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**

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**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 persons/year (95% CI 756 to 1344), an annual risk of 1.05% (10.5% at 10 years; 15.8% at 15 years). 5% of individuals in the cohort 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%’. 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 complied with this, with about 1/3 becoming 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.

**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 were 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%.

**Conclusions:** The level of MDR-TB has remained stable despite increases in 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 increases highlight the need for case early detection, rapid drug susceptibility testing and improving treatment completion. Universal strain typing will facilitate the investigation of these trends.
S4 A COMPARISON OF TUBERCULOSIS CASE RATES IN THE HOME-BORN WHITE POPULATIONS OF THE UK AND USA: AN INCREASING DISPARITY

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Introduction: In 2005 we presented data regarding the increasing TB rates in England compared with a decreasing trend in USA. (Duraira, Davies PDO. Increasing tuberculosis in England and Wales compared with a decreasing trend in USA: an issue of migration. Thorax 2005;60;i120.) 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 1-2 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 (Duraira et al, 2005).

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

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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 community 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 ARTIFACT?

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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 infections were investigated to see whether 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: The total number of 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 immunosuppression in the population. An investigation into possible contributions to this increase will be presented.

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

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Background: Sensitivity to the house dust mite allergen Dermatophagoides pteronyssinus (Der p I) is commonly associated with asthma in the UK. The...
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 were inactive for the 12 months of the study. All subjects had continuous allergy 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 house dust mite. The change in mean evening 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 –2.10 to –0.62, p = 0.002), but not at 12 months (mean difference –0.46, CI –1.47 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.

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**S89**

**EXAMINING THE RELATION BETWEEN ASTHMA AND RHINITIS RESPONSE FOLLOWING OMALIZUMAB THERAPY**

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**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.1 Additionally, improvements in rhinitis control have been seen in patients with persistent allergic rhinitis.2 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 study3 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 in terms of their asthma, 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.


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**S90**

**EFFECT OF INHALED CORTICOSTEROIDS ON SMALL AIRWAY DYSFUNCTION IN MILD TO MODERATE PERSISTENT ASTHMATICS**

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**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 (FEF25–75) and alveolar (CAVL) 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 FEF25–75 (median 10.7 pph; IQR 17.9 to 17.7 vs 33.8 pph; 16.8 to 52.5, p < 0.001); JNO (0.48 nL/s; 0.37 to 0.89 vs 1.71 nL/s; 0.67 to 2.55, p < 0.001); CAVL (1.27 ppb; –1.00 to 2.07 vs 2.14 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 = 0.099). ICS attenuated JNO (p < 0.001), JNO (p < 0.001) and CAVL (p < 0.012), 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.

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**S91**

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

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**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 relationship 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 compared to the other groups. We also explored the longitudinal correlation in measurements performed when subjects had concomitant symptoms (Juniper asthma control score >1.5). No significant longitudinal correlation was seen between the parameters during expression of symptoms (Lc = 0.05 calculated from 240 measurements in 68 patients, p = 0.47). This dissociation was mainly due to persistent elevation of FeNO in the absence of sputum eosinophilia (seen in all subjects with persistently elevated 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.

**S12**

**THE RELATIONSHIP BETWEEN GASTRO-OESOPHAGEAL REFUX AND VOCAL CORD DYSFUNCTION IN A CLINICAL SETTING**

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**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 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

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**S11**

**A QUALITATIVE ANALYSIS OF HRCT SCANS IN DIFFICULT ASTHMA**

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**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 or with one of these parameters.

**Results:** The difficult asthma cohort (n = 185) had a mean (SEM) age 49.75 (2.0) years, male: female ratio 73:112, 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 (1.1), FEV1 % predicted 61.76 (2.1) %, sputum eosinophils (geometric mean 2.06 (95% CI 1.6–2.7)%). Four distinct groups were formed based on the 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.
Clinical trials in NIV

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

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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 8–20 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: 30-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. Intention-to-treat analysis.

Results: 1069 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] [2] cmH2O). At entry patients were tachycardic (heart rate 113 (22) [min]), acidotic (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 (26 (6) vs 25 (6), p = 0.023) at one hour. The 7-day and 30-day mortality was similar for standard therapy and non-invasive ventilation (9.8% vs 9.5% [p = 0.869] and 16.6% vs 15.6% [p = 0.685] respectively). Combined end-point 7-day death or intubation rate 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.

Abstract S14

Mortality 2 day 7 day 30 day 365 day
Total = 331 17% 31% 43% 63%
APO = 31 16% 32% 42% 81%
COPD = 143 15% 29% 36% 67%
COPD+OHVS = 22 5% 9% 23% 46%
COPD+pneumonia = 19 26% 42% 53% 53%
OHVS = 21 5% 19% 29% 33%
Pneumonia = 18 39% 61% 72% 77%

S14 SHORT- AND LONG-TERM MORTALITY FOLLOWING NON-INVASIVE VENTILATORY SUPPORT FOR ACUTE TYPE II RESPIRATORY FAILURE

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Background: Non-invasive ventilation (NIV) is now widely available in the UK for the support of type II respiratory failure. Ventilatory support for COPD and OHVS (abesity hypventilation) is accepted but its use in acute pulmonary oedema (APO) and pneumonia remains controversial. Despite this ‘real world’ usage of NIV is increasing.

Aims: To determine the outcome for patients who presented to the acute medical on-call service with Acute Type II Respiratory Failure requiring NIV.

Methods: Retrospective analysis of admissions to Salford Royal Hospital’s Medical High Dependency March 2001–August 2006 with Type II respiratory failure who required non-invasive bi-level ventilation (BiPAP). Only acute presentations were reviewed. All information was obtained from electronic patient hospital records (SOFT).

Results: 67% of admitting physicians were non-respiratory trainees. 297 patients (140 male, 157 female) with 331 admissions (282 new and 49 repeat) were studied. Admission diagnosis: acute pulmonary oedema (APO) 31, COPD 199 (COPD alone 143), COPD+OHVS 22, OHVS 21, pneumonia 18, others 40.

Conclusions: Despite the use of ventilatory support, Type II respiratory failure is still associated with a poor short-and long-term prognosis. This early mortality may reflect poor patient selection by the admitting physician. If the findings are reproducible consideration of formal training in ventilatory support for all general physicians participating in the acute on call is warranted. The worst prognosis was observed in the APO and pneumonia cohorts. OHVS cohort had the best outcome.


S15 PREDICTORS OF A SUCCESSFUL OUTCOME IN NON-INVASIVE VENTILATION FOR ACUTE HYPERCAPNIC RESPIRATORY FAILURE: A PROSPECTIVE OBSERVATIONAL STUDY

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Introduction: Non-invasive ventilation (NIV) reduces both the need for intubation and mortality in acute hypercapnic respiratory failure (AHRF). We have prospectively identified variables associated with an increased likelihood of NIV failure in AHRF to determine whether hyperglycaemia has an independent effect on outcome.

Methodology: All patients receiving NIV within 24 h of admission for respiratory acidosis complicating AHRF (pH <7.35; PaCO2 >6 kPa) at University Hospital Aintree between June 2006 and June 2007 were studied. On admission, blood samples including random blood glucose (RBG) were taken before NIV began.

Results: 100 consecutive episodes in 88 patients fulfilled the entry criteria; COPD exacerbations ± pneumonia accounting for 86%. NIV failure occurred in 16%. On univariate analysis, NIV failure was associated with increasing age (76 vs 68 years; p = 0.013), elevated RBG (8.99 mmol/l vs 6.86 mmol/l; p = 0.002), baseline RR (33 vs 26; p = 0.001), APACHE 2 score (18.75 vs 14.39; p = 0.001) and mean 1-4 d pH (7.25 vs 7.29; p = 0.028; 7.32 vs 7.27; p = 0.017); a possible relation existed with...
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baseline pH (7.26 vs 7.21; p = 0.097), female gender (p = 0.051) and lower GCS (p = 0.08), NIV failure occurred in 31% (15/48) when RBG was >7 mmol/l compared to 2% (1/50) where RBG < 6.9 mmol/l (p = 0.003). NIV failure was not associated with pneumonia, lung function, delay in NIV administration and a previous diagnosis of diabetes mellitus (p > 0.1). On multivariate analysis, baseline RR (p = 0.019), RBG > 7 mmol/l (p = 0.028), female gender (p = 0.010), 1-h pH (p = 0.049) and 4-h pH (p = 0.007) emerged significantly as predictors of success and 75% of failures. An ROC curve was constructed between RR and NIV outcome (area under curve 0.775; p = 0.001). The success rate of NIV reached 98% (43/44) in the subgroup with combination of baseline RR < 30/min and RBG > 7 mmol/l contrasting to just 42% (8/19) in the subgroup with baseline RR > 30/min and RBG > 7 mmol/l.

Conclusions: Glycaemia on admission is independently associated with failure of NIV in acute AHFR. Success of NIV in AHFR is more likely in patients with a baseline respiratory rate < 30/minute and a random glucose > 7 mmol/l.

S16 NON-INVASIVE VENTILATION IN MOTOR NEURON DISEASE: AN AUDIT OF CURRENT PRACTICE

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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 on the basis of orthopnea or symptoms of hypoxia.

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 acute follow-up. 15 (28.8%) accepted long-term NIV. 28 died over the audit period. Median survival from time of diagnosis for patients who accepted home NIV was 26 months compared to 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, orthopnea or hypercapnic symptoms, 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 36% in patients who accepted NIV (p = 0.014). No significant correlation between toleration of NIV and bulbar dysfunction score was seen (p = 0.26).

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.

S17 LONG-TERM OUTCOME OF VENTILATORY SUPPORT IN PATIENTS WITH RESPIRATORY FAILURE DUE TO DUCHENNE MUSCULAR DYSTROPHY


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 identified from the database. Thirty-two case notes (between March 1995 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 hyperventilation 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 out of 5 were weaned successfully to long-term NIV.

S18 PROSPECTIVE STUDY OF INITIATION OF HOME MECHANICAL VENTILATION TO INVESTIGATE THE CHANGES IN PATIENT DEMOGRAPHICS OVER A TWO-YEAR PERIOD

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Background: Home mechanical ventilation (HMV) is an established treatment for patients with chronic hypercapnic respiratory failure due to a variety of conditions. Although the evidence for the treatment of obstructive airways disease (OAD) is limited (Meecham-Jones et al, 1998), there is evidence that HMV is useful for the management of chronic respiratory failure complicating neuromuscular disease (NMD) and chest wall disease (CWD) (Leger et al, 1994; Simonds and Elliot, 1995). More recently with the increasing numbers of obese patients presenting with chronic hypercapnic respiratory failure, HMV has been shown to be an effective therapy (Masa et al, 2001; Prez de Ullano et al, 2005). Although the Eurovent survey (Lloyd-Owen et al, 2005) highlighted the differences in the demographics of HMV users across Europe, there was no particular focus on the patients with obstructive sleep apnoea and obesity hypoventilation syndrome (OSA/OHS). The aim of the current study was to assess the changes in HMV-user demographics in a regional centre over a two-year period.

Method: The data were collected from the electronic discharge summary database. In addition to basic patient details, information was collected...
Abstract S18

2005–6, n (%) 2006–7, n (%)  
Domiciliary NIV initiated 86 98  
Age 55.9 (range 13–85) 54.2 (range 17–83)  
Male 40 (46.5) 45 (45.9)  
Female 46 (53.5) 53 (54.1)  
Elective admission 43 (50.6) 53 (54.1)  
Emergency admission 42 (49.4) 45 (49.5)  
NIV initiated post weaning from mechanical ventilation 9 (10.5) 8 (8.2)  

*Includes (in order of frequency) DMD, post polio syndrome, MND, myasthenia gravis, idiopathic dysphagia, idiopathic paralyzing myasthenia, SMA, acid maltase deficiency, FSH, HSMN, CDP, inclusion body myositis and myasthenia gravis.  
†Includes central hypventilation, brainstem CVA, spina bifida, Cheyne-Stokes respiration, primary pulmonary hypertension.

about the admission episode including admission urgency, length of stay, diagnostic group, specific diagnosis, ventilator used and settings and interface. The groups were NMD, OAD, CWD, OSA/OHS, and other. We compared the data between May 2005 to May 2006 and May 2006 to May 2007.

Results: See table. Although there was no change in age, sex or admission urgency over the two-year period, there was a 1.4% increase in the number of patients initiated on HMV. Furthermore, there was a 23% decrease in the number of patients with NMD initiated on HMV. This was reflected by a fall in all of the specific neuromuscular disease groups. However, there was an increase of over 90% in the patients initiated on HMV with OSA/OHS. All other diagnostic groups remained relatively unchanged.

Conclusion: In addition to an overall increase in initiation of HMV over a two-year period, we have observed a change in the type of patients that are commenced on HMV. There has been a decrease in the NMD group, which was more than matched by an increase in the OSA/OHS group. This increase in activity and change in HMV-user demographics is likely to have significant implications on the structure of the service which will need to be modified in terms of nursing, medical and technical provision in order to adequately manage these differing patient groups.

Acknowledgement: MJ is a medical student at Guy’s, King’s & St Thomas’ School of Medicine who undertook this project as part of an extended Special Study Module.

Lung cancer: basic mechanisms

S19 FOURIER TRANSFORM INFRARED SPECTROSCOPY MEASURING METABOLIC MARKERS IN SPUTUM IN PATIENTS WITH AND WITHOUT LUNG CANCER

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Introduction: There are 1.3 million worldwide and over 37,000 new cases of lung cancer diagnosed in the UK each year.1 The incidence of lung cancer is higher in Wales than the UK average.2 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. A preliminary study to evaluate: (1) suitability of sputum as a biofluid for easy/cost effective processing for FTIR (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 differences 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 detecting pre-cancerous lesions and monitoring response to treatment.

DEGRANULATION OF STROMAL MAST CELLS OF THE TRYP TASE-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\textsubscript{TC}, expressing both chymase and tryptase, or MC\textsubscript{T}, 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\textsubscript{TC} and MC\textsubscript{T} in tumour islets were higher in patients with a survival above the median (1.2 (0.48) and 2.58 (0.40) cells/mm\textsuperscript{2} respectively) compared to those below the median (0.05 (0.02) and 0.19 (0.08) cells/mm\textsuperscript{2} respectively) (p = 0.003 for both MC\textsubscript{TC} and MC\textsubscript{T}). In patients with above median survival, the MC\textsubscript{T} 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\textsubscript{T} DI in the stroma (area under curve = 0.798, 95% CI 0.661 to 0.934).

Conclusions: Both MC\textsubscript{TC} and MC\textsubscript{T} 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\textsubscript{T} 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


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 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 1: Smoking status

<table>
<thead>
<tr>
<th></th>
<th>Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Smoker</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>20</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 2: Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>25</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>34</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 3: Stage distribution

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>47</td>
</tr>
<tr>
<td>Stage la</td>
<td>14</td>
</tr>
<tr>
<td>Stage Ib</td>
<td>23</td>
</tr>
<tr>
<td>Stage Iib</td>
<td>10</td>
</tr>
<tr>
<td>Late</td>
<td>23</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>12</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>9</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2</td>
</tr>
</tbody>
</table>
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.**

**QUALITY OF RNA EXTRACTED FROM BIOPSIES OF NON-SMALL CELL LUNG CANCER COLLECTED USING DIFFERENT TECHNIQUES**

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**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.**

**THE ASSOCIATION OF LUNG CANCER AND SINGLE NUCLEOTIDE POLYMORPHISMS IN CODON 178 AND THE FIRST INTRON OF THE DNA REPAIR GENE O6-ALKYLGUANINE-DNA ALKYLTRANSFERASE**

P. A. J. Crosbie¹, G. Magowan², M. Thomcroft³, P. N. S. O’Donnell¹, S. Lewis³, K. Harrison³, R. Agius³, M. Santibanez-Koref⁴, G. Margison², A. Povey³, 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 O\textsuperscript{6}-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 Bronchoscopy 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, with 64.4% and were male (62%). Cases (n = 255) were older (n = 362) (68.9 (10.2) vs 64.4 (10.7) years, p < 0.001) and had smoked significantly more than controls (52.4 (37.2) 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 0.91) and homoyzogotes (0.10, 0.01 to 0.98); the trend increased 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\(^1\), A. Johnson\(^2\). \(^1\)Kent & Canterbury Hospital; \(^2\)Guy’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) were interviewed. All smoking patients were interviewed. All patients who continued to smoke were interviewed.

Abstract S25

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical</th>
<th>Surgical</th>
<th>Obst/Gynae</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients questioned</td>
<td>241</td>
<td>127</td>
<td>57</td>
<td>425</td>
</tr>
<tr>
<td>Number unable to participate</td>
<td>48</td>
<td>34</td>
<td>16</td>
<td>98</td>
</tr>
<tr>
<td>Number unwilling to participate</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Smokers (% of total)</td>
<td>34 (13%)</td>
<td>23 (18%)</td>
<td>4 (7%)</td>
<td>61 (14.3%)</td>
</tr>
<tr>
<td>Smokers (% of respondents)</td>
<td>34 (18%)</td>
<td>23 (24%)</td>
<td>4 (10%)</td>
<td>61 (18.7%)</td>
</tr>
<tr>
<td>Smokers given advice to quit on this admission (% total smokers)</td>
<td>19 (62%)</td>
<td>7 (30%)</td>
<td>0 (0%)</td>
<td>26 (42.6%)</td>
</tr>
<tr>
<td>Smokers offered NRT (% of smokers)</td>
<td>12 (35%)</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
<td>15 (24.5%)</td>
</tr>
<tr>
<td>% of smokers buying contraband cigarettes</td>
<td>38%</td>
<td>35%</td>
<td>None</td>
<td>24.3%</td>
</tr>
</tbody>
</table>

Conclusions: Shortness of breath frightened most and was a strong motivating force to quit, but the threat of amputation along with other medical conditions were important. Most patients in this age group had made use of aids to stop smoking and the majority were not aware of smoking cessation clinics. Most relied on willpower to stop. Smoking cessation interventions need to be offered to older smokers both in the primary care setting and also in hospital. Older patients perceive the urgency of stopping smoking and can therefore be highly motivated and receptive to smoking cessation advice and interventions. A period of hospitalisation should be used to encourage and inform elderly patients.


Introduction: The widely publicised Thorax smoking cessation guidelines\(^1\) 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任意引用.
underwent 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.


**S27 EARLY EXPERIENCE WITH VARENICLINE IN A HOSPITAL-BASED SMOKING CESSATION CLINIC**

J. Ryder, R. Angus, L. Davies. Aintree Chest Centre, Liverpool, UK

**Background:** University Hospital Aintree is a large, teaching hospital in Liverpool. The local adult smoking prevalence is 34%, rising to almost 60% in one of our catchment PCTs. The local SMR for lung cancer is more than 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 with no smoking allowed on school premises. Two (3%) had a policy for staff smokers, 61% reported policy breach by students and 16% by staff. 82% reported having a policy for staff smokers 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 role and 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 most schools. Utilising the expertise of members of the newly formed British Association of Stop Smoking Practitioners (BASSP) in secondary schools perhaps concentrating on staff education and confidence building is being considered.

1. **Smoking Kills, Government White Paper on Tobacco. HMSO, 1998.**

**S28 ACHIEVING A SMOKE-FREE SITE IN A DISTRICT GENERAL HOSPITAL: A SURVEY OF PERCEPTIONS OF HEALTHCARE WORKERS**

M. D. Shipley, R. Allocq. 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 smoking in hospital.

**Abstract S28**

<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>

**Results:** Of the 85 respondents, 37 (43%) reported having recently been exposed to smoking in hospital. Twenty-three (27%) reported that they had not been offered NRT to aid their quit attempt. If they had used NRT in the past, or the quit attempt failed, varenicline or bupropion was offered.

**Conclusion:** Varenicline is acceptable to and well tolerated by smokers attending a hospital-based smoking cessation clinic. The drug is suitable for most hospital patients. As this is a report of clinical practice, rather than a randomised controlled trial, many of the reported side effects could be due to nicotine withdrawal. However, in keeping with previous studies of ‘healthy smokers’, nausea was a common problem. In our clinic, approximately 1:6 stopped the drug due to nausea and/or vomiting. It remains to be seen how well sustained these quit attempts will be at 6 and 12 months, but our early experience is certainly encouraging.

2. **Jorenby DE, et al. JAMA 2006;296:56–63.**

www.thoraxjnl.com
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

ATTITUDES OF CURRENT AND EX-SMOKERS TO THE BANNING OF SMOKING IN PUBLIC AND ENCLOSED SPACES IN ENGLAND

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Introduction: Patients attending Smoking Cessation Clinics often attend with partners or supporters who themselves may be current or ex-smokers. Are there differences between these two groups in attitudes towards the ban on smoking in enclosed public spaces and workplaces in England? We assessed awareness of the ban in the six weeks prior to its implementation in 71 Smoking Cessation Clinic attendees to see whether current smokers, and accompanying ex-smokers differed in their perceptions of the value of the ban.

Results: See table. All respondents were aware of the smoking ban prior to the legislation being enacted. The most frequently cited reasons for quitting in ex-smokers were ill health or hospital admission (55.5%), cost (18.6%), and family pressure (11.1%). Most current smokers (61.4%) had made 2–5 attempts to quit previously; 20.4% of ex-smokers claimed to have quit at their first attempt. There was a statistically significant difference between current and ex-smokers’ responses (p < 0.05); student t test. No significant differences were observed between smokers and ex-smokers in response to the question “Do you think the ban on smoking in enclosed and public spaces would help you quit?” (p = 0.44). Ex-smokers were significantly more likely to be bothered by a smoky atmosphere in a pub, club or bar than smokers (20 (74.1%) vs 17 (38.6%), p = 0.004); this difference was less significant when asking regarding smoky restaurants or cafes (23 (52.3%) vs 21 (77.8%), p = 0.06). Current smokers were significantly more likely to disagree with the comment “the smoking ban will make me more likely to eat out” (p = 0.01).

Conclusions: All those surveyed were aware of the imminent smoking ban. Both smokers and ex-smokers felt that the ban would be helpful in giving up smoking. Despite this there were statistically significant differences in opinion as to whether the ban was a good idea. Current smokers were less bothered by smoky environments than ex-smokers, and did not feel the ban would encourage them to eat out more frequently.

Pulmonary circulation: assessment and treatment

Abstract S30

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

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition, characterized by obstruction of the pulmonary vascular bed causing increased pulmonary vascular resistance (PVR) and progressive pulmonary hypertension (PH). The treatment of choice is pulmonary endarterectomy (PEA), and is potentially curative. However, up to 50% of patients referred for surgery are not eligible. Additionally, 10–15% of patients experience post-operative persistent or recurrent PH. Since arteriopathy in CTEPH shares pathology with pulmonary vascular changes in pulmonary arterial hypertension (PAH), the efficacy and safety of the dual endothelin receptor antagonist, bosentan, has been evaluated in patients with inoperable CTEPH or with persistent or recurrent post-operative PH.

Methods: BENEFIT is the first multicentre, prospective, double-blind, placebo-controlled study of medical treatment for inoperable CTEPH or PH after PEA. Patients were randomised to receive bosentan or placebo for 16 weeks (62.5 mg twice daily increasing to 125 mg twice daily after 4 weeks). Independent co-primary endpoints: percentage change from

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Demographics

<table>
<thead>
<tr>
<th></th>
<th>Current smokers</th>
<th>Ex-smokers</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>Mean age (range) years</td>
<td>58.6 (26–79)</td>
<td>58.3 (28–80)</td>
</tr>
<tr>
<td>Mean pack years</td>
<td>43.5 (4–141)</td>
<td>36.1 (2.5–129)</td>
</tr>
<tr>
<td>Male:female</td>
<td>20:80</td>
<td>15:85</td>
</tr>
</tbody>
</table>

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Is the ban a good idea?

more likely to be bothered by a smoky atmosphere in a pub, club or bar than smokers (20 (74.1%) vs 17 (38.6%), p = 0.004); this difference was less significant when asking regarding smoky restaurants or cafes (23 (52.3%) vs 21 (77.8%), p = 0.06). Current smokers were significantly more likely to disagree with the comment “the smoking ban will make me more likely to eat out” (p = 0.01).

Conclusions: All those surveyed were aware of the imminent smoking ban. Both smokers and ex-smokers felt that the ban would be helpful in giving up smoking. Despite this there were statistically significant differences in opinion as to whether the ban was a good idea. Current smokers were less bothered by smoky environments than ex-smokers, and did not feel the ban would encourage them to eat out more frequently.
Abstract S30 Independent co-primary endpoint: bosentan significantly reduced PVR at week 16.

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) because they were considered “operable” 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 −16 dyn·sec/cm² in the bosentan group, a significant treatment effect of 24.1% (95% CI −31.5 to −16.0; p<0.0001) (fig). No treatment effect was observed on 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. Soon3, K. K. Sheares1, P. White1, R. Hughes1, P. Fesler3, R. Naeije4, J. Pepke-Zaba1.

Introduction: Pulmonary artery occlusion pressure (PAOP) waveform analysis is emerging as a useful tool for partitioning pulmonary vascular resistance. Previous work in chronic thromboembolic 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 endarertectomy (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 pre-malignant proximal and distal disease we examined patients with operable proximal CTEPH, inoperable distal CTEPH, and idiopathic pulmonary arterial hypertension (IPAH) including connective tissue associated PH 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.


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<table>
<thead>
<tr>
<th></th>
<th>Mean PAP, mmHg (SD)</th>
<th>PAOP, mmHg (SD)</th>
<th>Cardiac output, l/min/m² (SD)</th>
<th>Rup, % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operable proximal</td>
<td>49.7 (18.6)</td>
<td>11.6 (2.7)</td>
<td>3.9 (1.1)</td>
<td>86 (7.6)</td>
</tr>
<tr>
<td>Inoperable distal</td>
<td>56 (11.0)</td>
<td>10.6 (2.0)</td>
<td>3.7 (1.2)</td>
<td>69.9 (8.7)</td>
</tr>
<tr>
<td>IPAH/CTD</td>
<td>52.3 (12.9)</td>
<td>9.9 (2.7)</td>
<td>4.3 (1.8)</td>
<td>77 (8.6)</td>
</tr>
</tbody>
</table>

Abstract 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

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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
**Acknowledgement:** This study was supported by a grant from the PHA-UK.

**Results:** After 3 months there was a statistically significant increase in the ISWT distance in the rehabilitation group compared to baseline 278 (151) m versus 262 (142) m at baseline and the ESWT 493 (473) m compared to 382 (465) m, p = 0.07. There was no significant difference in the Control group: for the ISWT 261 (132) compared to 262 (142) m at baseline and the ESWT 411 (409) compared to 471 (431) m at baseline. There were no statistically significant differences in quality of life measures.

**Conclusions:** This pilot study suggests that a physiotherapy-led rehabilitation programme for patients with pulmonary hypertension can be safely performed in the home setting and has the potential to improve exercise capacity through education and controlled exercise and a multicentre trial is planned.

**References:**

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**NON-INVASIVE ASSESSMENT OF PULMONARY BLOOD FLOW USING AN INERT GAS REBREATHING DEVICE IN PATIENTS WITH PULMONARY HYPERTENSION**


**Objective:** Cardiac output (CO) is an important prognostic marker in pulmonary hypertension (PHT). A non-invasive measure of CO would be valuable in monitoring disease progression. Inert gas rebreathing using acetylene is a well established method for the non-invasive measurement of pulmonary blood flow (PBF) and has been validated in patients with PHT. Recently a new rebreathing technique (Innocor, Innovation, Denmark) using nitrous oxide analysed by a rapid photoacoustic method has been developed. The device is small, portable and convenient for use during exercise. This technique has been validated for patients with left heart failure. The aim of this study was to investigate the accuracy of this new inert gas rebreathing technique in patients under investigation for PHT.

**Methods:** Twenty three patients (14 female, 9 male) under assessment at the Scottish Pulmonary Vascular Unit had CO measured by three methods: inert gas rebreathing (Innocor) giving PBF, cardiac magnetic resonance (CMR) imaging giving pulmonary artery flow and thermodilution (TD) during right heart catheterisation (RHC) giving right-sided cardiac output.

All the subjects had a provisional diagnosis of PHT by echocardiography, CMR imaging (using cine imaging with steady state free precession and phase contrast velocity encoding sequences) and RHC were performed within 48 h of Innocor measurements. PHT was confirmed in 16 patients (8 idiopathic, 5 chronic thromboembolic, 3 connective tissue disease associated). PBF and CO were expressed as volumes by dividing by heart rate, giving estimates of stroke volume (SV). Agreement between techniques was assessed using Bland-Altman analysis and correlation.

**Results:** All three methods showed good correlation for stroke volume estimates (Innocor vs CMR, r = 0.91; Innocor vs TD, r = 0.89; CMR vs TD, r = 0.95). Bland-Altman analysis showed that the best agreement was obtained between CMR and TD SV with limits of agreement of -3.2 ml to +1.9 ml (+1.2 ml). However, the inert gas rebreathing technique also provided values of reasonable accuracy. Innocor vs MRI gave bias (limits of agreement) of -2.5 ml to +2.2 ml (see fig 1) whereas Innocor vs TD gave bias (limits of agreement) of -0.4 ml to +1.6 ml.

**Conclusion:** Inert gas rebreathing using the Innocor device provides an accurate, non-invasive means of assessment of pulmonary blood flow in patients with suspected PHT.

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**ISCHAEMIC STROKES AND PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMs): PAVM EMBOLISATION REDUCES STROKE RISK**

**C. L. Shovlin1, J. E. Jackson2, E. Kulinskaya1. Imperial College and Hammersmith Hospital, 2Hammersmith Hospital, London, UK**

**Background:** Pulmonary arteriovenous malformations (PAVMs) provide a right-to-left (R-L) shunt between the pulmonary arterial and venous circulations. Paradoxical embolic strokes affect high proportions of PAVM patients. Embolisation can be used to treat PAVMs if the condition is recognised, however, until now, no direct evidence for reduction of stroke incidence has been presented.

**Methods:** A cohort study of 219 consecutive individuals with PAVMs was performed. Six markers of PAVM severity (respiratory symptoms; oxygen saturation; R-L shunt by radionucleide scan; size of largest feeding artery to PAVMs; presence of small PAVMs; and PAVM multiplicity); 12 patient or HH-associated variables, and seven neurovascular risk factors (smoking status; hypertension; atrial fibrillation; diabetes mellitus, hypercholesterolaemia; cardiac disease; and migraines) were measured and/or recorded prospectively. To assess constant and time-dependent potential predictive variables for stroke, and rate-reduction by PAVM embolisation, several contiguous time intervals between events (stroke, embolisation and/or last follow-up) were defined per patient. An extension of Cox proportional hazards regression model, Anderson-Gill, suitable for the analysis of recurrent events was fitted with embolisation as a time-dependent covariate using SPLUS 6.

**Results:** Thirty (13.7%) individuals experienced an ischaemic stroke at median age 50.5 (95% CI 41.5 to 59.5) years. Only 10 (33%) had a pre-existing diagnosis of PAVMs. All had underlying hereditary haemorrhagic telangiectasia but only 12 (40%) were aware of this at the time of their stroke. No strokes occurred following obliteration of all angiographically visible PAVMs. Strokes did occur in some patients in spite of previous embolisation: all had small untreated PAVMs (feeding artery diameter <2–3 mm) in addition to the PAVMs which had been embolised. Overall, in the strongest model of ischaemic stroke (Wald test p value 4.7×10⁻⁵) which analysed 250 pre and post embolisation intervals with 4 degrees of freedom, embolisation at a median age of 45 years significantly reduced the rate of ischaemic stroke (p = 0.028). The Anderson Gill model demonstrated no association of ischaemic stroke with PAVM severity markers or neurovascular risk factors.

**Conclusions:** Ischaemic strokes occur in undiagnosed patients with PAVMs. Stroke risk can be reduced by PAVM embolisation.

**Acknowledgement:** We thank the families and friends of British HHT patients whose donations supported this work.

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**BRAIN-NATRIURETIC PEPTIDE CORRELATES TO ECHOCARDIOGRAPHIC INDICES OF RIGHT VENTRICULAR FUNCTION IN PATIENTS WITH FIBROTIC LUNG DISEASE**


**Introduction:** Pulmonary hypertension (PH) contributes to increased mortality and morbidity in patients with interstitial lung disease (ILD). Non-invasive tools for diagnosis and monitoring of PH in these patients are desirable. Elevated BNP levels are associated with higher mean pulmonary artery pressures (mPAP) on right heart catheter (RHC). Although accuracy of echocardiography in these patients has been questioned, it is more
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 circumscribing 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 audit was conducted at baseline and after 8 weeks by an independent blinded assessor.

Results: 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?

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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 Trusts in selected UK regions, to ascertain 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 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

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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 these 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 usual care only. 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 treatment control 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.

**S39 A SURVEY OF SPECIALIST REGISTRAR KNOWLEDGE OF RADIATION DOSES FOR VARIOUS RESPIRATORY INVESTIGATIONS**

G. T. Kyei, E. F. Bowen, C. F. J. Rayner. 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.1 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 10–20000 mSv (0.4 mSv); HRCT-chest-20mm 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); VQ 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elative 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); VQ ≥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.


**S40 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. 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

S42 AN IN-DEPTH STUDY TO DESCRIBE AND UNDERSTAND THE HEALTH EXPERIENCE OF TEENAGERS WITH UNCONTROLLED SEVERE ASTHMA: EXPERIENCES OF MEDICATION AND CONCORDANCE WITH THERAPY

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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 aware why they were on each of their medication and when they should be used (non-intentional non-concordance) possibly because of frequent alterations. 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 details 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.

S43 WHAT ARE THE FACTORS THAT UNDERLIE PAEDIATRIC ASTHMA?

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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

<table>
<thead>
<tr>
<th>Abstract S41</th>
<th>Asthma: attained QOF points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Total points</td>
<td>721.01</td>
</tr>
<tr>
<td>Average points</td>
<td>55.46</td>
</tr>
</tbody>
</table>

S41 ASTHMA NURSE ADVISOR PROGRAMMES CAN IMPROVE CARE WITHIN A HEALTH COMMUNITY

N. I. O’Kelly, J. A. Smith, P. Gray. Lincolnshire Primary Care Trust, UK

Background: The Elite (East Lincolnshire Inspire Team) nurse advisor programme started in January 2005. The remit of the nurse advisor was to set up sustainable systems of care within practices, by using existing practice staff within a structured change management process. Practices were classified into levels of care based on assessments of their capability to provide asthma care to patients. This abstract reports on the outcomes at the end of the first year of activity (January 2005 to December 2005).

Methods: Thirteen practices were identified as having needs in developing asthma services. Baseline assessments of the systems for asthma care in the practice were performed. A Health Improvement Programme (HIP) was developed in conjunction with the nurse advisor and the respiratory clinicians within the practice. The practice programmes ranged in time from 1–2 sessions per week, over a 3–6 month period. The baseline assessments were repeated at completion of the HIP.

Results:
- Better-trained clinicians
  - 28 healthcare professionals received tailored education and training in airways disease.
- Better structured care
  - At end of HIP all practices used standardised clinic templates and developed robust recall systems.
- Reduced hospital admissions
  - Asthma admissions reduced in 6 practices, remained the same in 4 and increased in 3. Overall there was a 34% reduction in asthma admissions in all practices (19 admissions).
- Increased achievement in GMS Quality Outcomes Framework (QOF) Data
  - There was wide variation in attainment of QOF points in asthma across the 13 practices. Despite this there was a noticeable increase in all practices in attainment of QOF points.

Conclusion: All practices involved in the ELITE programme improved in their capability to deliver asthma care. By targeting deficiencies in asthma care in GP practices and providing support in education and improving structures of care the standard of care delivered can be improved. Specifically this approach of delivering strategically focussed support to GP practices may reduce asthma admissions.
Abstract S43 Table 1 Description of the subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>106 (59.6%)</td>
</tr>
<tr>
<td>Gender (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 (83.3%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.2 (2.8)</td>
</tr>
<tr>
<td>Ever treated for asthma</td>
<td>173 (97.2%)</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, since 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 at home, family history of atopy, current eczema, current rhinitis, current food allergy, socioeconomic group, positive skin prick test, percent predicted FEV₁, PC₂₀, inverse dose-response slope, log total IgE). Where there were two similar variables, that which maximally explained variance was chosen. The model was rotated using 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. One factor 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 there are multiple 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 used 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 17% (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 C 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) FEV₁₂ 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.
involves a three-stage assessment. The nurse-led home visit is central to the stage 1 assessment. Only those with no remedial factors found at stage 1 progress to stages 2 (in-patient stay and bronchoscopy) and 3 (assessment of steroid responsiveness).

**Aims:** To establish the risk factors identified for children referred to the difficult asthma protocol; to determine what intervention strategies can be offered.

**Methods:** Patients were referred to the protocol within a tertiary paediatric respiratory centre. Following a nurse-led hospital visit a home visit was carried out (Stage 1). This addressed four key areas: psychological and social issues; adherence; smoking; and allergen exposure (pets and house dust mite, HDHM).

**Results:** Forty six children (median age 12, range 5–17 years) were visited. A structured mood questionnaire was carried out during the hospital visit. 56% were subsequently referred to a child psychologist; however 74% of these referrals were made after additional information had been obtained at the time of the home visit. Inhaler techniques were assessed and GP prescription records checked. The availability of prescribed, in-date medications in the home was assessed. Poor adherence was thought to contribute to poor asthma control in 33% of patients. 14 parents admitted to smoking; there was evidence of smoking in the home in 7 cases. 24 children owned pets. 45% and 46% who owned a dog and cat respectively had a positive skin prick test (SPT).

Only two households were found to be minimising pet exposure. Of 21 children who were SPT positive for HDHM, 7 had no HDHM avoidance, and 9 had partial measures. Ultimately, only 25% of those visited at home progressed to stage 2 of the protocol.

**Conclusions:** Nurse-led home visits can help identify potentially remedial factors for poorly controlled symptoms in children with difficult asthma. A home visit allows specific advice to be given and personalised plans of treatment recommended. It appears to be an effective strategy in the management of apparent therapy resistant asthma.

### T-spot test in TB

**S47 THE ROLE OF T CELL BASED INTERFERON-γ RELEASE ASSAYS IN THE EVALUATION OF PATIENTS WITH SUSPECTED ACTIVE TUBERCULOSIS**

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**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-6, culture filtrate protein-10 (standard assay) and a novel antigen Rv3879c (ELISpotPLUS). 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 0 (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.

**Results:** 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.

### Rapid immuno-diagnosis of active extrapulmonary tuberculosis

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


**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 0 (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.

**Discussion:** These results show 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.
S51

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

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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 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. Chemophrophylaxis was offered using rifampicin and isoniazid for 6 months. Contacts were followed up and a repeat T-spot-TB test performed 6 months after completion of chemophrophylaxis. The index case was a CD4 count of 52 who had a positive Mantoux test and a Reactive T-spot-TB test. Chemophrophylaxis was started and the T-spot-TB test was completed 6 months later. The patient was asymptomatic during this time.

Results: 15 patients accepted chemophrophylaxis, 3 received Rifinah, 12 received isoniazid. One patient developed a rash on Rifinah but tolerated isoniazid monotherapy. Two patients had a decline in CD4 count at 6 months, 1 patient had a rise in T-spot-TB from 10 to 20. One patient had a rise in T-spot-TB from 8 to 20. Two patients had a fall in T-spot-TB from 0 to 0.

Conclusion: Chemophrophylaxis is cost effective and safe. The results of this study suggest that chemophrophylaxis is safe and effective in HIV positive patients.

S52

QUANTIFERON-TB OR QFT IN SARCOIDOSIS

A. K. Khan, N. Healy, J. Kieran, M. Cullina, V. Twomey, A. O'Regan. Galway University Hospital, Republic of Ireland

Background: Sarcoidosis is a granulomatous disease of unknown aetiology and variable prognosis. Active disease is associated with suppressed delayed type hypersensitivity (DTH) to tuberculosis skin testing (TST). Therefore, a diagnosis of latent tuberculosis (MTB) in the setting of active sarcoidosis is difficult. Immunosuppressive therapy significantly increases the risk of reactivating latent tuberculosis. The introduction of interferon assays such as Quantiferon-G has provided an additional approach to diagnose latent MTB. No study has assessed the diagnostic yield of these assays in patients with sarcoidosis.

Methods: A study involving 24 patients with sarcoidosis were assessed for a history of MTB or previous exposure, prior BCG vaccination (confirmed with Scar), and prior tuberculosis skin testing. 2TU Tuberculin PPD-RT23 SSI skin testing and QFT-CP assays were performed. Four control subjects were used: 2 TST positive (one with active TB, one with latent TB); 2 TST negative.

Results: Of the sarcoidosis cohort 13(53%) were on no treatment, 10(43%) were on prednisolone and one (4%) was on INFLUXIMAB and methotrexate. Twenty-one (87%) patients had prior BCG vaccination. None described recent close contact with MTB. Three (13%) had TST and none had a +ve QFT-CP. All 3 patients had a previously documented negative TST. One patient, a nurse, was on immunosuppressant treatment (infliximab) and had prior negative TST on at least two occasions. She neither had evidence of prior BCG nor of active tuberculosis. The other two positive TST were stage 1 disease and not on immunosuppressive therapy. Both controls patients with positive TST had positive QFT-CP while those with negative TST were also negative on QFT-CP.

Conclusion: Interferon release assays for detecting latent tuberculosis added no clinically relevant information. These results suggest: (1) It is not cost effective to use QFT-CP in assessing patients with sarcoidosis; (2) Mechanistically, it is likely that the DTH immune suppression seen in sarcoidosis occurs at a cellular level rather due to migratory defect; (3) In view of the transient DTH immunosuppression and the risk of reactivating latent MTB in patients requiring corticosteroid or other treatment in sarcoidosis, our study demonstrated the need to perform yearly assessments for latent MTB on this population.

Basic mechanisms in interstitial lung disease

S53

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 uM) 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 (MMP) 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 uM and 400 uM 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 fibronectin, 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 B洋AL PROTEIN PERMEABILITY INDEX AND MATRIX METALLOPROTEINASES IN IDIOPATHIC PULMONARY FIBROSIS: A LINK BETWEEN ABERRANT VASCULAR PERMEABILITY AND PROGRESSION?

S. Mckeown², A. Richter¹, D. Mcauley², D. R. Thickett¹. University of Birmingham, UK; ²Queen’s University, Belfast, UK

Aberrant 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 (MMPs) 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 diagnosted IPF underwent bronchoscopy and bronchoalveolar lavage (BAL). BALM-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 (Pred- 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 (r²=0.35, p=0.004), MMP-7 (r²=0.32, p=0.005), MMP-8 (r²=0.42, p=0.001) and MMP-9 (r²=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=-.02, p=0.048) and MMP-7 (%Tco, r²=-.09, p=0.008). Protein permeability index was significantly elevated in those patients who died during the follow-up phase (died median 0.15, versus survived 0.0043, 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 survival 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 LYSOPHOSPHATIDIC ACID INDUCES αvβ6 INTEGRIN MEDIATED TRANSFORMING GROWTH FACTOR-BETA ACTIVATION VIA Gαq IN EPITHELIAL CELLS

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Introduction: Activation of latent transforming growth factor-beta (TGFβf) by the αvβ6 integrin is a critical step in the pathogenesis of acute lung injury and pulmonary fibrosis. Activation of the seven transmembrane domain G-coupled receptor, PAR1, can enhance αvβ6 integrin mediated TGFβf activity via RhoA and Rho kinase. Lysophosphatidic acid (LPA) is a 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 in paraffin embedded IPF and normal lung was assessed by TUNEL and immunohistochemical staining for Active Caspase 3 (AC3), Fas Ligand (FasL), FADD and p53. Wild type and heterozygous COX-2 deficient mice received oropharyngeal bleomycin (2 mg/kg) or saline. Apoptosis at day 14 was assessed by TUNEL. Fibrinolysis primary II AECs and fibroblasts were obtained from IPF patients undergoing lung transplant and control fibroblasts from patients undergoing lung resection. AECs and fibroblasts were serum starved and treated overnight with the non-selective COX inhibitor, indomethacin (1 µg/ml), a COX-2 selective inhibitor (NS398, 5µg/ml) or PGE2 (32 ng/ml). Cells were then exposed to FasL (50 ng/ml) for 24 hours, harvested, stained with annexinV/propidium iodide and analysed by flow cytometry.

Results: Only occasional apoptotic cells were observed in normal human lung tissue. TUNEL and AC3 staining of IPF lung demonstrated frequent epithelial cell apoptosis, but an absence of fibroblast apoptosis. Expression of FasL, FADD and p53 was dramatically upregulated in IPF lung tissue. TUNEL staining showed increased AEC, but decreased fibroblast, apoptosis in COX-2 deficient mice compared to WTs. FasL caused apoptosis of normal fibroblasts (51.5% (mean) ± 10.3% (SEM)) increase compared to controls). FasL inhibited COX-2 expression in IPF fibroblasts (2.2 fold) compared to normal fibroblasts (1.6 fold). FasL significantly reduced FasL apoptosis in normal fibroblasts by 35% (0.01) and 23% (p=0.03), respectively. Fibroblasts fibroblasts were resistant to FasL induced apoptosis (8.7% ± 4.3% increase compared to controls). PGE2 inhibited fibroblast fibroblasts susceptible to apoptosis (42.3% ± 15.5%, increase compared to control (p=0.04)). PGE2 reduced FasL induced apoptosis in primary fibroblasts by 18.2% (p=0.02).

Conclusion: Reduced COX-2 and PGE2 expression has previously been demonstrated to play a role in the pathogenesis of IPF. These results suggest that increased AEC loss due to apoptosis and fibroblast persistence due to resistance to apoptosis are important mechanisms by which reduced COX-2/PGE2 expression leads to pulmonary fibrosis.

S56 DIFFERENTIAL MODULATION OF LUNG FIBROBLAST AND AEROLAR EPITHELIAL CELL APOPTOSIS BY CYCLO-OXYGENASE (COX)-2 AND PROSTAGLANDIN E2 IS AN IMPORTANT MECHANISM IN THE PATHOGENESIS OF IDIOPATHIC PULMONARY FIBROSIS

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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 in paraffin embedded IPF and normal lung was assessed by TUNEL and immunohistochemical staining for Active Caspase 3 (AC3), Fas Ligand (FasL), FADD and p53. Wild type and heterozygous COX-2 deficient mice received oropharyngeal bleomycin (2 mg/kg) or saline. Apoptosis at day 14 was assessed by TUNEL. Fibrinolysis primary II AECs and fibroblasts were obtained from IPF patients undergoing lung transplant and control fibroblasts from patients undergoing lung resection. AECs and fibroblasts were serum starved and treated overnight with the non-selective COX inhibitor, indomethacin (1 µg/ml), a COX-2 selective inhibitor (NS398, 5µg/ml) or PGE2 (32 ng/ml). Cells were then exposed to FasL (50 ng/ml) for 24 hours, harvested, stained with annexinV/propidium iodide and analysed by flow cytometry.

Results: Only occasional apoptotic cells were observed in normal human lung tissue. TUNEL and AC3 staining of IPF lung demonstrated frequent epithelial cell apoptosis, but an absence of fibroblast apoptosis. Expression of FasL, FADD and p53 was dramatically upregulated in IPF lung tissue. TUNEL staining showed increased AEC, but decreased fibroblast, apoptosis in COX-2 deficient mice compared to WTs. FasL caused apoptosis of normal fibroblasts (51.5% (mean) ± 10.3% (SEM)) increase compared to controls). FasL inhibited COX-2 expression in IPF fibroblasts (2.2 fold) compared to normal fibroblasts (1.6 fold). FasL significantly reduced FasL apoptosis in normal fibroblasts by 35% (0.01) and 23% (p=0.03), respectively. Fibroblasts fibroblasts were resistant to FasL induced apoptosis (8.7% ± 4.3% increase compared to controls). PGE2 inhibited fibroblast fibroblasts susceptible to apoptosis (42.3% ± 15.5%, increase compared to control (p=0.04)). PGE2 reduced FasL induced apoptosis in primary fibroblasts by 18.2% (p=0.02).

Conclusion: Reduced COX-2 and PGE2 expression has previously been demonstrated to play a role in the pathogenesis of IPF. These results suggest that increased AEC loss due to apoptosis and fibroblast persistence due to resistance to apoptosis are important mechanisms by which reduced COX-2/PGE2 expression leads to pulmonary fibrosis.

S57 SERUM BIOMARKERS IN SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY FIBROSIS: KL-6 CORRELATES WITH DISEASE SEVERITY

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Background: A third of patients with systemic sclerosis (SSc) develop clinically significant pulmonary fibrosis (SSc-PF), with an associated 30%
Abstract S58

INCREASED SYSTEMIC INFLAMMATORY CYTOKINES IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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Background: Idiopathic pulmonary fibrosis (IPF) is characterised by chronic inflammation and fibrosis of the alveolar spaces and pulmonary interstitium. Mortal survival is less than three years. In other progressive pulmonary conditions elevated serum levels of interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and its soluble receptors (TNF-α srI and TNF-α srII) 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 divided into groups treated with combined corticosteroid/immunosuppressive therapy (4/23) and non-steroid groups (19/23). All patients underwent pulmonary function testing and had body composition assessed using body mass index (BMI) and bioelectrical impedance for fat free mass (FMM). Serum levels of IL-6, TNFα, TNF-α srI and TNF-α srII were measured using quantitative ELISAs and compared with measurements from 20 age and gender matched healthy controls.

Results: Circulating IL-6 (p < 0.01) and TNF-α srII (p < 0.01) were higher in patients with IPF compared with controls with no difference in serum levels of TNF-α srI (p = 0.23) and TNF-α srI (p = 0.32). (see table). Both TNF-α srI (r = -0.425, p < 0.05) and TNF-α srII (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 srI 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 srI 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.
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.

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**S60 SLEEP DISORDERED BREATHING IN PATIENTS WITH UNILATERAL PARALYSIS OR SEVERE WEAKNESS OF THE DIAPHRAGM**

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**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 pumps, while patients with unilateral diaphragm 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 diaphragm paralysis. After placing balloon catheters to measure oesophageal and gastric pressures, we measured diaphragm strength (sniff 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 diaphragm 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 REM sleep (18.1 (8.5) %max) during REM sleep (control group 0.2 (0.3) and 0.7 (0.9)/h, 7.6 (10.5)/h during non-REM sleep, and an RDI of 27.0 (18.4)/h)

**Conclusion:** We confirmed that patients with unilateral diaphragm paralysis or weakness do not develop SDB.

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

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**Introduction:** Sleep disordered breathing (SDB) is becoming increasingly recognised in heart failure (HF) occurring in 40–80% 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 spironolactone. 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, FEV1 <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, Respirins 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 61.9 (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 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 intervention trials.


**S62 ENDOTHELIAL FUNCTION IN PATIENTS WITH MILD–MODERATE OBSTRUCTIVE SLEEP APNOEA**

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**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

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Basic mechanisms in COPD

S64 HYPOXIA DECREASES HDAC2 IN U937 CELLS AS A POSSIBLE MECHANISM FOR GLUCOCORTICOID RESISTANCE IN COPD

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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 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 impairment of histone deacetylase 2 (HDAC2) in lungs of COPD patients can contribute to the inflammation and corticosteroid resistance seen (Ito K et al, NEJM 352, n19, 1967–76; Ito et al, JEM 203,7–13). Many patients with severe COPD suffer from prolonged exposure to hypoxemia adding to the morbidity and mortality associated with the condition. However, little is known about the effect of hypoxia on HDAC function and on the inflammation and corticosteroid resistance.

Methods: In this study U937 cells, a human monocytic cell line, were exposed to hypoxia (1% oxygen, 5% carbon dioxide, nitrogen balance) and hypoxia mimetic (0.5 mM CoCl₂) followed by measurements of HDAC2 mRNA, protein and activity in nuclear extracts. A reduction in total HDAC activity was observed after 20 hours of exposure to hypoxia and 0.5 mM CoCl₂ (74% ± 20% and 43.5 ± 12% of normal, p<0.05). Using Western blotting, HDAC 2 expression was decreased under the same treatments within nuclear extracts. This correlated with an increased stabilisation of HIF-1α, confirming that the treatments were leading to a normal hypoxic response.

Results: To examine the effect of hypoxia on inflammation, cells were stimulated overnight with TNF-α after a 24 hour exposure to low oxygen. Hypoxia significantly increased both non-stimulated and TNF-α-stimulated IL-8 secretion (normoxia: 0.2 ± 0.2 pg/ml, TNFα: 1005 ± 293.4 pg/ml). Hypoxia significantly increased both non-stimulated TNF-α (1005 ± 293.4 pg/ml, p<0.05) TNF-α: 3909.8 ± 694.7 pg/ml (p<0.05) as measured by ELISA. Dexamethasone treatment under hypoxia failed to return IL-8 to basal levels. This correlated with lower total HDAC activity in similarly treated cells. The decrease in HDAC2 protein and activity seems to be mediated at the transcriptional level as hypoxia and 0.5 mM CoCl₂ decreased the levels of HDAC 2 mRNA, while increasing the levels of VEGF mRNA (a known target of HIF-1α) as measured by RT-QPCR.

Conclusion: We have found that hypoxia causes a reduction in HDAC2 mRNA, protein and total HDAC activity. This is associated with enhanced inflammation and corticosteroid resistance. This is a novel mechanism for HDAC impairment and may provide new targets in the treatment of COPD.

S65 SPUTUM INTERLEUKIN-5 IS ELEVATED IN COPD SUBJECTS WITH EOSINOPHILIC AIRWAY INFLAMMATION AND DECREASES IN RESPONSE TO TREATMENT WITH ORAL CORTICOSTEROIDS

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Background: Eosinophilic inflammation is reported in 20–40% of subjects with stable chronic obstructive pulmonary disease (COPD). Eosinophilic inflammation is associated with airways hyper-responsiveness (AHR). Interleukin-5 (IL-5) is the key cytokine regulating eosinophil development, migration and survival. A proportion of COPD patients show eosinophilic airway inflammation, which may be responsive to oral corticosteroids (OCS) and reduces markers of airway inflammation.

Methods: Sputum samples were collected from 198 patients with severe obstructive emphysema. Sputum granulocyte influx was measured in 142 patients, sputum IL-5 was measured in 100 patients. Sputum eosinophilic inflammation was defined as a granulocyte influx of >3% and a sputum IL-5 concentration of >20 pg/ml. The sputum eosinophilic index (SI) was defined as the sputum IL-5 concentration divided by the percentage of sputum granulocytes. Patients were divided into those who had a sputum SI of >2% and those whose sputum SI was <2%.

Results: The SI was >2% in 53% of patients. There was a significant reduction in sputum IL-5 concentration in patients whose SI was >2% compared to patients whose SI was <2% (p<0.001). The SI was >2% in 60% of patients receiving OCS treatment compared to 25% of patients receiving OCS treatment (p<0.001). There was a significant reduction in sputum IL-5 concentration in patients whose SI was >2% compared to patients whose SI was <2% (p<0.001). There was a significant reduction in sputum IL-5 concentration in patients whose SI was >2% compared to patients whose SI was <2% (p<0.001). There was a significant reduction in sputum IL-5 concentration in patients whose SI was >2% compared to patients whose SI was <2% (p<0.001).

Conclusion: Sputum IL-5 concentration is elevated in patients with severe COPD and eosinophilic airway inflammation. Sputum IL-5 concentration reduces in response to treatment with OCS, thus confirming the value of this marker in assessing response to treatment with OCS.

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<table>
<thead>
<tr>
<th>Age</th>
<th>% So2 below 90% So2</th>
<th>Mins below 90% So2</th>
<th>BMI</th>
<th>Neck (m)</th>
<th>W/hip</th>
<th>W/ht</th>
<th>% insulin sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean or median</td>
<td>54.3</td>
<td>32.7</td>
<td>55.0</td>
<td>16.0</td>
<td>36.7</td>
<td>17.7</td>
<td>0.99</td>
</tr>
<tr>
<td>SD or interquartile range</td>
<td>11.0</td>
<td>18.3/49.8</td>
<td>18.3/120</td>
<td>12/18</td>
<td>8.5</td>
<td>1.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Bivariate correlation (p)</td>
<td>-0.0</td>
<td>-0.22</td>
<td>-0.33</td>
<td>0.06</td>
<td>-0.33</td>
<td>-0.51</td>
<td>-0.30</td>
</tr>
<tr>
<td>with % insulin sensitivity</td>
<td>0.06</td>
<td>(0.01)</td>
<td>(0.01)</td>
<td>(0.02)</td>
<td>(0.02)</td>
<td>(0.02)</td>
<td>(0.02)</td>
</tr>
<tr>
<td>with &gt;4% So2</td>
<td>0.21</td>
<td>-</td>
<td>0.05</td>
<td>0.37</td>
<td>0.44</td>
<td>0.18</td>
<td>0.36</td>
</tr>
<tr>
<td>with &gt;4% So2 dip rate</td>
<td>0.06</td>
<td>(0.67)</td>
<td>(0.001)</td>
<td>(0.10)</td>
<td>(0.001)</td>
<td>(0.001)</td>
<td>(0.001)</td>
</tr>
</tbody>
</table>
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 plucks 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 study subjects, stability was determined by measuring sputum IL-5 on two 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 was increased in those COPD subjects with a sputum eosinophilia 0.58 (0.71) pg/ml compared to those without a sputum eosinophilia 0.70 (0.19) pg/ml (p < 0.005). The sputum IL-5 within subject repeatability was good (mean (SEM) difference 2.20(1.43); r = 0.6, p < 0.001). 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 was increased in those subjects with a sputum eosinophilia IL-5 decreased in response to treatment with systemic corticosteroids. Our findings support the view that IL-5 is associated with eosinophilic airway inflammation in COPD and raises the possibility that specific therapies directed at IL-5 may have a role in the treatment of some patients with COPD.

**S66 THEOPHYLLINE RESTORES CORTICOSTEROID SENSITIVITY IN COPD CELLS VIA AN INHIBITORY EFFECT ON PI3K SIGNALLING**

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Although corticosteroids are the most effective anti-inflammatory agents in asthma, patients with chronic obstructive pulmonary disease (COPD) are corticosteroid-insensitive. Here we showed that low concentrations of theophylline (Theo) restore corticosteroid sensitivity in COPD cells in vitro, via modification of phosphatidylinositol-3 kinase (PI3K) signalling. Peripheral blood mononuclear cells (PBMCs) collected from moderate COPD patients (COPD: n = 20) and healthy volunteers (HV: n = 8) were stimulated with TNFα (1 ng/ml) for 16 h in the presence or absence of dexamethasone (Dex) (10⁻¹²–10⁻⁶M) and Theo (10⁻⁶M, equivalent to 0.18 g/l). IL-8 concentrations in supernatant were significantly correlated with % enhancement by LY (r = 0.5385, p < 0.05) in COPD was significantly higher than that of HV (r = 0.3585, p = 0.047), suggesting that responders to theophylline are nearly identical to the responders to LY. As a surrogate marker of PI3K activation, phosphorylation of the downstream target enzyme Akt (pAkt) was determined by Western blotting and normalised to total Akt protein. Theo completely inhibited H₂O₂-induced phosphorylation of Akt in U937, human monocyte-like cell line (IC₅₀ 0.68g/l) and Theo itself also inhibited activity of immunoprecipitated PI3K (α isoform directly (IC₅₀ 24 nM) and Theo itself also inhibited activity of immunoprecipitated PI3K-δ isoform directly (IC₅₀ 2uM). Furthermore, Theo increased activity of phosphatase and tensin homolog, PTEN, which antagonises PI3K-dependent cell activation by dephosphorylation of PI3P, a PI3K product. Taken together, modification of PI3K signalling by PI3K inhibition and PTEN activation is the main molecular mechanism of Theo for restoration of corticosteroid sensitivity in COPD.

This work has been supported by GSK, Wellcome Trust and MRC

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

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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 1i (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 were 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 in 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.

**S68 THE CONTRIBUTION OF GROWTH RELATED ONCOGENE ALPHA TO CHEMOTAXIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ALPHA 1 ANTITRYPSIN DEFICIENCY**

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Background: Neutrophil recruitment to the airway is thought to be of great importance in the development and progression of chronic obstructive pulmonary disease (COPD). Growth related oncogene alpha (GROα) is raised in sputum from patients with COPD and in vitro studies have shown an enhanced chemotactic response of peripheral blood monocytes to the CXC chemokine. Interleukin 8 and leukotriene B4 each account for an enhanced chemotactic response of peripheral blood monocytes to the CXC chemokine. Interleukin 8 and leukotriene B4 each account for

Results: The mean (SE) contribution of GROα (expressed as % n-formylmethionyl leucylphenylalanine) in COPD with A1ATD was 4.9% (3.4%) and without A1ATD was 9.0% (5.0%). When all the subjects were
Variation in the surfactant protein B gene is associated with development of emphysema in alpha 1 antitrypsin deficiency


Introduction: Polymorphisms in a number of genes, including surfactant protein B (SFTPB), have been associated with features of chronic obstructive pulmonary disease (COPD). The only widely accepted genetic risk factor is alpha one antitrypsin deficiency (AATD), which is caused by a number of deficiency alleles, most commonly the PiZ allele. There is considerable variation in the clinical phenotype of patients with AATD, even when comparing subjects with the same AATD genotype. Previous family studies have suggested that there may be additional genetic influences, as yet unknown. We hypothesised that polymorphisms in SFTPB may affect specific clinical phenotypes within AATD patients.

Methods: 424 patients with the PiZZ genotype were selected from the UK National Registry for AATD. All had full phenotypic information and smoking history available. DNA was extracted from whole blood using a modified Nucleon Bacc II kit (Tepnel Life Sciences), quantified using Picogreen (Molecular Probes Inc). 480 DNA samples from healthy, ethnically matched, control subjects were also selected and prepared using the Nucleon Bacc II kit. Genotyping for both SNPs was performed using TaqMan (Applied Biosystems) genotyping technologies.

Statistical analyses: Comparisons of genotype and allele frequency between cases and AATD subjects with 4 distinct phenotypes—(1) FEV1/FVC <70%, with FEV1 <80% predicted; (2) Emphysema on HRCT; (3) Bronchiectasis on HRCT; (4) Chronic bronchitis—were carried out using the chi-squared test. Logistic regression allowed comparison of AATD subjects with and without each phenotype, accounting for differences in smoke exposure. Power calculations showed we were powered to detect an allele conferring an odds ratio (OR) of developing airflow obstruction or emphysema of 1.5 relative to controls. Both SNPs were in Hardy Weinberg equilibrium in both cases and controls.

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. Lower 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

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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 [V]: 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 viscosity/elasticity measurements were carried out in triplicate using a CSL 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 in a paired study. In contrast, 24 hour sputum weight was significantly (p < 0.05) lower at the end of the Ab treatment (visit 1: 54.6 ± 12.59 g, visit 2: 47.35 ± 20.30 g, n = 19) and there was a trend towards reduction in solid content (visit 1: 5.15 ± 0.30; visit 2: 4.82 ± 0.48, n = 18, p = 0.06). Sample size calculations indicated that approximately 50 subjects would have been required to achieve significance in this assay. We also correlated these assays with each other and various assays carried out as part of the tracking study. There were significant correlation between sputum weight and DNA content (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). 24 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 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 (FEV1) improvement the overall quantity of expectorated sputum did not change significantly 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 INTRAVENTRUS ANTIBIOTICS

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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 and total solids, DNA and cell count and differential, serum inflammatory markers (CRP, white blood cell (WBC) count). Patients also completed a symptom score sheet. 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 P. aeruginosa, 8 with B. cepacia complex organisms and 14 with S. aureus (2 MRSA). Significant changes from baseline were observed in FEV1 (s3.3 (1.5) to 6.2 (1.7), p < 0.001), sputum P. aeruginosa colony count (log 10 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) to 3.5 (1–165) mg/l, p < 0.001) and symptom score (0.4 (2.4) to 2.6 (5.4), p < 0.04). 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), these 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.

**S72** COMPUTED TOMOGRAPHY IN INFECTIVE EXACERBATIONS IN CYSTIC FIBROSIS: SERIAL CHANGE AND OBSERVER AGREEMENT

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Introduction: Computed tomography (CT) is a potential outcome measure in clinical intervention trials of patients with cystic fibrosis (CF) lung disease. The ability to reproducibly demonstrate and quantify change are important criteria for the validation of an imaging biomarker. The purpose of this study was to determine whether changes in CT features could be identified in patients with CF following treatment for an infective exacerbation. Secondary objectives were to determine the observer agreement of a semi-quantitative scoring system designed to detect subtle changes in CT features and to compare two methods of scoring serial CTs. Methods: Thirty-six patients with CF were admitted with an infective exacerbation (CT1) and at 2 weeks following standard treatment (CT2). CTs from the first and second visits were scored randomly by two independent observers blinded to patient identity and timing of the scan. CT features for each lobe were scored using a semi-quantitative graded scoring system for extent and severity of bronchiectasis, bronchial wall thickness, small and large mucus plugging. Air trapping, consolidation and ground glass opacification

Table 1: Paired differences (CT1–CT2)

| Feature | Lower | Upper | p Value | 95% CI of the difference
|---------|-------|-------|---------|-----------------
| Ext. bronchiectasis | 0.18 | 0.89 | 0.02 | (0.88, 0.66) |
| Ext. bronchiectasis | 0.19 | 0.88 | 0.02 | (0.87, 0.66) |
| Branchial wall thickness | 0.43 | 5.31 | 0.01 | (0.81, 0.02) |
| Small mucus plugs | 0.43 | 6.48 | 0.03 | (0.81, 0.02) |
| Large mucus plugs | 0.14 | 6.48 | 0.03 | (0.81, 0.02) |

*Significant p value*
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 single outlier (p = 0.18, but p = 0.045 after removal of outlier).

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 ANTIBIOTIC TREATMENT FOR EXACERBATION


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 Expression Consorium "Treating Lung" 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%. 29 patients (15 male) completed both LCI and CT assessments. Mean age (range) was 21 (11–40) years, mean FEV1% predicted was 50%.

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.

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

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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: Our initial survey confirmed 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.

Aims: There are several randomised controlled trials providing evidence for efficacious treatment regimens for non-tuberculous mycobacterial infections. The results suggest that a single antibiotic regimen is as effective as multiple antibiotic regimens, and that further studies are required to determine the optimal duration of therapy. We conducted a case control study to determine which factors which are associated with an increased risk of ARF.

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 (9/24 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) per 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 8/43 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.

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DO MICRO NUTRIENTS USED AS SUPPLEMENTATION TO STANDARD TREATMENT SPEED RESOLUTION OF TUBERCULOSIS?


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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 adult patients who have been treated for tuberculosis in the past 6 months. Group A (the placebo arm) received standard treatment plus placebo, group B received the same anti-tuberculosis chemotherapy but with zinc supplement in addition; and group C, standard treatment plus zinc supplement in addition to vitamin A. Assessment of a number of factors, including socio-economic status, weight, body mass index, delivery of drugs in a double blind randomised prospective placebo controlled three arm study. Group A (the placebo arm) received standard treatment plus placebo, group B received the same anti-tuberculosis chemotherapy but with zinc supplement in addition; and group C, standard treatment plus zinc supplement in addition to vitamin A. Assessment of a number of factors, including socio-economic status, weight, body mass index, delivery of drugs in a double blind randomised.

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 to patients receiving treatment for tuberculosis. In fact possible harm may have resulted as seen by the increased mortality. This may have resulted from an immune reconstitution effect caused by immunological boosting by the micronutrients. Supplementation with these micronutrients cannot be recommended on the basis if this study.

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

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Aims: There are few randomised controlled trials providing evidence for efficacious treatment regimens for non-tuberculous mycobacterial infections. 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: Our initial survey confirmed 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 (9/24 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) per 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 8/43 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
Abstract S76 Treatment outcomes

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<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
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<td>Sputum AFB positive (%)</td>
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<td>10.3*</td>
<td>4*</td>
<td>4*</td>
<td>4.5*</td>
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<tr>
<td>Sputum culture positive (%)</td>
<td>100</td>
<td>17.2*</td>
<td>4*</td>
<td>8*</td>
<td>4.5*</td>
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<td>ESRI (median IQR) (30.7–89)</td>
<td>60.5 (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>
<td></td>
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<td>Cough (%)</td>
<td>87</td>
<td>58.5*</td>
<td>44.7*</td>
<td>58*</td>
<td>45*</td>
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<tr>
<td>Sputum (%)</td>
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<td>5*</td>
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<tr>
<td>Anaemia (%)</td>
<td>44</td>
<td>6*</td>
<td>12*</td>
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*p<0.005 compared to baseline value.

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) timepoint, 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 neuropitis (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.

S77 IS THE WORLD HEALTH ORGANIZATION REGIMEN OF THRIC WEEKLY CATEGORY 1 (NEW SPUTUM SMear POSITIVE PATIENTS) TREATMENT SUFFICIENT FOR PATIENTS WHO HAVE A HIGH DENSITY OF ACID-Fast BACILLUS IN THE SPUTUM?

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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 Emmanuell Hospital Association, an NGO, based in the Palamu 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+AFB 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. 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 2 months of intensive phase therapy 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 ETHAMBUTOL THERAPY RECEIVING ADEQUATE OPTIC NERVE FUNCTION SCREENING?

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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 eight 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. 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,

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approximately 8% of men in the general population are congenitally colour blind; although there is no evidence that those with pre-existing colour deficiency receive any greater benefit or suffer any worse toxicity, the usefulness of colour vision testing to diagnose or monitor optic nerve dysfunction in those who subsequently develop vision changes is severely reduced.

In addition, as in our female patient diagnosed with an isochromatic optic neuropathy, colour vision screening has the additional benefit, particularly in females, of identifying potentially serious ophthalmic and systemic disorders.

We recommend BTS guidelines for screening of ethambutol treatment be amended to incorporate colour vision.

S79 BARRIERS TO INITIATING ANTIRETROViral THERAPY IN HIV INFECTED PATIENTS WITH TUBERCULOsis CO-INFECTION
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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)1 in severely immunocompromised HIV infected individuals. However, the risk of IRIS is also highest in this group.2 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. These guidelines are based on available evidence.3

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. 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 OI; TB not commenced; patient fear of side effects = 3/57; patient refusal = 9/57; TB therapy intolerance/toxicity = 10/57; concurrent AIDS defining OI = 4/57; TB medication adherence issues = 4/57; other = 13/57, reason not documented = 14/57. 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, and ART was started within 3 months. Despite this, there was good. There were no relapses of TB before initiation of ARV. 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.


S80 THE TREATMENT OF ISONIAZID RESISTANT TUBERCULOSIS WITH PROMINENTLY A 9 MONTH REGIMEN (2RZE/3RE)
L. P. Ormerod, S. A. Haines. Royal Blackburn Hospital, UK

Background: Treatment Guidelines from the JTC (1988) and subsequently from NICE (2006) recommend for isoniazid resistant TB, an initial phase of 2 months rifampicin, (R) pyrazinamide (Z) and ethambutol (E), with a continuation phase of 7–10 months rifampicin and isoniazid.

Methods: 38 patients with proven or presumed isoniazid (H) resistance were treated between 1989–2006. 14 were female, all of South Asian ethnic origin (4 UK born), mean age 28.9 (range 3–59). 24 were male, 2 white, 1 Afghan, and 21 South Asian (2 UK born), mean age 28.7 years (range 12–72). One boy of 12 and 2 girls of 3 and 9 were treated on presentation as household contacts.

Results: Of the culture-confirmed cases, 15 had pulmonary disease, 11 sputum smear and culture positive, 4 smear-negative culture positive. The other sites were cervical gland (12), abdomen and bone/joint (2), and military, mediastinal glands, meninges and subcutaneous abscess (1). 34 cases were treated with a 9 month regimen of rifampicin and ethambutol, with 2 months initial pyrazinamide (2RZE/3RE). 4 patients were treated with other durations or regimens. All patients self-administered treatment but had regular random urine tests for rifampicin. All were followed up at 6 and 12 months with no clinical or x ray recurrence and then discharged.

Conclusion: This small study shows that good clinical results can be achieved with a 9 month 2RZE/3RE therapy in patients with close adherence monitoring. These results may not be applicable in other settings, eg, some of the patients in the North London outbreak who have multiple risk factors for non-adherence. Theoretically, however, a thrice weekly supervised regimen could deliver a satisfactory outcome.
survival benefit with neo-adjuvant chemotherapy at 5 years (1507 patients, HR 0.88, 95% CI 0.76 to 1.01, p = 0.071).

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

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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% (20/32) 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 stop, and a parallel clinic arrangement with adjacent respiratory medicine, thoracic surgery, oncology and palliative care colleagues working simultaneously to allow immediate specialist with no 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. Bowan3. 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) 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

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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>
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<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>
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<td>9%</td>
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<tr>
<td>Probable non-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 probable NSCLC. Performance status was recorded at diagnosis according to ECOG criteria. Staging for NSCLC was grouped into early (1a–2b), locally advanced (3a and 3b) and advanced (4). Vital status was confirmed by reference to the Thames Cancer Registry, Hospital PMI, GP practices and the NHS tracing service. Only those with a confirmed vital status were included. Survival was censored at 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: 944 patients were registered with lung cancer and a confirmed vital status could be established for 909 (96%). The median age was 71 years (65–74 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, SCLC and probable NSCLC, NSCLC and those with unconfirmed histology. 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 no 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.

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 no 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.

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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 2003. 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 I; 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 46.5% (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

**Abstract 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**

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**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.

**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.


**Abstract S88**

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

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**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 endotoxaemia in mice, large numbers of the inflammatory Gr-1high monocyte subset migrate 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...
Abstract S88 **p<0.01, different from control non-treated mice; †p<0.01, different from each other.

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 monocyes and margination to the lungs was assessed in C57BL/6 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 clodarotide-liposome mediated depletion of monocyes.

Results: Early mobilisation of bone marrow Gr-1high 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±106 to 1.8±0.2±106/106/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 monocyes (see fig). However, this protective effect was reversed at 48 h post-clodarotide treatment, when LPS-induced Gr-1high monocyte margination to the lungs had returned to normal levels, n = 4–6/group.

Conclusion: These results suggest that recruitment of bone marrow Gr-1high monocytes to the pulmonary microcirculation during subclinical endotoxaemia transforms the lungs into a ‘primed’ state. Upon further systemic septic challenge, these pre-marginated monocyes 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.


S89 TRANSFORMING GROWTH FACTOR BETA (TGFβ) INDUCES CELLULAR SENESCENCE IN PRIMARY BRONCHIAL EPITHELIAL CELLS: A POSSIBLE ROLE IN AIRWAY REMODELLING


Introduction: The profibrotic cytokine transforming growth factor beta (TGFβ) has been implicated in the pathogenesis of obliterative bronchiolitis (OB) after human lung transplantation. TGFβ has pleiotropic actions including the development of cellular senescence in fibroblasts and cell lines, however the relevance of this process to airway epithelium is unclear. Cellular senescence is a fundamental cellular response to stress, cells adopt a characteristic morphology and are growth arrested with a profound inflammatory phenotype. Consequent lack of tissue regenerative capacity and release of proinflammatory mediators could contribute to an aberrant response to airway injury and subsequent remodelling seen in OB.

Aim: To examine whether TGFβ can induce cellular senescence in primary bronchial epithelial cells (PBECs) derived from lung transplant recipients.

Methods: PBECs (n=4) grown from stable lung transplant recipients were treated for 72 hours with TGFβ (10 ng/ml). Cellular senescence was assessed by looking at cell phenotype and staining parafluoromethylene fixed cells for senescence associated beta galactosidase. Cellular proliferation was assessed by Ki 67 immunofluorescence. Levels of the cell cycle inhibitor proteins p16 and p21 were assessed by western blotting. Intracellular reactive oxygen species (ROS) were measured on FACs by staining with mitoSOX and dihydrodorhodamine.

Results: A proportion of cells treated with TGFl (10 ng/ml) for 72 hours adopted an enlarged senescent like morphology with increased SA α-gal staining (mean number SA α-gal positive cells: control 6.6±1.4%, TGFl 28±4.7%, p<0.05) and fewer Ki 67 expressing proliferating cells (mean number Ki 67 positive cells: control 73.5±5.78%, TGFl 13.4±8.73%, p<0.05). Levels of p16 and p21 were increased in i.v. LPS pre-marginated samples compared to control 1.58±0.25, p<0.05) as were levels of p21 (mean fold increase compared to control 2.75±1.37, p=ns). Intracellular ROS were increased (mean fold increase compared to control 1.68±0.48, dihydrodorhodamine 1.66±1.47 p<0.05 for both).

Conclusion: TGFβ can induce features consistent with cellular senescence in PBECs and this is associated with an increase in intracellular oxidative stress. An accumulation of senescent cells in the airway could contribute to the development of OB and other airway diseases associated with remodelling.

S90 ADAM33 IN LUNG DEVELOPMENT AND THE EFFECT OF MATERNAL ALLERGY

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Rationale: Polymorphisms of ADAM33 are strongly associated with asthma and bronchial hyperresponsiveness (BHR) (Van Eerdewegh P et al. Nature 2002). The murine homolog for ADAM33 has also been associated with BHR (BHR1 locus) (DeSanctis et al. Nat Genet 1995). SNPs in ADAM33 predict impaired lung function in young children (Simenson A et al. AJRCCM 2005). To investigate a role for ADAM33 in early life, we studied the expression of ADAM33 in mouse embryonic lungs from healthy and allergic mothers.

Methods: MF-1 mouse lungs were harvested at embryonic day (ED) 11–19 and day 1 and day post partum (PD) (n = 5–8). A/J mice (BHR positive) were sensitised with ovalbumin (ova), time-mated and exposed to ova or saline (1 hour, 3 times/week). ED15 and 18 and PDS lungs and newborn lungs (n = 4–19) were harvested from normal and allergic mice. Samples were processed for mRNA analysis of ADAM33 and p-smooth muscle actin (α-SMA) by RT-qPCR.

Results: ADAM33 mRNA expression increased in 4 significant (p<0.002) steps during mouse lung development. These corresponded to the recognised stages of lung development. The greatest increases in ADAM33 expression occurred from ED11–12 and postpartum. A similar pattern of expression was observed for α-SMA. In the Ovalbumin allergic challenge mouse model, ADAM33 mRNA expression was significantly (p<0.05) depressed and α-SMA mRNA showed a tendency (p = 0.027) for suppression in PDS offspring from allergic A/J mice.

Conclusion: The increase in ADAM33 in the early stages of lung development and postpartum suggest that it might be induced by tubular contraction that starts in the pseudoglandular stage and mechanical stretch from breathing after birth. The down regulation of ADAM33 in newborn mice from allergic mothers suggests, for the first time, a link between environmental influences associated with TH2 type inflammation and a locally acting asthma susceptibility gene.


S91 STRUCTURE AND FUNCTIONAL ANALYSIS OF LIPOPOLYSACCHARIDE AND LIPID A OF BURKHOLDERIA MULTIVORANS STRAINS ISOLATED FROM CYSTIC FIBROSIS TRANSPLANT RECIPIENTS

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Background: The Burkholderia cepacia complex (BCC) is a group of Gram negative bacteria of nine phenotypically similar but genetically distinct species which cause severe and life-threatening infections in cystic fibrosis (CF) patients. The most prevalent and also most virulent strains isolated from CF centres are B cepacia and B multivorans. Pre-transplant infection with B cepacia is associated with poor outcomes following lung transplantation whereas infection with B multivorans does not. Lipopolysaccharide (LPS) molecules are potent virulence factors in Gram negative bacteria. The cystic fibrosis airway is believed to induce specific LPS changes in both Pseudomonas and Burkholderia spp. A complete analysis of the bacterial
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 clonally 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-arabinose residues conferring resistance against defensins. Interestingly the post-transplant strain demonstrated a decreased lipid A acylation status consistent with the reduction in TNF cytokine inducibility. 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.

S92  K5, A KAPOSI SARCOMA HERPESVIRUS GENE PRODUCT, TARGETS BONE MORPHOGENETIC PROTEIN RECEPTOR II FOR UBQUITINATION AND ENDOSOMAL 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 possible 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. Concanamycin 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 cells compared to wild type. Treatment of K5 HeLa cells with Concanamycin 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

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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 (FeNO)), 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.

Abstract S93 Table 1: results of investigations

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>FEV1, pre BD (%)</td>
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</tr>
<tr>
<td>FEV1, post BD (%)</td>
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<tr>
<td>Reversibility (%)</td>
<td>88</td>
<td>45–124</td>
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<tr>
<td>FeNO (ppb)</td>
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<td></td>
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Abstract S93 Table 2: contributing factors (NB: more than one could be assigned per child)

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<th>Factor</th>
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<tr>
<td>Psychosocial issues</td>
<td>18</td>
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<tr>
<td>Poor adherence</td>
<td>15</td>
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<td>Unsuitable inhaler</td>
<td>6</td>
</tr>
<tr>
<td>Poor inhaler technique</td>
<td>5</td>
</tr>
<tr>
<td>Passive smoking</td>
<td>11</td>
</tr>
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<td>Vocal cord dysfunction</td>
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</table>
S94 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 + TNF-α) at 10 ng/ml for 24 hours) AEC monolayers at passage 2 was determined by cytokometric 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 (77%) 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 significant differences in the 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 mediator release from children with asthma compared to healthy children 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.


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>0.002</td>
</tr>
<tr>
<td>RANTES</td>
<td>0.09 (0.20)</td>
<td>0.08 (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.

S95 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. Saglani2, 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. 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).

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 eosinophilic inflammation and total inflammation as previously measured on EBB. Subgroup analysis was performed by current atopic, non-atopic phenotype and current wheeze status defined as transient (asymptomatic in previous year) or persistent.

Results: Children with a history of recurrent wheeze (n = 25, median age 5.1 (range 4–6.9) 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, mean diff −0.037 (95% CI −0.022 to −0.052) p < 0.005). There was no significant difference in the other pre-bronchodilator lung function parameters. There was no correlation between lung function and previous EBB findings. Measurements after bronchodilator showed significant improvement in srAw (1.276 vs 1.030, −0.245 (95% CI −0.130 to −0.360) p < 0.0005) and Scond (0.059 vs 0.036, −0.022 (95% CI −0.007 to 0.002), at −0.170 (95% CI −0.032 to 0.008) p < 0.005), but Sacin values remained higher than in controls (0.036 vs 0.022, −0.014 (95% CI −0.003 to −0.031) p < 0.012). There was no difference in lung function parameters between atopic and non-atopic or persistent and transient wheezers. Persistent wheezers were more likely to have had RBM thickening (p = 0.028).

Conclusion: Conductive airways heterogeneity, only partially responsive to bronchodilator, is already present in severe preschool wheetzers 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.


S96 EVIDENCE OF PERSISTENT SMALL AIRWAYS DISEASE MEASURED BY LUNG CLEARANCE INDEX IN WELL-CONTROLLED ASTHMATIC CHILDREN WITH NORMAL FEV1
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Introduction: In asthmatic patients, conventional spirometry (FEV1, PEF) 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. We hypothesised that heterogeneity of disease in the small airways, with bronchodilator reversibility, at 4–6 years of age in children completed 3 washouts at one visit only. Well-controlled asthmatic children and healthy age-matched controls.

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 baseline visit 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 is 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
L. Fleming 1, N. Regamey 1, C. Bossley 2, N. Wilson 2, A. Bush 1. 1Imperial College; 2Royal 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 eosinophils (eos)), spirometry (pre- and post-bronchodilator (BD)) and clinical evaluation (asthma control test (ACT)) on 1 day if 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

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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), 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), infarct (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>Results of investigations</td>
<td>Good response</td>
<td>Poor/no 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>
DOBDOES THE USE OF PREOPERATIVE CT-PET IMPROVE THE SURGICAL MANAGEMENT OF THE SOLITARY PULMONARY NODULE?

M. H. Chamberlain, A. Martin-Ucar, S. Muller, J. Entwistle, D. A. Woller. Glenfield Hospital, Leicester, UK

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 granuloma. 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.

IS SURGERY CONTRAINDICATED FOR PATIENTS WITH SMALL CELL LUNG CANCER AND CLINICAL N2 DISEASE?


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 chemo-radiation 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 excellent survival of conventional clinical TNM criteria in the selection of patients with very limited disease for surgery. The presence of clinical N2 disease per se should not be a contraindication to surgery.

Methods: We identified 59 patients who underwent complete resection with nodal dissection for SCLC during 2006. We sought to determine the implications of establishing a service from both cost and time-to-treatment perspectives.

Results:

- Of the 59 patients, 47 (80%) had stage I to III disease (32% stage I, 21% stage II, 5% stage III).
- Of the 12 patients with stage IV disease, 5 (42%) were classified as stage IVB.
- Of the 47 staging mediastinoscopies performed, 27 showed malignant nodes (57%)
- Of the 22 node-positive patients, 14 underwent complete resection and 8 underwent palliative management.

Conclusions: Our results demonstrate excellent survival for stage I to III patients who underwent lung resection with nodal dissection for SCLC. With improved preoperative and intraoperative staging these results supports the need to re-evaluate surgery as primary treatment and the use of conventional clinical TNM criteria in the selection of patients with very limited disease for surgery. The presence of clinical N2 disease per se should not be a contraindication to surgery.
Techniques and outcomes in bronchoscopy and lung biopsy

R. Naseer1, W. L. Williams2, J. Howells3, J. Edwards1, J. Mills1, M. Munavvar1.
1Lancashire Teaching NHS Trust; 2University of Manchester, UK

Introduction: Diagnosis is related to the stage of lung cancer and therefore effective staging procedures are required to help determine treatment and prognosis. Many lung cancers usually metastasise to hilar and mediastinal lymph nodes first and so sampling of these play an important role. Conventional transbronchial needle aspiration (c-TBNA) was first used in the 1980s to increase the yield of bronchoscopic procedures. It is still a relatively undervused procedure with only one third of chest physicians performing the procedure (Munavvar M et al. Survey of the Practice of Interventional Bronchoscopy in the UK. Thorax 2004;59(Suppl II); c-TBNA yield can vary between 20–80% and is dependent on operator experience and site of lesion. Endobronchial ultrasound (EBUS) was first developed in Japan in the mid 1990s to more accurately image mediastinal lymph nodes. This procedure is performed using a specially designed curved linear array bronchoscope with a transducer at the tip to perform EBUS guided TBNA's, to try and further increase the yield of bronchoscopic procedures, and so far has shown good results (Yasufuku K et al. Chest 2004;126:122–8; Rintoul RC et al. Eur Res J 2005;25:416–21; Herth FJ et al. Thorax 2006;May 31-epub).

In this retrospective study we looked to compare the diagnostic yield of c-TBNA and EBUS-TBNA in a Lancashire Teaching Hospital. We also looked at whether the lymph node station from which the EBUS-TBNA was taken alters diagnostic yield.

Method: The EBUS service was started in May 2006. We looked at all the bronchoscopy reports of patients who had EBUS-TBNA between May 2006 and May 2007 and recorded the site of sample (selected by CT appearances) and cytology results. We then compared this with all the c-TBNAs done between May 2004 and May 2005. All procedures were performed by a single operator (MM) and done in the endoscopic suite of a teaching hospital. The c-TBNA and EBUS-TBNA results were compared to the lung cancer MDT result and a diagnostic yield was defined as correlation between the final diagnosis at the MDT and the TBNA findings (that is, diagnostic yield includes both true positives and true negatives).

Results: Endoscopy-related complications included two self-limiting bleeding episodes (one in each group) and one patient in the EBUS group with excessive coughing. None of the complications required further treatment. In the c-TBNA group there were 33 patients (22 male, 11 female) with a mean age of 65.1. The EBUS-TBNA group contained 52 patients (38 male, 14 female) with a mean age of 64.2. In the EBUS group, two patients had no samples taken due to intolerance to the procedure. Three patients in the EBUS group were from a different Trust and were not discussed at our MDT and therefore were excluded, as no final diagnosis was available. EBUS samples were taken from different nodal areas: left hilar (LH), right hilar (RH), right paraatracheal (RP), subcarinal (SC), mass (M), or other—per stated in notes (O). Diagnostic yield: c-TBNA, 42% (14/33); EBUS-TBNA, 66% (31/47).

Conclusion: EBUS guided TBNA in this study increased the diagnostic yield of TNBAs by 24%, which is a relative increase of more than 50%. Therefore we can conclude that EBUS-TBNA is a better diagnostic choice of bronchoscopic procedure where available. However c-TBNA still has an important role to play as it helps increase the yield of routine bronchoscopic procedures. Both c-TBNA and EBUS-TBNA are relatively safe procedures and reduce the need for invasive methods of lymph node sampling, which are more expensive, complicated and have greater risks associated with them. Site-dependent yield for EBUS-TBNA does seem to vary, with lymph node sampling from the left hilar region and subcarinal region providing the greater yield.

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>68%</td>
<td>3.7%</td>
<td>9%</td>
<td>80%</td>
<td>81%</td>
</tr>
</tbody>
</table>

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percutaneous CT-guided lung biopsy can aid the diagnostic yield in patients with suspected lung cancer where bronchoscopy is unhelpful. We were interested in assessing the diagnostic and complication rate using this technique in our large lung cancer unit (400 cases per year).

Methods: We audited the last 150 CT-guided percutaneous lung biopsies (mean patient age 70 years (range 25–90), mean FEV1 73% (range 24–131)), 79 male), looking for delays in access, the type of biopsy and number of samples taken, the grade of the operator, and any complications.

Results: Mean time from request to biopsy was 7.8 days (range 0–34). 147 were performed as outpatients, using day case facilities. Biopsies were taken using a co-axial needle in 132 cases (88%); 86 (57%) by single pass, 24 (16%) two-passes and 3 (2%) three-passes. 83 biopsies (55%) were performed by consultant radiologists who biopsied smaller and deeper lesions than junior staff (p < 0.001). All patients had a chest X-ray (mean time 1.3 h (range 1–3) post-biopsy). 45 patients (32 the operator was a consultant radiologist) had a pneumothorax on this film, not related to the patient’s pulmonary function, age or gender, or the number of passes or chest wall thickness. The pneumothorax rate was greater in those with smaller lesions (p < 0.001) and in those further from the chest wall (p < 0.001). Treatment was conservative in 29 cases (62%), by aspiration in 7 (13%) and via intercostal tube drainage in 9 (20%). There was minimal pulmonary haemorrhage in 6 patients (4%) but none required blood transfusion. No patient had an air embolism or haemorrhaxia, and there were no deaths. As regards diagnostic yield, 108 (72%) were positive for malignancy.

Conclusions: More technically difficult biopsies are associated with a higher complication rate and tend to be done by the more experienced radiologists (consultants). The diagnostic yield is similar to that reported in the literature. This technique is suitable for outpatients using a day case facility and can help to speed up the diagnostic pathway for patients with suspected lung cancer.

S107 Diagnostic value and risks of transbronchial lung biopsies

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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 pneumothoraces 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 was 89%. No patients with usual interstitial pneumonia (UIP) had TBB. A definitive diagnosis was achieved in 75 (77%) of cases.

Abstract S107 Diagnostic accuracy of transbronchial lung biopsy

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>n</th>
<th>Confirmed by TBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoïdosis</td>
<td>31</td>
<td>90%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>22</td>
<td>64%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>86%</td>
</tr>
<tr>
<td>Organising pneumonitis</td>
<td>6</td>
<td>67%</td>
</tr>
<tr>
<td>Lung infection</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3</td>
<td>0%</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>77%</td>
</tr>
</tbody>
</table>

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 cytology. 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.

Abstract S106 Comparison of positive cytological samples using conventional cytology (CC) vs liquid based cytology (LBC)

<table>
<thead>
<tr>
<th>Year</th>
<th>Endo tumour?</th>
<th>Total patients</th>
<th>Positive diagnosis cancer</th>
<th>BAL (% positive)</th>
<th>Bronchial brushings (% positive)</th>
<th>TBNA (% positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–4 CC</td>
<td>+</td>
<td>48</td>
<td>38 (79%)</td>
<td>19/45 (42)</td>
<td>12/30 (40)</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>2006–7 LBC</td>
<td>+</td>
<td>48</td>
<td>41 (85%)</td>
<td>25/44 (57)</td>
<td>19/29 (64)</td>
<td>5/11 (45)</td>
</tr>
<tr>
<td>2003–4 CC</td>
<td>–</td>
<td>20</td>
<td>4 (25%)</td>
<td>3/20 (15)</td>
<td>ND</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>2006–7 LBC</td>
<td>–</td>
<td>26</td>
<td>8 (30%)</td>
<td>6/23 (26)</td>
<td>ND</td>
<td>2/3 (75)</td>
</tr>
</tbody>
</table>
by TB8 in 77%. 21% patients needed other procedures for a definitive histological diagnosis. A further 2% had samples that were insufficient for examination and were not further investigated.

Conclusions: In conclusion, transbronchial lung biopsies were found to be a safe procedure with the main complication being pneumothorax, although all these were manageable without surgical intervention. TB8 had a high diagnostic yield except in patients with vasculitis and no patients with UIP were investigated in this study.

S108  SIMPLE BLOOD PRESSURE MONITORING USING THE AIRTAG SYSTEM: A PROSPECTIVE STUDY OF THE EFFECT OF HYPERTENSION ON PRIMARY CARE PATIENTS’ VITAL SIGNS

Introduction: The prevalence of hypertension is rising. We undertook a prospective study of the effect of hypertension on primary care patients’ vital signs.

Methods: 300 consecutive patients attending a primary care clinic were recruited. An AirTag blood pressure monitor was used to measure systolic and diastolic blood pressure. The patients were then divided into normotensive and hypertensive groups. The effect of hypertension on vital signs was determined.

Results: Of the 300 patients recruited, 150 were normotensive and 150 were hypertensive. The normotensive group had significantly lower systolic and diastolic blood pressures compared to the hypertensive group. The effect of hypertension on vital signs was significant for both systolic and diastolic blood pressures.

Conclusions: Hypertension is a significant risk factor for cardiovascular disease. Simple blood pressure monitoring using the AirTag system can provide valuable information for primary care practitioners.

S109  LUNG TRANSPLANTATION FOR IDIOPATHIC PULMONARY FIBROSIS: RECIPIENT CHARACTERISTICS AND SURVIVAL OUTCOMES IN A SINGLE CENTRE 1987–2007

D. Cooper, J. Kerr, G. Parry, J. H. Dark, J. Lordan, P. A. Corris, A. J. Fisher. 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, TLCO, PaO2 and PAP), 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 53.9 years (25.2–64.7). Mean pre-transplant PaO2 was 6 minutes walk distance 210 m (15–570 m), with a median desaturation to below 85% on 6MWT had (1) greater resting 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 = 0.35, 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 < 0.0001; 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 < 0.0001), 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 decompensation.
S111 THE RISK OF ACUTE CORONARY SYNDROMES, CEREBROVASCULAR ACCIDENTS AND DEEP VEIN THROMBOSES IN PEOPLE WITH IDIOPATHIC PULMONARY FIBROSIS AND THE GENERAL POPULATION

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Background: People who have factor V Leiden homozygosity have an increased tendency to clot and also to have restricted lung function. 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 marked 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></th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before IPF diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>72</td>
<td>192</td>
<td>1.53 (1.15 to 2.03)</td>
</tr>
<tr>
<td>DVT</td>
<td>19</td>
<td>38</td>
<td>1.98 (1.13 to 3.48)</td>
</tr>
<tr>
<td>CVA</td>
<td>53</td>
<td>191</td>
<td>1.09 (0.79 to 1.50)</td>
</tr>
<tr>
<td>After IPF diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>43</td>
<td>113</td>
<td>3.14 (2.02 to 4.87)</td>
</tr>
<tr>
<td>DVT</td>
<td>14</td>
<td>29</td>
<td>3.39 (1.57 to 7.28)</td>
</tr>
<tr>
<td>CVA</td>
<td>25</td>
<td>125</td>
<td>1.60 (0.98 to 2.62)</td>
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</table>

S112 DOES BODY MASS INDEX INFLUENCE INFLAMMATION AND PLASMA LIPIDS IN PIGEON FANCIERS’ ALLERGIC ALVEOLITIS

S. Brennan1, I. Fraser2, L. Jolly3, C. Lynch3, L. Urquhart3, N. Sattar3, M. R. Adamson1, C. McCharry4, K. Anderson1. 1Crosshouse Hospital, Kilmarrock; 2Thorax Unit, University of Glasgow; 3Biochemistry, 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 clefs in the lung 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 lipophilic burden to inhaled avian antigens by 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 [2.5-46.0], p<0.01), higher CRP levels (28.1 [1.6-8.0], 1.7 [1.2-6.4], 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), with ox-LDL (r=0.423, p=0.010), and a trend to higher antibody (r=0.278, p=0.011). 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

<table>
<thead>
<tr>
<th></th>
<th>Baseline walk test</th>
<th>Optimal O2 walk test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance walked (m)</td>
<td>76.5 ± 6.5</td>
<td>93.4 ± 6.6</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>Borg score</td>
<td>11 ± 5.3</td>
<td>1 ± 1.3</td>
<td>p = 0.22</td>
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<tr>
<th></th>
<th>Baseline walk test</th>
<th>Optimal O2 walk test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance walked (m)</td>
<td>135.0 ± 108.8</td>
<td>216.2 ± 6.3</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Borg score</td>
<td>1 ± 1.7</td>
<td>1 ± 1.7</td>
<td>p = 0.07</td>
</tr>
</tbody>
</table>

S113 AMBULATORY OXYGEN IN IDIOPATHIC PULMONARY FIBROSIS: OF WHAT BENEFIT?

S. Hicks, L. G. Spencer, A. Duck, E. Barnett, C. T. Leonard. Wythenshawe Hospital, Manchester, UK

Introduction: Exercise limitation/exercise-induced breathlessness is a key problem which limits activities of daily living and reduces self-reported quality of life in patients with idiopathic pulmonary fibrosis (IPF). Ambulatory oxygen (amb O2) is widely prescribed for IPF patients but benefits gained from this practice have not been reported. We set out to assess the benefits of amb O2 in 70 IPF patients in terms of walking distance and dyspnœa (Borg) score.

Methods: Retrospective case note study (n=70) of IPF patients who were assessed for amb O2 using 6-minute walk test (6MWT) at our hospital between 2004–7. IPF diagnosis was as ATS/ERS guidelines. Data were collected on distance walked, O2 saturations (SpO2) and Borg score pre- and post-test. Forty one patients were already using O2 pre-amb O2 assessment and performed a baseline 6MWT with O2. Reasons for using pre-amb O2 assessment included long-term oxygen therapy, PRN or amb—but need for reassessment identified. Twenty nine patients were not using O2 and performed baseline 6MWT without O2. All patients were required to have resting PaO2 levels >8 kPa to commence test. During walking, if SpO2 fell <90% the test was terminated, patients rested, then test repeated with increased O2 flow rates (2 l/min increments). This was continued until a maximum of 10 l/min was reached or SpO2 level of ≥90% was achieved.

Abstract S113
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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 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). Poisson 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.
**S116** ERDOSTEINE IN ASSOCIATION WITH AMOXICILLIN IMPROVES THE OUTCOME OF ACUTE EXACERBATIONS COMPARED TO AMOXICILLIN ALONE IN COPD PATIENTS

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**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 a 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, catarrh rhonchi at auscultation, cough and dyspnoea. Secondary endpoints were the overall physician’s and patient’s judgement of efficacy, and pulmonary function tests (FEV1, FVC, MMF25–75%). An analysis of variance (ANCOVA) was performed.

**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 (ANCOVA 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

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**Introduction:** Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with reduced quality of life, increased morbidity and mortality. Management of AECOPD is aimed at returning 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 2500 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 (£0.02939/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.

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**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; (serum)</td>
<td>TBARS</td>
<td>Minutes*: 5 (I), 30 (I)</td>
<td>Basgivy et al, 2005</td>
</tr>
<tr>
<td>Chronic bronchitis current smokers: 300 mg bid/ placebo for 5 days; (BAL)</td>
<td>GSH</td>
<td>Hours: 2 (I), 12 (I)</td>
<td>Mitrea et al, 1998</td>
</tr>
<tr>
<td>Healthy current smokers: 300 mg bid for 7 days; (serum)</td>
<td>GSSG, MDA</td>
<td>Days: 2 (I), 12 (I)</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>ROS</td>
<td>Days: 4 (I), 7 (I), 10 (I)</td>
<td>Dal Negro et al, 2006</td>
</tr>
<tr>
<td>IL-8</td>
<td>4 (I), 7 (I), 10 (I)</td>
<td>Dal Negro et al, 2006</td>
<td></td>
</tr>
<tr>
<td>8-iso</td>
<td>4 (I), 7 (I), 10 (I)</td>
<td>Dal Negro et al, 2006</td>
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</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.

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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 oxidative stress. 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.
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 (Δ 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 (Δ pH = −0.02 (SD 0.05); 95% CI −0.02 to −0.04, p < 0.003). Pleural fluid pH was stable in samples left at room temperature for 1 h. Significant changes were observed at 4 h (Δ pH = 0.02 (SD 0.08); 95% CI −0.04 to −0.003, p = 0.03) and at 24 h (Δ pH = −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. Stric
Spoken sessions

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. SneesJ, Steele6, M. Nankivell7, C. Pugh8, 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 × 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: 66 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: 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 significantly 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

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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 (<1.4F), 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 related to 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 one year) and surgery rate (guide-wire, death and surgery rate (guide-wire, death and surgery rate (guide-wire, death rate (guide-wire, death rate (%) surgery (%) surgery rate at 1 year) 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.

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

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 97/263 (37%), blunt 57/140 (41%) OR = 1.19, 95% CI 0.79 to 1.81, $\chi^2$ 1df = 0.66, p = 0.42), nor with any other outcome. 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.

Abstract S123 PREDICTORS OF LONG-TERM POSTOPERATIVE SURVIVAL IN MALIGNANT PLEURAL MESOTHELIOMA: A MULTIVARIATE ANALYSIS IN 300 PATIENTS TREATED IN A SINGLE INSTITUTION

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Background: Current guidelines advocate surgery for malignant pleural mesothelioma (MPM) for symptom control; the role of therapeutic surgery remains controversial. There is no randomised evidence for a multi-modality approach including extrapleural pneumonectomy (EPP) or radical pleurectomy/decortication (P/D) or non-radical by thoracoscopy (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 S121

<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>

$\chi^2$ 3df = 1.41, p = 0.70

$\chi^2$ 3df = 1.53, p = 0.67

$\chi^2$ 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 < 0.01). On univariate analysis, younger age (p = 0.003), epithelial type cell (p = 0.010), radical surgery in favour of radical P/D (p < 0.001), negative node staging following mediastinoscopy (p = 0.014), haemoglobin > 14 g/dl (p = 0.012), WCC > 8.3 x 10^9/l (p = 0.005) and adjuvant chemotherapy (p < 0.01) were good significant prognostic factors. On multivariate analysis, age > 60 years (p = 0.006, HR 1.7), non-epithelial histology (p < 0.001) 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

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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 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.

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 pneumothorax in pregnancy (seven cases), together with a review of the relevant literature, and offer advice regarding the management of such patients.

S125 PLEURECTOMY/DECORTICATION FOR MALIGNANT MESOTHELIOMA

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Objective: Pleurectomy/decortication offers patient palliation from symptoms of pain and management of pleural fluid in an attempt to improve quality of life. We wanted to assess the effectiveness, safety and survival of patients undergoing surgery.

Methods: A retrospective analysis of 27 patients undergoing pleurectomy/decortication from 1 November 2003 to 30 April 2007 entered in our thoracic database was undertaken. All patients had undergone VATS to establish the diagnosis of malignant mesothelioma.

Results: Twenty two males and five females had undergone pleurectomy/decortication. The age range was 38–80 years with a mean of 66 years. Preoperatively: 6 patients had tcalc pleurodesis, 6 had chemotherapy, 5 had tcalc pleurodesis and chemotherapy, and 10 patients had VATS only to establish diagnosis. The commonest presentations of mesothelioma included pleural effusion (n = 13), non-specific shortness of breath (n = 7), chest pain (n = 6), persistent cough (n = 2), weight loss (n = 2), haemoptysis/empyema/pneumonia (n = 1). The histology was 14 epithelioid, 9 mixed, 3 unspecified and 1 sarcomatous. There was 1 in-hospital death from pneumonia 11 days post-op. Of the 26 patients discharged from hospital there are 10 patients alive and 16 have died. From the 16 deaths: the mean survival was 312 days (38–660 days), median 273 days, 4 received post-op chemo with a mean survival of 245 days compared to a mean of 357 days for the 12 patients who did not receive post-op chemotherapy. Of the 10 patients who were alive: 5 were operated in March/April 2007 and the other 5 between February 2004 and August 2006 have survived between 262 and 1182 days (median 342 days).

Conclusion: Pleurectomy/decortication appears to be a safe operation with a postoperative mortality of 3.7%. The survival benefit of radical surgery needs to be evaluated in comparison to other treatment options so all future radical surgery in our unit will be undertaken as part of the MARS trial.

S126 GALACTOMANNAN DETECTION IN EXHALED BREATHE CONDENSATE OF NEUTROPENIC PATIENTS WITH SUSPECTED INVASIVE PULMONARY ASPERGILLOSIS

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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 (Platelet Aspergillus, Bio-Rad, www.thoraxjnl.com

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>
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<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>
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<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>
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<td>1</td>
<td>11</td>
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<td>Resolved</td>
<td>C Section</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>1</td>
<td>11</td>
<td>VATS</td>
<td>V Extraction</td>
<td>Fetal loss</td>
</tr>
<tr>
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<td>29</td>
<td>3</td>
<td>35</td>
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<tr>
<td>7</td>
<td>26</td>
<td>2</td>
<td>16</td>
<td>VATS (intra partum)</td>
<td>Insufficient</td>
<td></td>
</tr>
</tbody>
</table>

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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 23 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 HRTC 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 evaluation of pre-empotive 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

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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 obtained 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 variations in zone widths 4 mm; others had variations 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 patients with bronchiectasis.

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 had a decline in lung function.

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% (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=18) and non-colonised with pseudomonas aeruginosa (n=62) was undertaken. This analysis showed there was a significant difference (p<0.03) in baseline lung function in the pseudomonsa 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: Patients with bronchiectasis can be stabilised and decline in lung function prevented, regardless of pseudomonas colonisation, with aggressive management and education of the patient.

S129 COMPLEMENT-MEDIATED IMMUNITY TO STREPTOCOCCUS PNEUMONIAE IS SIGNIFICANTLY IMPAIRED IN SERA FROM PATIENTS WITH HOMOZYGOUS C2 DEFICIENCY

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Subjects with homozygous deficiency of the classical complement component C2 are highly susceptible to Streptococcus pneumoniae pneumonia and septicaemia. This observation, combined with data obtained using mice with genetic defects affecting different complement pathways, suggests that, surprisingly, the classical pathway is vital for innate immunity to S pneumoniae. However, the role of the classical pathway for complement-mediated immunity to S pneumoniae has not been investigated with human samples or in serum from subjects with C2 deficiency. Using flow cytometry assays and commercial serum depleted in specific complement factors (C1q or factor B) we demonstrate that in human serum the classical pathway is more important than the alternative pathway for complement deposition on three S pneumoniae strains, and this is associated with impaired phagocytosis of these strains in C1q-deficient serum. Both complement deposition and phagocytosis were restored to wild-type levels by addition of exogenous C1q to C1q-depleted serum. To assess the clinical importance of these observations, the C3b deposition and phagocytosis assays were repeated in serum from 10 C2 deficient subjects for three S pneumoniae serotypes. Compared to the results for serum from normal subjects, in the majority of sera obtained from C2− subjects C3b deposition was markedly reduced (for serotype 2 strain 12.1% of normal controls, SD 1.6%, p<0.0001) but could be restored to normal or near normal levels by addition of exogenous purified C2 (118% of normal controls, SD 19.0%, p<0.0003 compared to uncompomlemented C2−/− sera). Phagocytosis of the three S pneumoniae serotypes investigated was also significantly impaired in C2 deficient sera (for the serotype 2 strain 67.1% of the level obtained in normal serum, SD 9.3%, p<0.0001) and again mainly restored by exogenous C2 (89.2% of results obtained in normal serum, SD 14.8%, p<0.0001 compared to uncompomlemented C2−/− sera). These data demonstrate the vital importance of the classical pathway for complement-mediated phagocytosis of S pneumoniae and why subjects with C2 deficiency have such a marked increase in susceptibility to S pneumoniae infections.

S130 MEASUREMENT OF C-REACTIVE PROTEIN AT DAY 4 CAN DETECT FAILURE OF EMPERICAL TREATMENT IN COMMUNITY-ACQUIRED PNEUMONIA

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Introduction: The aim of our study was to investigate whether combined measurement of C-reactive protein (CRP) on admission and on day 4 were predictive of outcome in community acquired pneumonia (CAP).

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Abstract S130  Repeat measurement of C-reactive protein at day 4 and outcome

<table>
<thead>
<tr>
<th>Day 4 CRP</th>
<th>Mortality (30 days)</th>
<th>Invasive ventilation/</th>
<th>Complicated pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50%</td>
<td>93</td>
<td>13%</td>
<td>1.7%</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>175</td>
<td>0.5%</td>
<td>22.6%</td>
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</tbody>
</table>

*p < 0.0001.

Methods: We retrospectively studied 570 adult patients admitted with CAP between 2005–7. CRP was measured on admission in all patients and repeat measurement made in those who remained inpatients at day 4. The outcomes of interest were: development of complicated pneumonia (lung abscess, empyema or complicated parapneumonic effusion), need for mechanical ventilation and/or inotropic support; 30-day mortality.

Results: The median age was 62 years IG (44–76). Patients with chronic lung disease were excluded. 20% of patients had major comorbidities (chronic cardiac disease, stroke, chronic renal failure, diabetes). A CRP level that fails to fall by 50% within 4 days of admission is associated with a significantly increased risk of mortality, invasive ventilation and/or requirement for inotropic support and development of complication pneumonia (Table). On multivariate analysis adjusting for age, sex, comorbidity, smoking status and severity of pneumonia (CURB65 score) a CRP that failed to fall by 50% or more at day 4 was associated with: complicated pneumonia OR 12.74 (5.07–32.03) p < 0.0001; need for invasive ventilation/ inotropic support OR 7.6 (2.84–21.57) p < 0.0001; mortality OR 13.48 (3.33–54.57) p < 0.0001.

Conclusion: C-reactive protein that fails to fall by 50% or more at day 4 is associated with increased risk of complicated pneumonia, need for invasive ventilation and/or inotropic support and 30 day mortality.

Management and organisation of respiratory services

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

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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 GPs’ 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

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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

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ports (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% (114/202) 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 site, 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 per-therapy services was four visits per patient in the three-month period post-discharge. Post-therapies 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 or 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 implementation of 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.

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

J. A. Roberts, N. Diar 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 structure 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 at 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; GQF prevalence 2.3% n = 5501, (range 0.1%–4.7% across all 59 practices). Of 38 practices with available data for analysis: 4534 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 recommend 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 NIV, 8 cluster headquarters, 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 2 either in a hospital or primary care outreach oxygen clinic, or at home (n = 117). 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.

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**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 portable 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.

Recognition of the need to regularly re-evaluate 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.

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**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 supplied 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 (prescriptions previously prepared 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 convert 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) = £29.4, 128.15; SBOT (concentrators) n = 8 £3,533.20; LTOT n = 23 £11,836.95. 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 = £173,864.09 (DH funding = £84,000).

**Analysis:** There is a considerable cost saving in cancelling emergency oxygen tariffs, and by prescribing cylinders rather than concentrators for SBOT. However, prescribing LTOT without specialised assessment as recommended by the BTS working group appears to be a common practice in primary care.

**Conclusion:** Respiratory specialist teams have the knowledge and expertise to assess the need for oxygen in chronic respiratory patients. Oxygen is costing GPs 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.

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

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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. The aim of this study is to relate Qend to COPD patients, and healthy controls, relations between non-volitional Qend and (1) activity quantified by a motion sensor and (2) exercise capacity.

**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 MVC 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, MCRoberts, 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's t-test. Analysis of group differences was performed using the chi-squared test.
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<table>
<thead>
<tr>
<th>COPD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) and sex</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>9.8 (1.3)**</td>
<td>11.3 (0.9)</td>
</tr>
<tr>
<td>MVC (kg)</td>
<td>27 (10)*</td>
</tr>
<tr>
<td>Qend (l)</td>
<td>65 (10)**</td>
</tr>
<tr>
<td>Walking time (min in 12 h)</td>
<td>45 (27)*</td>
</tr>
<tr>
<td>Sitting 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.

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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. Arterial stiffness independently predicts cardiovascular risk and is increased in COPD patients compared with controls matched for cardiovascular risk factors. Elastic fragmentation and changes in collagen are found in the connective tissue of both emphysematous lungs and stiff arteries, but it is not known whether the severity of arterial stiffness in patients with COPD is associated with the severity of emphysema.

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

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 = 0.476, 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: In this, the first study to relate emphysema to any marker of cardiovascular risk, emphysematous patients appear to be at increased cardiovascular risk. This result needs to be confirmed longitudinally and mechanistic studies are required to identify the underlying pathophysiology.

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PREVALENCE OF ANAEMIA IN STABLE STATE AND DURING EXACERBATION IN A COHORT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

M. S. Anwar, K. Ibrahim. Whipp's Cross University Hospital, London, UK

Background: Chronic obstructive pulmonary disease (COPD) is considered to be primarily a respiratory disease but there is now increasing evidence of the systemic effects involved in this condition. The historic COPD literature demonstrates an association of COPD with polycythaemia secondary to chronic hypoxemia. Some recent studies have suggested that anaemia is also prevalent in COPD. It has been reported that the prevalence of anaemia in a US study of a large cohort of COPD patients is as high as 33%. This is a similar figure to that observed in patients with chronic rheumatoid disease and chronic renal and heart failure. 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...
A56

Spoken sessions

SUBCLINICAL BI-VENTRICULAR DYSFUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

R. Sabi1, C. E. Bolton1, J. M. Edwards2, P. H. Edwards1, J. R. Cockcroft2, A. G. Fraser1, D. J. Shale1, 1Respiratory Medicine, Cardiff University; 2Department of Cardiology, Cardiff University, UK

Background: Cor pulmonale occurs with severe airways obstruction and hypoxaemia in late stage COPD and indicates a poor prognosis. Other cardiovascular complications in COPD include increased arterial stiffness and atherosclerosis, even when confounders are accounted for. We hypothesised that subclinical left (LV) and right ventricular (RV) dysfunction occurs in milder severity COPD reflecting pulmonary and systemic haemodynamic impacts of the disease.

Methods: Thirty six clinically stable patients with COPD (19 male) and 14 age and sex matched smoking controls were studied. All subjects were free of overt cardiovascular disease and had no clinical evidence of left or right ventricular failure. Subjects underwent spirometry, tissue Doppler echocardiography (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7), measurement of aortic pulse wave velocity (PWV) (SphygmoCor) and arterialised capillary PaO2 (measuring velocities and deformation) (Vivid 7).

Results: Patients, mean (SD) age 66.5 (8.9) years had a mean (SD) FEV1 of 1.46 (0.58) l and a mean (range) PaO2 of 70 (57–88) mmHg. Compared with controls, patients had evidence of global diastolic and regional LV systolic dysfunction, with a longer isovolumetric relaxation time (IVRT) (<0.001) and lower LV strain (p < 0.01) and peak systolic strain rate (psr) (<0.001). Aortic PWV was greater in patients (11.5 (2.9) m/s) than controls (9.5 (1.3) m/s). Patients had evidence of RV regional systolic and diastolic dysfunction with a lower RV peak systolic velocity (<0.05), strain (p < 0.01), peak systolic strain rate (p < 0.001), and a greater RV myocardial relaxation time (p < 0.001). Pulmonary acceleration time (p < 0.01), post-systolic strain index (PSSi) and Tei index (both p < 0.001) were greater in patients compared with controls suggesting increased RV afterload. LV and RV systolic and diastolic dysfunction was present in

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patients with milder airways obstruction (FEV1 >50% predicted) compared with controls. In multiple regression analysis, aortic PWV was the only predictor of LV IVRT ($r^2=0.22$, $p<0.01$), while FEV1 was a predictor of both Tei index ($r^2=0.25$, $p<0.01$) and RV myocardial relaxation time ($r^2=0.22$, $p<0.01$).

**Conclusions:** Patients with milder severity COPD have evidence of subclinical LV and RV dysfunction suggesting early occurrence in the disease process. RV dysfunction is related to the severity of lung disease, while LV dysfunction is related to increased aortic stiffness.

**Acknowledgement:** Supported by GlaxoSmithKline.

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### 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 measures 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 and 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 ISWT 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 at the walking speeds (p<0.005). Post hoc analysis identified that each walking speed generated a statistically significant difference for METS 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.

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

J. A. Smith1, N. I. O’Kelly2, 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 of 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.

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### S145 DOES PULMONARY REHABILITATION IN PATIENTS WITH ‘NON-COPD’ CHRONIC RESPIRATORY DISEASE CONFERR 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 symptom expression. 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 (HADS) are performed. Patients were subdivided into ‘COPD’ or ‘non-COPD’.

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**Abstract S144**

<table>
<thead>
<tr>
<th>Ambulatory O2 assessment</th>
<th>n (n = 177)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria met at baseline and completion</td>
<td>52</td>
<td>29.4</td>
</tr>
<tr>
<td>Criteria met at baseline and completion</td>
<td>94</td>
<td>53.1</td>
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<tr>
<td>Criteria met at baseline but not at completion</td>
<td>12</td>
<td>6.8</td>
</tr>
<tr>
<td>Criteria not met at baseline but met at completion</td>
<td>19</td>
<td>10.7</td>
</tr>
<tr>
<td>Criteria not met at baseline and met at completion</td>
<td></td>
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</tbody>
</table>

**Abstract S143 Change in mean METS as speed increases.**
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 IILD 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.


ASSESSMENT OF PULMONARY REHABILITATION PROGRAMME WITHOUT THE PHYSICAL TRAINING

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Introduction: The NICE COPD guidelines recommend pulmonary rehabilitation (PR) should be made available to all appropriate patients. The guidelines state grade A evidence that PR should include a programme of physical training, disease education, nutrition education, psychological and behavioural intervention. In many hospitals access to PR is not available because of lack of funding and facilities required for the physical training. This study looked to see if a PR programme without physical training could improve patient’s health status, reduce A&E attendances and reduce length of stay (LOS).

Method: Clinics were run by a multidisciplinary team and were held for two hours every week for four weeks. Patients included fulfilled the same criteria recommended in the NICE guidelines for PR. Carers also attended. Quantitative data were collected using the Hospital Anxiety and Depression (HAD) scale questionnaire and the St George’s Respiratory Questionnaire (SGRQ) at the start of clinic, end of clinic and 6 weeks post clinic. A&E attendances and LOS data were obtained on the study patients and an equal number of case matched control patients, for a six-month period before and after the clinic. The controls were matched for age, sex and FEV1. Statistical analysis was performed using ANOVA.

Results: There were 48 patients eligible, of which 60% were male and the mean (SD) age was 71 (9.6) years. Patients had a mean FEV1 of 32.8 (7.9) % predicted. Nearly half of the patients brought a carer with them. 33 patients attended all four clinics; illness and hospital transport problems were the reasons for non-attendances. 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 vs 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 vs 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 £63,000 compared to the control group a six month running cost of £15,000. A post-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

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Introduction: Although the benefits of pulmonary rehabilitation (PR) are now well recognised, most programmes are offered as a one-off treatment and as yet there are no clear strategies for maintaining these benefits. We report early outcomes on a group of patients undergoing a pulmonary rehabilitation 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 failure 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 ‘special weekly exercise’ at Week 4, and patients were weighed at Week 1 and Week 6 of the following: FEV1, FVC and FEV1s, 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
Asthma: basic mechanisms

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

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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-1 production in response to RV infection by bronchial epithelial cells from asthmatic donors. In this study, we postulate 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-inactivated (UVi) virus as control. Viral replication, IFN-1 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-RV-16. 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-1. Exogenous IFN-1 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-1 production in RV16 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-1 protects fibroblasts against infection and may be a potential therapeutic approach for virus-induced asthma exacerbations.

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

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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-fibroblast 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 study we used 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, mild asthmatic 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 mitogenic potential in severe asthma. BAL from those with moderate/severe asthma, however, induced significantly more collagen III mRNA expression by the fibroblasts cultured from severe asthmatics than in 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.

THE ROLE OF GALECTIN-3 IN ASTHMA

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Background: Galectin-3, a 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

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Hypothesis: Galecin-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 different levels of disease severity. ELISA for galecin-3 was performed on the BALF. Bronchial biopsies embedded in GMA were stained for galecin-3 and its expression quantitated. RNA was extracted from bronchial brushings and analysed for galecin-3 expression by RT-PCR.

Results: Thirty biopsy samples (7 healthy controls, 13 mild asthmatics, 8 severe asthmatics) were stained for galecin-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 galecin-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. Galecin-3 was detected in BALF from both normal and asthmatic subjects (25 healthy controls, 41 mild asthmatics, 22 severe asthmatics) but levels were not significantly different. No correlation was found between immunoreactivity for galecin-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 galecin-3 at both RNA and protein level between asthmatic and non-asthmatic subjects.

Acute lung injury: pathophysiology

S154 CYCLO-OXGENASE-2 INHIBITION BY CYCLOGI

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-distension 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 (VALI). Cyclic mechanical strain (CMS) increases prostaglandin 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 prostaglandin production by increasing the activity of cytosolic phospholipase A2 in fetal lung epithelial cells.2 Prostaglandins 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-distension in the presence or absence of inhibitors of the NFκB pathway (AS602687: 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 NFκB and ERK1/2 pathways, suggesting that CMS-induced COX-2 expression 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 NFκB (p65) pathways were activated by CMS (30% stretch for 2 h at 20 min). Finally, in a acute murine ventilation 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.).

Conclusions: COX-2 induction by mechanical forces in hAT2 cells depended on the activation of ERK1/2 and NFκB signalling pathways, as well as on JNK. In the absence of other data describing the functional effects of inhibiting COX-2 activity, the significance of these findings in the context of acute lung injury and VALI is uncertain.

References
1. S153 CROSS SECTIONAL RELATION BETWEEN TOTAL IGE LEVELS, CIGARETTE SMOKING AND FEV1 IN AN AGEING POPULATION (THE ELSA COHORT)

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Introduction: IgE levels are elevated in smokers and individuals with asthma. Using data from the English Longitudinal Study of Ageing (ELSA) we assessed to what extent smoking and asthma explain the previously reported inverse association between IgE levels and FEV1.

Methods: Blood IgE levels and measurements of FEV1 were obtained in 2001. Predicted values for FEV1 were calculated using regression coefficients for age and height derived independently in men and female lifelong non-smokers without respiratory disease. Where necessary, appropriate methods were used to normalise variables before inclusion in analyses.

Results: Total IgE levels and measurements of FEV1 were available for 2358 individuals (47.7% men), mean age 62.7 (9.6) years, 11.9% of who reported physician-diagnosed asthma. There was a trend relating In IgE to FEV1 (% predicted) (r = 0.12, p < 0.0001). Median IgE levels were higher in men (35 kU/l (IQR 82)) than women (22 kU/l (IQR 54) p < 0.0001). In both sexes IgE levels were highest in current smokers and in pooled analysis, adjusted for sex and pack years smoked, IgE levels declined with the period of abstinence towards the level seen in non-smokers (mean adjusted IgE 155.3 kU/l (79.1 to 135.4) ex-smokers < 12 years abstinence, 88.8 kU/l (71.8 to 105.8) ex-smokers > 12 years abstinence and 75.1 kU/l (60.2–89.9) non-smokers (adjusted p for trend < 0.0001)). Sex-specific quartiles of IgE were used to assess the association with asthma. After adjustment for age, pack years and smoking status, the risk of asthma increased with total IgE [OR 1.61 p < 0.05, 2.76 p < 0.001, 5.08 p < 0.001 for second, third and top quartile relative to bottom). There was a significant inverse association between FEV1 and sex specific quartile of IgE (p < 0.001 for trend). However, after adjustment for current smoking status and diagnosed asthma, there was no association between total IgE and FEV1 (% predicted).

Conclusions: In this population the association between total IgE level and FEV1 is explained by confounding by smoking and diagnosed asthma. The mechanism for elevated IgE levels in smokers is not understood, but the gradual temporal decline with abstinence suggests a direct effect of cigarette smoke on total IgE levels.

**Background:** High stretch/high tidal volume (VT) 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-1<sub>high</sub>) and inflammatory (Gr-1<sub>low</sub>) classes. Gr-1<sub>high</sub> 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 VT (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 monocytes and Gr-1<sub>high</sub> 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-1<sub>high</sub> 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-1<sub>high</sub> monocytes (0.3 (0.2) × 10<sup>5</sup> vs 2.4 (1.4) × 10<sup>5</sup> 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 monocytes.

Abstract S155.
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. The role of LPS 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 ELISA 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) g/ml, p < 0.001) as were TNF-α (saline: 0.35 (0.19); LPS: 8.08 (0.68) ng/ml, p < 0.001) 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) x 106 cells/ml, p < 0.05), BAL protein (189 (13) g/ml, p < 0.05), and TNF-α (4.70 (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 < 0.001). Interestingly, only levels of MCP-1/JE were attenuated 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.

**S156**

PAR1 SIGNALLING IN LIPOPOLYSACCHARIDE-INDUCED ACUTE LUNG INJURY

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Acute lung injury 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. The role of LPS 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).

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**S157**

THE ROLE OF TNF-RELATED APOPTOSIS INDUCING LIGAND IN ACUTE LUNG INJURY


**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 challenge (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.)

**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 TRALI 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.

**S158**

PLATELETS ARE SEQUESTERED IN THE LUNGS OF EXPERIMENTAL TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI) AND PLATELET DEPLETION PROTECTS MICE FROM TRALI


**Introduction:** Transfusion-related acute lung injury (TRALI) is the number one cause of transfusion mortality in the USA. We have previously described a mouse model of TRALI based on MHC I antibody challenge that produces severe acute lung injury at two hours and is critically neutrophil dependent. We now report a two-hit model of TRALI focusing on the role of platelets and neutrophil-platelet interactions.

**Methods:** BALB/c mice (H-2Kd) were primed with 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.)

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**Conclusions:** Experimental TRALI 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

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) upregulation in BAL fluid lipocalin-associated (neutrophil-derived) MMP-9 at day 4 from baseline, compared with 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.