendances and LOS. The PR programme was both economically valuable and subjectively valuable to patients and carers. We conclude that patients, carers and the hospital benefit from a PR programme without physical training.

S147 EARLY OUTCOMES OF A PULMONARY REHABILITATION MAINTENANCE PROGRAMME

C. I. Bloom 1, C. Howard 2, T. Hargadon 2, S. Dupont 3. 1Hillingdon Hospital, London; 2Hillingdon Primary Care Trust, London; 3Central and North West London Mental Health Trust, UK

Introduction: Pulmonary rehabilitation; it would act as a natural social support group; the six-week PR maintenance programme with individually tailored exercise regimes. Pulmonary rehabilitation is defined as a “multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise physical and social performance and autonomy” [ATS, 1999]. Exercise intolerance is complex and results from: ventilatory limitation, due to hyperinflation and impaired gas exchange; premature muscle fatigue due to hypoxaemia and lactic acidosis; and skeletal and cardiac muscle deconditioning. Exercise training improves skeletal and cardiac muscle function, and improves mood, motivation and symptoms. There is extensive evidence that PR improves exercise capacity, fatigue, dyspnoea and patients' perception of control over their disease. The treatment effect of PR on health-related quality of life and functional exercise capacity is greater than other modalities used in COPD, such as bronchodilators, and it is an extremely cost-effective intervention. However, these effects wane from 6–12 months, although quality of life benefits are still detectable at 2 years. Additionally, this group of patients are often socially isolated by their disease and feel it difficult to exercise at local public facilities such as leisure centres. There is thus no easily identifiable mechanism for maintaining fitness for patients who have attended a formal PR programme. We hypothesised that a locally-based exercise programme would offer many benefits for this group: it would present a secure environment for exercising, with paramedical support, and would therefore extend the benefits of pulmonary rehabilitation; it would act as a natural social support group; and it would act as a focal point for early intervention to prevent exacerbations of the underlying lung disease.

Methods: All patients in Cambridgeshire Primary Care Trust Huntingdon locality, who had been through a full pulmonary rehabilitation programme (based at Papworth Hospital NHS Foundation Trust) between 6 months and 3 years previously, were invited to attend a six-week PR maintenance programme at a local health centre in Huntingdon. The programme was supported by two respiratory physiotherapy technical instructors and group size was limited to eight patients. The course was centred upon individualised, patient-targeted goals and home exercise plans; pedometers were used throughout the course, with a portable weekly pedometer count given at Week 1 and Week 6 of the following: FEV1, FVC and FEVs1, SaO2 6-minute walk, exercise capacity in an individualised exercise circuit, MRC breathlessness score and quality of life score.

Results: Two groups (A and B) have completed the course so far. A total of 8/15 (53%) invited patients have attended and completed the course. Of the seven who declined or failed to complete, 2/7 have declined long term; 4/7 failed as a result of unrelated intercurrent illness and are rebooked to attend later groups; 1/7 attends an alternative local exercise group. Of the eight who
Spoken sessions A59

have so far completed the course, one persevered despite developing an unrelated severe respiratory condition (excluded from analysis). After 6 weeks, FEV1 improved by a mean of 8.7%, FVC increased by a mean of 6.1%. 6-minute walk distance improved by a mean of 59% and individually-tailored exercise circuit results improved by a mean of 20%. MRC breathlessness score improved by a mean of 23.5%; quality of life scores improved by a mean of 6%. All patients completed a Satisfaction Questionnaire. 100% felt an improvement in the way their breathing affected their lives; 100% felt the group and social support was paramount; 100% requested that this service become permanent. As a direct result there is now an "open extension" of the maintenance programme, running in parallel and on-site with the main group, self-directed by the patients.

Conclusions: These early results suggest that a locally-based exercise programme, supported by rehabilitation assistants, has the potential to have a marked benefit in maintaining the confidence and physical fitness of patients with COPD who have previously experienced a formal pulmonary rehabilitation programme. Additionally, it is an inexpensive intervention, which is having a very positive response from the patient population, which seems to be a key factor in its benefit. Further positive results are expected from ongoing groups.

Asthma: basic mechanisms

**ST148** BRONCHIAL FIBROBLASTS EXHIBIT A PROINFLAMMATORY RESPONSE TO RHINOVIRUS-16 INFECTION BUT LACK A TYPE I INTERFERON RESPONSE

N. J. Bedke, S. Holgate, D. Davies. University of Southampton, Southampton, UK

Introduction: Rhinoviruses (RV) are a major cause of asthma exacerbations. RV infections usually trigger a proinflammatory response accompanied by an innate immune response mediated by the type I interferons (IFNs) which trigger an antiviral response in infected and neighbouring cells to limit viral replication. We have previously reported deficient IFN-γ production in response to RV infection by bronchial epithelial cells from asthmatic donors. In this study, we postulated that a deficient Type I interferon response also affects other airways structural cells in asthma.

Methods: Primary fibroblasts were grown from bronchial biopsies from 10 normal and 10 asthmatic patients, and were infected with RV-16 (moi = 0.01-1), using UV-irradiated (UVi) virus as control. Viral replication, IFN-γ and cytokine expression were measured by RT-qPCR and ELISA.

Results: Regardless of patient group, bronchial fibroblasts were highly susceptible to RV-16 infection. IL-8 and IL-6 were rapidly induced with RV16 and UVi-RV16. IL-8 and IL-6 was expression was partially inhibited by a PI3K inhibitor. In contrast, RANTES expression was only induced in the presence of viral replication but this was not accompanied by significant induction of endogenous IFN-γ. Exogenous IFN-γ was highly protective against viral replication. Fibroblasts respond to RV16 with a vigorous proinflammatory response, some of which may be independent of viral replication. However, RANTES mRNA expression was more sustained and required active viral replication. The absence of IFN-γ production in RV16-infected fibroblasts may explain their high susceptibility to viral infection.

Conclusions: Our data suggest that in asthma where epithelial shedding occurs, the underlying fibroblasts may be vulnerable to RV infection and permissive for viral replication. This will facilitate the persistence of the infection and augment the proinflammatory response, both of which can contribute to asthma exacerbations. Exogenous IFN-γ protects fibroblasts against infection and may be a potential therapeutic approach for virus-induced asthma exacerbations.

**ST149** ALTERED AIRWAY FIBROBLAST COLLAGEN SYNTHESIS IN SEVERE ASTHMA AND THE INVOLVEMENT OF AKT PHOSPHORYLATION

P. N. Sanders, L. C. Lau, D. Sammut, P. H. Howarth. Southampton University, Southampton, UK

Introduction: Fibroblasts in the asthmatic airways are able to secrete increased levels of extra-cellular matrix (ECM) proteins such as collagen I and III, fibronectin and laminin, and this is accompanied by fibroblast hyperplasia, perpetuating the remodelling process. Bronchoalveolar lavage (BAL) contains factors present in the airway lining fluid secreted, in part, by epithelial cells. Epithelial-mesenchymal interactions are believed to play an important role in normal wound repair as well as the remodelling process in asthma. By challenging fibroblasts grown from bronchial biopsies with BAL, a basic model of the airway can be constructed and used to investigate fibroblast behaviour in asthma.

Method: In fibroblast primary culture we have studied six mild asthmatics and six severe asthmatic patients were grown from biopsies and challenged with BAL from six healthy, six mild asthmatic or six moderate/severe asthmatic volunteers. The [3H]-thymidine incorporation assay and TaqMan real-time PCR were used to assess their mitogenic potential and ability to synthesise collagen III mRNA. The phosphorylation status of a variety of MAPks within healthy, asthma and severe asthmatic fibroblasts was determined after challenge with moderate/severe asthmatic BAL using the R&D systems MAPK-phosphorylation kit.

Results: Bronchoalveolar lavage stimulated [3H]-thymidine incorporation in fibroblasts grown from biopsies from healthy and mild asthmatics but not in those from severe asthmatics (p<0.0001), indicative of an altered phenotype in severe asthmatics. BAL from those with moderate/severe asthma, however, induced significantly more collagen III mRNA expression by the fibroblasts cultured from severe asthmatics than fibroblasts cultured from the airways of either healthy subjects (p<0.05) or mild asthmatics (p<0.005). There was a marked increase in Akt1 and Akt2 phosphorylation in severe fibroblasts compared to mild asthmatic fibroblasts after a 30 min challenge with moderate/severe asthmatic BAL, with no Akt1 or Akt2 phosphorylation seen in healthy fibroblasts.

Conclusion: Fibroblasts from severe asthma thus have an altered phenotype favouring a synthetic rather than proliferative phenotype. Signalling pathways influencing Akt phosphorylation are implicated in this process. These findings have relevance to structural airway changes in asthma and processes underlying disease severity.

**ST150** SELDI-TOF MASS SPECTROMETRY SCREENING OF SPUTUM SUPERNATANTS IDENTIFIES NOVEL BIOMARKERS DISTINGUISHING EOSINOPHILIC FROM NON-EOSINOPHILIC ASTHMA

I. Pavord, P. Bradding, K. Molyneux, S. Patel, J. Barratt. 1University of Leicester; 2John Walls Renal Unit, Leicester, UK

Introduction: Asthma affects 10% of the population and is an important cause of morbidity and mortality at all ages. Current treatments are either ineffective or carry unacceptable side effects for a number of patients. We know that applying a management strategy aimed at suppressing the sputum eosinophil count leads to a marked reduction in severe asthma exacerbations compared to current guidelines advocating symptom-guided treatment. However, analysis of induced sputum for eosinophilia is labour intensive and time consuming, and therefore unlikely to be used widely.

Methods: Surface enhanced laser desorption/ionisation time of flight mass spectrometry (SELDI-TOF MS) enables the analysis of complex biological samples through firstly "on-Chip" reverse chromatography followed by detection of captured proteins by mass spectrometry. We analysed supernatants from induced sputum samples from 40 well-characterised asthmatics (20 eosinophilic (≥3% sputum eosinophilia) and 20 non-eosinophilic (<1.8% sputum eosinophilia)) and healthy controls. All sputum samples were stored at −80°C before analysis and samples were normalised by correcting to a common final total protein concentration.

Results: A biomarker scouting study we found consistent differences in the proteomic profile of sputum from patients with non-eosinophilic versus eosinophilic asthma. Two ProteinChip chemistries were particularly informative: H50 (reverse phase), and IMAC-Zn (binds proteins with an affinity for the metal ion zinc, such as certain metalloproteinasises). Those biomarkers showing modest promise were m/z 13,265; 12,749, 10,875 (H50) and 25,581, 12,961, 3,410 (IMAC-Zn).

Conclusions: Biomarker validation studies are now underway using prospectively collected induced sputum samples from a new cohort of patients to confirm these initial findings. The biomarkers thus far identified all have predicted masses of less than 30 kDa, making it extremely likely that they may also be present in urine. We are also therefore analysing urine in parallel as there is increasing evidence that many systemic diseases are associated with the urinary excretion of disease-specific biomarkers. Urine dipstick testing for biomarkers is likely to be more readily integrated into primary and secondary care than regular assessment of induced sputum.

**ST151** THE ROLE OF GALECTIN-3 IN ASTHMA

D. Sammut, H. M. Hailchi, L. Lau, S. Wilson, J. Holloway, D. Davies, P. H. Howarth. University of Southampton, Southampton, UK

Background: Galactose-binding lectin has been implicated in fibrotic processes in a number of organs in humans. In vitro studies have shown that it is secreted from epithelial cells and can activate fibroblasts to fibrotic processes in a number of organs in humans. In vitro studies have shown that it is secreted from epithelial cells and can activate fibroblasts to

www.thoraxjnl.com

Thorax: first published as on 19 November 2007. Downloaded from http://thorax.bmj.com/ by guest. Protected by copyright.
increase collagen deposition. Human studies in COPD and interstitial lung disease have revealed higher levels of expression of this protein in biopsies and bronchoalveolar lavage fluid (BALF) respectively of patients with these two lung conditions. **Hypothesis:** Galectin-3 expression is upregulated in human asthmatic epithelium. It may have a role in airway remodelling by activation of submucosal fibroblasts to secrete more extracellular matrix proteins.

**Methods:**BALF, bronchial epithelial brushings and biopsies were obtained from healthy controls and asthmatics with mild or severe disease. ELISA for galectin-3 was performed on the BALF. Bronchial biopsies embedded in GMA were stained for galectin-3 and its expression quantitated. RNA was extracted from bronchial brushings and analysed for galectin-3 expression by RT-PCR.

**Results:**Thirty biopsy samples (7 healthy controls, 15 mild asthmatics, 8 severe asthmatics) were stained for galectin-3 which was detectable in the bronchial epithelium. Quantification of expression by computer-assisted image analysis showed no difference in expression between the groups. RT-PCR for galectin-3 was performed on epithelial brushing mRNA from 17 subjects (6 healthy controls, 2 mild asthmatics, 9 severe asthmatics). No significant difference in expression levels was detected. Galectin-3 was detected in BALF from both normal and asthmatic subjects (25 healthy controls, 41 mild asthmatics, 22 severe asthmatics) but levels were not statistically different. No correlation was found between immuno-reactivity for galectin-3 and biopsy eosinophil counts, neutrophil counts, collagen I staining, collagen III staining or basement membrane thickness.

**Conclusion:**Despite the evidence from in vitro and animal studies, as well as its role in other lung diseases, we have failed to identify significant differences in the expression of galectin-3 at both RNA and protein level between asthmatic and non-asthmatic subjects.

**S152** INTERSTITIAL AIRWAY WALL FIBROSIS IN ASTHMA AND ITS RELATION TO DISEASE SEVERITY

L. Shui, S. Wilson, D. Sammut, H. Rigden. University of Southampton, Southampton, UK

**Introduction:**Tinctorial staining of endobronchial biopsies identifies a dense band beneath the true basement membrane and this has been referred to as sub-basement membrane thickening. It is a characteristic feature of asthma and is appreciated to relate to enhanced collagen deposition. Changes in collagen deeper within the tissue have not been evaluated. Such structural changes may be more likely to alter airway wall behaviour and relate to disease severity than those evident more superficially.

**Methods:**To evaluate interstitial airway wall collagen deposition, endobronchial biopsies were obtained at fibre-optic bronchoscopy from healthy controls (n=10) and those with mild (n=9) and severe (n=10) asthma. The biopsies, embedded in glycol methacrylate (GMA), were stained with monoclonal antibodies against collagen I (1:500) and collagen III (1:1500). The extent of interstitial staining was calculated in the submucosal fibroblasts, using an image analysis program, excluding areas of smooth muscle and glands and also excluding the superficial sub-basement area of collagen.

**Results:**Interstitial collagen was present in all biopsies and there was a progressive increase in interstitial collagen I deposition from that seen in healthy bronchial controls to more severe asthma. The differences were significant: p=0.027 (healthy bronchial controls vs mild asthma), p<0.0001 (healthy controls vs severe asthma) and p<0.05 (mild asthma vs severe asthma). A similar trend was observed in lower airway collagen stained with monoclonal antibodies against collagen I (1:500) and collagen III (1:1500). The extent of interstitial staining was calculated in the submucosal fibroblasts, using an image analysis program, excluding areas of smooth muscle and glands and also excluding the superficial sub-basement area of collagen.

**Conclusion:**Tinctorial staining of endobronchial biopsies identifies a dense band beneath the true basement membrane and this has been referred to as sub-basement membrane thickening. It is a characteristic feature of asthma and is appreciated to relate to enhanced collagen deposition. Changes in collagen deeper within the tissue have not been evaluated. Such structural changes may be more likely to alter airway wall behaviour and relate to disease severity than those evident more superficially.

**S154** CYCLO-OXYGENASE-2 INDUCTION BY CYCLIC MECHANICAL STRAIN IN HUMAN PRIMARY ALVEOLAR TYPE 2 CELLS AND IN MURINE WHOLE LUNG IS DEPENDENT ON ACTIVATION OF ERK1/2


**Background:**Mechanical stimulation of the gas exchange surface of the lung is an inevitable consequence of mammalian anatomy. Mechanical forces affect the phenotype and function of cells and tissues, and over-differentiation of the mechanically ventilated lung contributes to the mortality of patients with acute lung injury. 1 Mechanical forces enhance the release of mediators that exacerbate lung damage, and contribute to systemic inflammation and death—the syndrome of ventilator-associated lung injury (VAU). Cyclic mechanical strain (CMS) increases prostanoi d production from several cell types but the reported mechanism has varied between studies. For example, CMS induced cyclo-oxygenase-2 (COX-2) and the availability of arachidonic acid substrate for prostanoi d production by increasing the activity of cytosolic phospholipase A2 in fetal lung epithelial cells. 2 Prostanoids affect multiple processes that are relevant to lung injury and repair including: inflammation, wound healing, fibrosis, host defence and control of vascular tone.

**Methods and Results:**We applied CMS (flexercell FX2000 apparatus: 0 30% stretch for 2 h at 20/min) to human primary alveolar type 2 cell (hAT2) monolayers in vitro as a model of lung over-dentension in the presence or absence of inhibitors of the Nf-kB pathway (AS602688: 3 μM), ERK1/2, pathway (U0126 or its inactive counterpart U0124: 10 μM) and JNK (SP600125: 10 μM). COX-2 mRNA (real-time PCR: fig A) and PGE2 (ELISA: fig B) in supernatants collected after 4 and 24 h were increased by CMS. Both effects were attenuated by inhibitors of the NF-kB and ERK1/2 pathways, suggesting that CMS-induced COX-2 transcription was dependent on these pathways and contributed to increased PGE2 release. In separate experiments, we have confirmed by western blotting using specific antibodies against phosphorylated intermediates that the ERK1/2 and NF-kB (p65) pathways were activated by CMS (30% stretch for 2 h at 20/min). Finally, in an acute murine ventilator-induced lung injury model, 3 injurious mechanical ventilation increased COX-2 mRNA in whole lung and PGE2 in lavage fluid after one hour, but this effect was prevented by pre-treatment with U0126 (30 mg/kg i.p.).

**Conclusion:**COX-2 induction by mechanical forces in hAT2 cells is dependent on the activation of ERK1/2 and NF-kB signalling pathways, 4 but not on JNK. In the absence of data describing the functional effects of inhibiting COX-2 activity, the significance of these findings in the context of acute lung injury and VAU is uncertain.

www.thoraxjnl.com

**Spoken sessions**

A60
Marginated Monocytes Exacerbate Pulmonary Oedema in a Murine Model of Ventilator-Induced Lung Injury


Background: High stretch/high tidal volume (V_t) mechanical ventilation induces pulmonary oedema and inflammation, characterised by production of soluble mediators and lung leukocyte recruitment. Historically, analysis of leukocyte involvement in ventilator-induced lung injury (VILI) has focused on neutrophils, largely ignoring other leukocytes such as monocytes. Monocytes are cells of the mononuclear phagocytic system, and can be phenotypically divided into resident (Gr-1low) and inflammatory (Gr-1high) classes. Gr-1high monocytes migrate to sites of acute inflammation, and we have previously demonstrated recruitment to pulmonary microcirculation following either systemic endotoxin or high stretch ventilation. It is however unknown whether such “lung-marginated” monocytes play any role in the development of VILI.

Methods: Anaesthetised male C57BL/6 mice were ventilated with high V_t (25–30 ml/ kg) for 2 h. In some animals, monocytes and neutrophils were pre-marginated to the lungs by a subclinical dose of lipopolysaccharide (LPS; 20 ng, intraperitoneal) before starting ventilation. In order to differentiate the effects of pre-marginated monocytes from neutrophils, monocytes were depleted using intravenous clodronate liposomes in a subgroup of LPS-treated animals. Lung-marginated neutrophils and Gr-1high monocytes were quantified in lung cell suspensions using flow cytometry. Pulmonary oedema formation was assessed by increased peak inspiratory pressure (PIP) and changes in respiratory system mechanics.

Results: LPS pre-treatment enhanced lung margination of Gr-1high monocytes and neutrophils prior to ventilation (p < 0.05). LPS pre-treatment also exacerbated stretch-induced pulmonary oedema, shown by increased PIP (fig A) and decreased respiratory system compliance (fig B). Clodronate (clod) pre-treatment depleted lung-marginated Gr-1high monocytes (0.3 (0.2) × 10^5 vs 2.4 (1.4) × 10^5 cells/lungs; p < 0.001; mean (SD)) but not neutrophils, and significantly attenuated stretch-induced oedema formation (fig A, B).

Conclusions: In this clinically-relevant “two-hit” model of VILI, subclinical systemic endotoxaemia sensitised the lungs to the effects of mechanical ventilation, exacerbating pulmonary oedema formation. This was attenuated by clodronate pre-treatment, which depleted lung-marginated...
PAR1 antagonism in vivo significantly reduces both neutrophilia and elevated by RWJ58259 (ND post RWJ58259). These data demonstrate (0.039) ng/ml, p
levels, including MIP-2 (saline: 0.43 (0.11); LPS: 5.76 (0.8) ng/ml, p
molecule expression, endothelial barrier dysfunction and vascular permeability, however the role of PAR1 in ALI remains unknown. The aim of this study was to determine the role of PAR1 in neutrophil recruitment and lung oedema following intranasal challenge with lipopolysaccharide (LPS) using a selective PAR1 antagonist (RWJ58259).

Female BALB/c mice (n=5/group) were anaesthetised and challenged with LPS (0.1 mg/kg) or saline (50 µl/mouse, i.n.), followed by i.p. administration of RWJ58259 (5 mg/kg) or saline 30 min later. Three hours after LPS challenge, bronchoalveolar lavage (BAL) was performed and BAL leukocytes counted, cytokine levels measured by ELSA and total BAL protein determined. BAL neutrophils were significantly elevated 3 h following LPS challenge (saline: 1.90 (0.55) SEM; LPS: 179.97 (37.84) × 10^6 cells/ml, p<0.01) as were TNFα (saline: 0.35 (0.19); LPS: 8.08 (0.68) ng/ml, p<0.01) and protein levels (saline: 196.41 (11.39); LPS: 236.47 (15.47) µg/ml, p<0.05). RWJ58259 treatment significantly attenuated LPS-induced neutrophil influx (73.63 (21.61) × 10^6 cells/ml, p<0.05), BAL protein (189 (13) µg/ml, p<0.05) and TNFα levels (4.87 (0.71) ng/ml, p<0.05). LPS challenge increased lung chemokine levels, including MIP-2 (saline: 0.43 (0.11); LPS: 5.76 (0.8) ng/ml, p<0.001) and MCP-1/JE (saline: not detectable (ND); LPS: 0.089 (0.039) ng/ml, p<0.01). Interestingly, only levels of MCP-1/JE were reduced by RWJ58259 (ND post RWJ58259). These data demonstrate that PAR1 antagonism in vivo significantly reduces both neutrophilia and microvascular leak in this model of ALI. We propose that therapies aimed at specifically inhibiting coagulation proteinase signalling may prove useful in the treatment of ALI.

**S155**

**PAR1 SIGNALLING IN LIPOPOLYSACCHARIDE-INDUCED ACUTE LUNG INJURY**

P. F. Mercer¹, J. D. Moffatt¹, C. J. Scottson¹, C. K. Derian², R. C. Chambers¹.

Acute lung injury (ALI) is characterised by neutrophilic inflammation of the air spaces, alveolar epithelial damage and severe oedema, caused by increased vascular permeability. This condition is also associated with increased procoagulant activity, characterised by alveolar fibrin deposition and decreased fibrinolysis. Activated coagulation proteinases exert proinflammatory effects via activation of their cellular receptors, the proteinase activated receptors (PARs). Activation of PARs has been shown to induce proinflammatory effects including cytokine release, adhesion molecule expression, endothelial barrier dysfunction and vascular permeability, however the role of PAR1 in ALI remains unknown. The aim of this study was to determine the role of PAR1 in neutrophil recruitment and lung oedema following intranasal challenge with lipopolysaccharide (LPS) using a selective PAR1 antagonist (RWJ58259).

Female BALB/c mice (n=5/group) were anaesthetised and challenged with LPS (0.1 mg/kg) or saline (50 µl/mouse, i.n.), followed by i.p. administration of RWJ58259 (5 mg/kg) or saline 30 min later. Three hours after LPS challenge, bronchoalveolar lavage (BAL) was performed and BAL leukocytes counted, cytokine levels measured by ELSA and total BAL protein determined. BAL neutrophils were significantly elevated 3 h following LPS challenge (saline: 1.90 (0.55) SEM; LPS: 179.97 (37.84) × 10^6 cells/ml, p<0.01) as were TNFα (saline: 0.35 (0.19); LPS: 8.08 (0.68) ng/ml, p<0.01) and protein levels (saline: 196.41 (11.39); LPS: 236.47 (15.47) µg/ml, p<0.05). RWJ58259 treatment significantly attenuated LPS-induced neutrophil influx (73.63 (21.61) × 10^6 cells/ml, p<0.05), BAL protein (189 (13) µg/ml, p<0.05) and TNFα levels (4.87 (0.71) ng/ml, p<0.05). LPS challenge increased lung chemokine levels, including MIP-2 (saline: 0.43 (0.11); LPS: 5.76 (0.8) ng/ml, p<0.001) and MCP-1/JE (saline: not detectable (ND); LPS: 0.089 (0.039) ng/ml, p<0.01). Interestingly, only levels of MCP-1/JE were reduced by RWJ58259 (ND post RWJ58259). These data demonstrate that PAR1 antagonism in vivo significantly reduces both neutrophilia and microvascular leak in this model of ALI. We propose that therapies aimed at specifically inhibiting coagulation proteinase signalling may prove useful in the treatment of ALI.

**S157**

**THE ROLE OF TNF-RELATED APOPTOSIS INDUCING LIGAND IN ACUTE LUNG INJURY**

University of Sheffield, Sheffield, UK

**Rationale:** Neutrophils play a central role in a number of inflammatory lung diseases. Since neutrophil apoptosis is essential to the resolution of inflammation, understanding the mechanisms regulating this process in vivo are important, as is the potential to drive apoptosis using appropriate pro-apoptotic stimuli. We showed that a death receptor ligand, TNF-related apoptosis inducing ligand (TRAIL), accelerates neutrophil apoptosis in vitro without associated cell activation (J Immunol 2003;170:1027–33). The aim of this project was to study the role of TRAIL in the regulation of neutrophil apoptosis during pulmonary inflammation in vivo in TRAIL deficient compared with wild-type mice.

**Methods:** The response of wild-type and TRAIL-deficient mice to intratracheal LPS (0.1 mg/kg) 24 h prior to i.v. challenge with MHC I antibody (H-2Kd mAb, 4.5 mg/kg). Lung injury was measured using the gravimetric method (excess lung water, ELW) and lung vascular permeability to 125I-labelled albumin (extravascular plasma equivalents, EVPE). Neutrophils were depleted with Gr-1 mAb (250 µg i.p.) and platelets were depleted using a rabbit, anti-mouse platelet serum (50 µl i.p.) Corresponding control antibodies were used in all experiments. Platelet sequestration was determined by measuring the radioactivity of 51Cr-labelled platelets and expressed as whole lung/blood (100 µl) counts.

**Results:** There is a significant increase in platelet sequestration in the lungs of mice challenged with MHC I mAb compared with isotype control mAb (fig 1). There was no difference in the measured blood volume (QB) in the lungs of the two groups. Neutrophil depletion with Gr-1 mAb decreased platelet sequestration after MHC I mAb-challenge (fig 1). Platelets were 90% depleted with the rabbit, anti-mouse platelet serum leading to significant protection from TRALI (fig 2).

**Conclusions:** Experimental TRAIL is characterised by lung neutrophil and platelet sequestration and neutrophils appear to be critical to the sequestration of platelets. Platelet depletion leads to significant lung protection and is an attractive, potential therapeutic target in TRALI.
SALBUTAMOL DRIVES UPREGULATED MMP-9 ACTIVITY IN THE ALVEOLAR SPACE IN ACUTE RESPIRATORY DISTRESS SYNDROME

S. T. Mckeeon1, C. M. O’Kane1, G. D. Perkins2, K. Pettigrew3, F. Gao2, D. R. Thickett2, D. F. Mcauley1. 1Queen’s University, Belfast; 2University of Warwick; 3Birmingham University, UK

Background: Acute respiratory distress syndrome (ARDS) is characterised by damage to the alveolar-capillary barrier with leak of protein-rich fluid into the alveolar space. Matrix metalloproteinases (MMPs) are enzymes that degrade extracellular matrix including basement membrane and tight junction proteins. MMPs are inhibited in vivo by the tissue inhibitors of metalloproteinases (TIMPs). Several studies have implicated increased MMP-2/-9 in pathogenesis of ARDS. In the BALTI trial 40 patients with ARDS were randomised to placebo or intravenous salbutamol. Salbutamol reduced extravascular lung water but not inflammatory cytokines or neutrophil recruitment. We hypothesised that salbutamol downregulates MMP activity in the alveolar space in ARDS.

Methods: MMP-1/-2/-3/-7/-8/-9/-12/-13 were measured in supernatants of distal lung epithelial cells (DLECs) or BAL fluid of patients from the BALTI study by multiplex bead array, TIMPs-1/-2 by ELISA, and lipocalin-associated, and pro-/active forms of MMP-9 were measured by gelatin zymography. Net MMP-9 activity was measured using MMP-9 fluorokine assay (R&D).

Results: BAL fluid from patients with ARDS in the BALTI study showed a non-significant reduction in MMP-1/-2/-3 and a trend to increased MMP-8/-12/-13 by day 4. MMP-9 was significantly upregulated by day 4 compared with baseline, and the upregulation was unexpectedly augmented by salbutamol (fig 1). Salbutamol had no effect on any of the other MMPs studied. Salbutamol induced a 13.2-fold (IQ range 3.9–35.7) increase in BAL fluid lipocalin-associated (neutrophil-derived) MMP-9 secretion compared with baseline, compared with a 1.3 (0.9–2.7)-fold increase from baseline in placebo group, p=0.01. Salbutamol dose-dependently induced MMP-9 secretion by DLECs (fig 2). Salbutamol did not affect BAL fluid TIMP-1/-2. Net MMP-9 activity (accounting for the effect of TIMPs/other inhibitors in BAL fluid) was 2.1 (1.5–8.8)-fold upregulated by day 4 from baseline in the salbutamol group but unchanged in the placebo group (1.0-fold; IQ range 0.9–1.1).

Conclusion: Salbutamol appears to specifically upregulate MMP-9 activity both in vitro and in vivo in patients with ARDS. Since salbutamol reduced extravascular lung water in the BALTI patients, these data suggest that MMP-9 may play a previously unrecognised role in alveolar epithelial repair in ARDS.