Spoken sessions

Epidemiology of tuberculosis

S001 SUBSTANTIAL INCREASE IN TUBERCULOSIS INCIDENCE IN ENGLAND AND WALES IN 2005

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Background/Aim: The epidemiology of tuberculosis in England and Wales has changed over the last two decades with a gradual increase in overall incidence. The majority of cases are now reported in the foreign-born while cases among the UK born are more likely to be from certain risk groups. Using national surveillance data, this study examines recent trends in tuberculosis epidemiology, including clinical and demographic characteristics of cases.
Methods: The Enhanced Tuberculosis Surveillance (ETS) system collects information on tuberculosis cases, including demographic, clinical and microbiological data. Cases occurring in England and Wales have been reported to this system since 1999. Population figures used for calculating national rates were calculated using mid year estimates provided by the Office for National Statistics (ONS).
Results: Provisional ETS data show that 8136 tuberculosis cases were reported in 2005 in England and Wales, a rate of 15.3 per 100 000. This compares with 7086 cases (13.4 per 100 000) reported in 2004. The rate increased by 14%, significantly more than in previous years (4% average annual increase between 1999 and 2004). This large increase is seen in both adults and children, and in those born in the UK (6% increase between 2004 and 2005 *v* no increase from 1999–2004). The trend differs considerably by region and is mainly comprised of non-pulmonary cases (27% increase versus 7% for pulmonary).
Discussion: Preliminary surveillance data indicate an increase in the incidence of tuberculosis in England and Wales in 2005 that is considerably larger than in previous years. Differential reporting by clinicians is an unlikely explanation, as we found a similar increase in the number of isolates reported from mycobacterial reference laboratories. While the final corrected figure for 2005 will be lower than the preliminary estimate, the increase is likely to remain substantial. The factors driving the increase need to be determined.

S002 CLINICAL PRESENTATION OF PULMONARY TUBERCULOSIS WITH AND WITHOUT HIV CO-INFECTION

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As part of a study of the effects of adding micronutrients to the treatment of pulmonary tuberculosis, a total of 1186 patients presenting with symptoms consistent with a diagnosis of pulmonary tuberculosis to one of eight Chest Clinics in Abuja, Nigeria had sputum tested for smear and culture for M tuberculosis. Of these 731 (62%) were culture positive and of these 353 (48%) smear positive. 1002 patients were tested for HIV and 546 (55%) were positive. Of the 625 patients who were culture positive and tested for HIV 329 (53%) were HIV positive. A total of 217 (58%) of 377 culture negative patients were HIV positive.

Of the 329 culture and HIV positive patients 158 (48%) were sputum smear positive compared with 182 (62%) of the culture positive but HIV negative patients. (χ^2 11.4, $p<0.001$)

Comparing symptoms and other aspects of presentation between the culture positive HIV positive and culture positive HIV negative groups the following were found to be statistically significant between the two groups; anaemia (OR 3.04), Hypoalbuminaemia (2.34) and raised ESR (9.5), were independently associated with TB/HIV co-infection.

Some symptoms associated with tuberculosis were commoner in HIV+ve patients; fever $p<0.04$), weight loss ($p<0.002$), night sweats ($p<0.002$), loss of appetite ($p<0.001$), and breathlessness ($p<0.05$). The presence of cough, haemoptysis, and chest pain were not significantly different between the two groups.

By the design of the protocol of the study only sputum smear positive patients were entered and had a chest *x* ray. No statistical difference was found in extent of radiographic disease and cavitation between the HIV positive and negative groups.

HIV co-infection was unexpectedly high in both those with culture confirmed tuberculosis and those with symptoms suggestive of tuberculosis but not culture proven. The degree of loss of appetite, loss of weight, fever, breathlessness, night sweats, hypoalbuminaemia, and raised ESR may be useful distinguishing features between HIV positive and HIV negative patients.

In keeping with WHO guidance on the diagnosis of tuberculosis where sputum smear positivity is the only means to a diagnosis of tuberculosis, nearly half (48%) of all patients with culture positive TB were sputum smear positive but those who were HIV negative were statistically significantly more likely to be sputum smear positive than those who were HIV positive.

S003 TUBERCULOSIS IN HEALTHCARE WORKERS IN NORTH EAST LONDON

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Introduction: We have investigated the occurrence of tuberculosis (TB) in healthcare workers in North East London.
Methods: The TB Network receives notification data from all boroughs within the sector. Those identified as healthcare workers were analysed by site of disease, place of birth, GP registration and place of work for the period 2003–05.
Results: We identified 105 healthcare workers with tuberculosis (TB), 4% of all cases of TB seen in North East London in this period. Most (79/105) were born outside the UK and were predominantly Black African (46/105) or from India (29/105). 12% of healthcare workers with TB were not registered with a GP. 20% had developed TB within 1 year of entry to the UK. 33/105 were sputum smear positive and thus potentially infectious. Recorded workplace contact tracing was only available for 21 of these 33; 6 of the 33 cases had clear reasons why screening was not performed and for 6, records of screening were not available. Doctors represent 9% of the NHS workforce (Government Statistical Service: Staff in the NHS 2004), but account for 26% of the healthcare workers notified with TB.
Comment: TB is common in our healthcare workers with doctors appearing to be over represented. The large number of smear positive cases create a substantial workload in terms of risk assessment for spread to patients and colleagues. We were struck by the numbers of healthcare staff who were not registered with a GP. While firm conclusions cannot be drawn from this study, the very high proportion of overseas-born cases suggests that most TB was probably not contracted from patients in these healthcare workers. This reinforces the need for effective occupational screening.

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

Abstract S003

	Sputum smear positive TB (n = 33)	All cases with TB (n = 105)
Not registered with GP	9%	12%
Non-UK born	85%	79%
Workplace screening completed and recorded	64%	21%
Doctor	18%	25%
Nurse	9%	15%
Healthcare assistant	15%	16%
GP	0%	5%
Midwife	3%	3%
Other	55%	36%
Developed TB within 1 year of entry to the UK	21%	19%

S004 THE INCIDENCE OF TUBERCULOSIS IN RELATION TO DISTANCE FROM A DIAGNOSTIC AND TREATMENT CENTRE. A STUDY IN RURAL ZIMBABWE

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Background: The millennium development goals (MDG) target a 70% detection rate and 85% treatment completion rate for patients with tuberculosis (TB) (Dye, *et al. JAMA* 2005). Progress towards these targets is satisfactory in many parts of the world but poor in sub-Saharan Africa (World Health Organization 2006). Zimbabwe has one of the highest rates of TB in the world with an estimated incidence of 674 cases/100 000/year. We have been reviewing the TB programme in Buhera health district, Manicaland, Zimbabwe. The district is rural, has a population of 230,000 and is 120 km long and 50 km wide. TB diagnosis and initiation of treatment occurs from Murambinda hospital which is at least 80 km from some of the primary health care clinics (PHC). We wanted to determine whether the distance patients have to travel for diagnosis acts as an obstacle to case detection.
Methods: The PHC catchment area of residence was established, for all patients with TB, identified in the district, between 1 January 2005 and 1 April 2006. The population of each PHC catchment area was identified from the 2002 census. PHC areas which could be sending their patients out of the district for treatment were excluded. The incidence of TB in each PHC catchment area was calculated and compared with the distance from the district hospital by linear regression.
Results: Seven hundred and five patients with TB were identified, 579 (82.1%) had pulmonary disease and 285 (40.4%) were documented to be smear positive (SS+). The overall incidence of TB was 282/100 000/year and appeared to vary between 20 and 1176/100 000/year in different PHC catchment areas. The overall incidence of SS+ was 114/100 000/year and varied between 0 and 410/100 000/year. The apparent incidence of TB was strongly, inversely related to the distance from the diagnosis and treatment centre. The incidence of TB appeared to fall by 66 (95% CI 35, 97) patients/100 000/year for every 10 miles from the district hospital. The incidence of SS+ disease fell by 26 (95% CI 14 to 39)/100 000/year for every 10 miles from the hospital.
Conclusion: These data suggest that many people with TB in this rural area have problems accessing diagnosis and treatment. There is a need to bring TB diagnostics closer to the patients' home. This should be a stimulus to further operational and laboratory research.

Supported by TB Alert.

S005 OUTCOMES OF NEW IMMIGRANT SCREENING FOR TUBERCULOSIS: IMPLICATIONS FOR IMPLEMENTATION OF NICE GUIDELINES

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Background: NICE guidelines for tuberculosis published in March 2006 have recommended changes in immigrant screening.[1] Tuberculin skin test (TST) is recommended for selected groups only (<16 years and 16–35 years from SubSaharan Africa or from a country with incidence >500/100 000). Recommendations in the use of Interferon Gamma Testing (IGT) depends on the proportion of infection within a community: below a prevalence of 10% none of the testing strategies are cost effective, between 10–40% prevalence, the two-stage TST/IGT strategy is cost effective and above 40% IGT alone is the most cost effective.
Methods: Retrospective audit of new immigrants invited for screening in a six month period, from August 2004 to January 2005.
Results: Of 367 new immigrants invited for screening, 243 attended (DNA rate of 30%). Of those who attended for TST, 3% did not attend to have it read. The results of immigrant screening from each of the WHO regions is shown in the table. Of the 92 African immigrants who attended, 74 were <35 years old. Of these, 24 had positive TST (32%). In the non-African countries (Asia, Western Pacific, and Middle East), out of the total 133 who attended, 29 (22%) were <16 years old and they all had a negative TST.
Conclusions: Immigrant screening of patients from very high prevalence countries is worthwhile. Among Africans the frequency of positive TST is close to the threshold reported by NICE at which IGT alone is more cost effective. Screening immigrants from countries of lower prevalence (although above WHO recommended prevalence of 40/100 000) may not be worthwhile.

1. **National Collaborating Centre for Chronic Conditions**. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians, 2006.

Lung transplantation: bench to bedside

S006 EVIDENCE OF INCREASED GASTRIC ASPIRATION IN ACUTE LUNG ALLOGRAFT REJECTION

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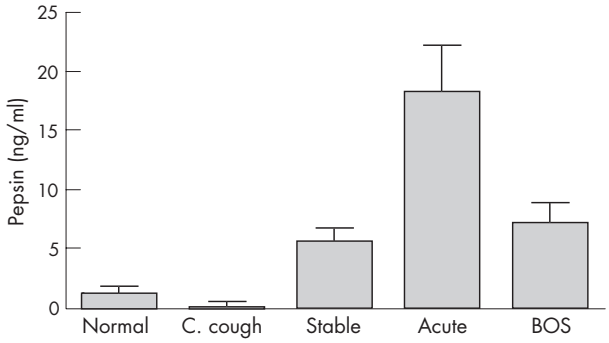
A major limitation to long term survival in lung transplantation is bronchiolitis obliterans syndrome (BOS), a chronic disease involving airway fibrosis. BOS is thought to be an overall response to epithelial injury resulting from multiple insults to the graft and acute rejection is a consistently documented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

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

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



Abstract S006.

Abstract S005

	Invited, n	Attended, n	TST Recorded	TST +ve	TB cases
Africa	109	92	84	27 (32%)	1
Asia	105	57	55	6 (10%)	1
W Pacific	70	39	35	3 (8.5%)	0
Middle East	62	37	36	4 (10%)	0

S007 THE EFFECT OF IMMUNOSUPPRESSANTS ON SECRETORY LEUCOPROTEINASE INHIBITOR PRODUCTION BY LUNG EPITHELIUM IN THE PRESENCE OF TRANSFORMING GROWTH FACTOR-BETA

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Introduction: Secretory leucoproteinase inhibitor (SLPI) is the major inhibitor of human neutrophil elastase within the lung and can also act as an endogenous antibiotic. We have previously demonstrated that lung transplant recipients with bronchiolitis obliterans syndrome (BOS) have lower airway levels of SLPI than stable recipients. This may be because BOS is associated with increased levels of transforming growth factor-beta (TGFβ) which has been shown to be a potent inhibitor of SLPI production (Jaumann, *et al. Eur Respir J* 2000). Immunosuppressive drugs used post lung transplant may also contribute to the lower SLPI levels as their use is associated with an increased risk of infection.
Aims: We aimed to determine whether the two commonly used calcineurin inhibitors, Ciclosporin A and Tacrolimus can modify SLPI production in the lung and whether exogenous TGFβ causes an exaggerated loss of SLPI production in the presence of calcineurin inhibitors.
Methods: A549 cells were serum starved for 24 hours and pretreated with either Ciclosporin A 100, 10 and 1 ng/ml or Tacrolimus 10, 1 and 0.1 μg/ml for 1 hour. Cells were stimulated with IL1β 20 ng/ml and TNFα 20 ng/ml for 24 hours to induce SLPI production. These experiments were then repeated in the presence of TGFβ 10 ng/ml. Cytotoxicity was excluded by an MTT assay.
Results: Neither immunosuppressant altered the basal production of SLPI in unstimulated cells. Stimulation with IL1β and TNFα significantly increased SLPI production compared to basal levels. Cyclosporin increased SLPI production in stimulated cells in a dose dependent manner when compared with control. The mean increase in SLPI at 100 ng/ml of cyclosporin was 19.6 ng/ml (0.12 SD) $p<0.001$. Tacrolimus significantly reduced SLPI production in stimulated cells in a dose dependent manner compared to stimulated control cells. The mean decrease in SLPI at 10 μg/ml of tacrolimus was −25.8 ng/ml (0.5 SD) $p<0.001$. The addition of TGFβ 10 ng/ml to the experiments significantly reduced SLPI production upon stimulation in the presence of both immunosuppressants.
Conclusion: The elevated levels of TGFβ seen in BOS are likely to reduce levels of SLPI in the airway leading to increased susceptibility to damage from human neutrophil elastase. Changing immunosuppressant from Ciclosporin A to Tacrolimus, which is commonly done in BOS will further reduce SLPI production in response to inflammatory stimuli and increase susceptibility to airway damage.

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

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Introduction: Immune-mediated chronic rejection significantly limits survival following lung transplantation, and tends to be glucocorticoid resistant. The role of alveolar macrophages (AM) in this process is not well characterised. AM glucocorticoid resistance is noted to be an important feature of many respiratory diseases. Glucocorticoids (for example, Prednisolone) are a key part of the anti-rejection regime after lung transplantation. This study investigated glucocorticoid sensitivity in AM from clinically stable lung transplant (LTx) recipients and compared it to glucocorticoid sensitivity in their peripheral blood mononuclear cells (PBMC).
Objective: To compare glucocorticoid sensitivity in of AM and PBMC from ''healthy'' LTx recipients.
Methods: Nine LTx recipients were recruited (6M:3F). Five had a single LTx for a variety of interstitial lung diseases and 4 had a double LTx for COPD. At the time of bronchoscopy and blood collection all were clinically stable—that is, free of acute or chronic rejection and infection. AM and PBMC were isolated from bronchoalveolar lavage fluid and peripheral blood respectively. Cells were suppressed with dexamethasone (10, 100 and 1000 μM) for 2 hours (h) then stimulated with lipopolysaccharide (LPS) (1 μg/ml) for 4 h. Cell supernatant was collected and TNF-α and IL-8 was measured using ELISA (R&D Systems). Data were analysed using paired *t* tests.
Results: The inhibitory effect of dexamethasone on TNF-α release in PBMC was significantly greater ($p=0.044$) than on AM. There was no significant difference in percent inhibition of IL-8 release between PBMC and AM ($p=0.14$).
Discussion: In clinically stable lung transplant recipients we have found that LPS induced TNF-α release from AM is steroid resistant compared to PBMC from the same patients. No significant steroid resistance was demonstrated from the same samples when LPS induced IL-8 release was measured. This is the first report of differential glucocorticoid resistance in the lung compartment compared to peripheral blood compartment in lung transplantation. We are progressing with this model of lung AM and PBMC activation induced by LPS to investigate mechanisms of corticosteroid resistance in lung transplantation.

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

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Background: Natural killer cells are potential effector and/or mediatory cells of allograft rejection, as they display receptors allowing them to recognise self from allogeniec tissue, and act as a critical bridge between the innate and adaptive response. In this study, we aimed to determine if NK cell activation in peripheral blood and bronchio-alveolar lavage (BAL) fluid correlated with clinical outcome following lung transplantation.
Methods: Fifty patients were included in the study. Lysosomal associated membrane proteins (CD107a and CD107b) were used as markers of NK cell activation, and immunophenotyping was performed using CD3, CD16, and CD56. The activating receptor, NKR-P1A (CD161) was also included as a surrogate marker of cytotoxicity.
Results: We found significant associations between early onset obliterative bronchiolitis OB (at 12 months as determined by BOS grade), and mean expression of CD107a+ CD56+ ($p=0.001$, co-ef 0.7370-), CD107b+ CD16+ ($p=0.001$, co-ef 0.8754) and CD107b+ CD56+ ($p=0.051$, co-ef 0.8900) NK cells in peripheral blood. Using Pearson's correlation co-efficients, there was a significant negative correlation between BOS grade and the percentage of NKR-P1A+ NK cells in peripheral blood ($p=0.006$). Comparing NK cell populations in broncho-alveolar lavage fluid from patients ($n=5$) with or without acute rejection (grade A3 or A0 respectively), we found a substantial NK cell population in A3 patients, compared to no NK cells in A0 patients.
Discussion: We describe the potential migration of NK cells from peripheral blood to the lung during acute rejection. We also describe a systemic activation of NK cells in patients with bronchiolitis obliterans syndrome. The NK cell has largely been ignored in solid organ

Abstract S008

	% Inhibition of TNF-α release		% Inhibition of IL-8 release	
Dexamethasone μM	AM	PBMC	AM	PBMC
10	20.8	36.50	55.80	60.5
100	40.0	75.40	22.50	55.7
1000	54.8	84.50	54.70	74.6

transplantation. Our data implicate this cell type in the complex cellular orchestration of the rejection cascade.

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

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Background: Lung transplantation (LT) provides a realistic therapeutic option for selected patients with end-stage respiratory disease. Many of the patients referred for consideration of this procedure are deemed unsuitable by international criteria and will never reach formal inpatient assessment. This may unnecessarily raise expectations among patients as well as stretch resources in the transplant centre.
Aims: Data on patients who were referred to our centre for lung transplant assessment over a 6 year period were reviewed. We aimed to identify which patients were deemed unsuitable on referral information and determine why they were not formally assessed.
Methods: A retrospective review of the referral database, prospectively collected, for demographic information, clinical information and any contraindication as measured against international referral guidelines for all patients referred to our centre from January 2000 to December 2005. Those patients who were deemed suitable on referral data and received a formal assessment were than compared with those who did not get formally assessed.
Results: 1249 patients were referred over this 6 year period, 749 (60%) underwent formal inpatient assessment, average 124 (range 78–151) per year, of these 193 (26%) have subsequently received a transplant. 500 (40%) did not get to assessment. Age spread is similar for all patients referred with a small peak at 21–30 years old and larger peak at 51–60 years old. Patients assessed are younger compared to those who did not receive assessment, mean values 41 years (standard deviation 15) and 50 years (13) respectively ($p<0.0005$ unpaired *t* test). Significantly more cystic fibrosis (CF) patients received assessment compared to not assessed, only 37 CF were not assessed compared to 192 assessed (χ^2 $p<0.0005$).

Death very soon after referral was a major reason for no assessment, 22% of patients who were not assessed died within 3 months of referral. Of the remaining patients, 10% had absolute contra-indications (CI) for LT, 22% had a single relative CI and 68% had multiple CI. Common relative CI included age, severe osteoporosis, cardiovascular disease, low and high BMI or performance status. All these relative CI are increasing over the years from 2000 to 2006.
Conclusion: Significant numbers of patients referred to our transplant centre never reach formal assessment. This is due to a significant proportion of deaths early after referral suggesting that referral was too late. In addition increasing numbers of absolute and relative CI contributed, suggesting better awareness of referral criteria and better work up of patients ahead of referral may provide a better insight into a patients suitability for formal assessment.

S011 PULMONARY VASCULAR REACTIVITY IN INFECTED SINGLE LUNG ALLOGRAFTS

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Introduction: Infection is a major cause of mortality in the first year following single lung transplantation, and a risk factor for the development of obliterative bronchilitis, limiting 5-year survival to approximately 45%. Better understanding of the effects of infection on pulmonary allograft vasculature could aid in development of better diagnostic and therapeutic targets.
Methods: After single lung transplantation, dogs were immunosuppressed with methylprednisolone acetate, cyclosporine, and azathioprine. After 5 days, infection was induced in one group of dogs by endobronchial inoculation of antibiotic resistant Eschericia coli (infection group, n = 5); in the second group, the same amount of culture medium without bacteria was flushed into the bronchus (control group, n = 4). All animals were medicated under the same drug protocol. On post-operative day 8, all animals were sacrificed, the pulmonary arteries were recovered, cut into rings and suspended for pharmacological characterisation in organ chambers.
Results: Contractions to phenylephrine and angiotensin-1, but not endothelin-1were reduced in rings with endothelium from pulmonary arteries from infected lungs ($p<0.05$). Inhibition of nitric oxide synthase with L-NMMA, restored these contractions. Rings without endothelium did not demonstrate altered reactivity. Endothelium-dependent relaxations to adenosine diphosphate and calcium ionophore, which stimulate release of endothelium-derived nitric oxide by receptor and non-receptor mediated processes, respectively, were not different between groups. Relaxations to nitric oxide were also not different between groups.
Conclusions: These results suggest that infection selectively affects contractions of the allograft pulmonary vasculature and that those effects are mediated in part by endothelium-derived nitric oxide.

This abstract is to be presented at the annual meeting of the European Association of Cardio-thoracic surgeons (EACTS) in September 2006.

Can we improve respiratory healthcare provision?

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

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The 2003 RCP/BTS UK National COPD audit[1] demonstrated wide variations in quality of care and outcomes between hospitals linked to resources and notably staffing. In 2005 the same units collected additional data on resources and organisation of care in preparation for a future audit programme. Data below are from 237 hospitals in 2003 and 163 in 2005. They suggest improved resources and best practice organisation of care. There remain significant deficiencies in some areas that should be addressed by clinicians and managers working together.

The 2006/7 NCROP intervention will pair hospitals with differing quality attainments in order to share good practice and develop bilateral improvements in COPD services. This group intends to report on the success of this strategy at next years BTS meeting.

1. **Price LC**, *et al.* Thorax Online First: 31 January 2006.

Abstract S012 Table 1

Staffing levels in UK Respiratory Units	Mean WTE 2003	Mean WTE 2005
Number of Consultants	2.20	2.78
Number of Associate Specialists	0.08	0.15
Number of SpRs	1.18	1.95
Number of SHOs	1.68	2.41
Number of PRHOs	1.37	1.81
Number of COPD Nurses	1.09	1.43
Number of other Specialist Respiratory Nurses	1.80	1.69
Number of Specialist Respiratory Physiotherapist	1.01	1.61

Abstract S012 Table 2

Organisation and resources	Yes (%) 2003	Yes (%) 2005
Written local guidelines for COPD management?	46	73
Do you have a Specialist Respiratory Ward?	65	71
Do you have Specialty Triage?	33	49
Is there a formal pulmonary rehab programme?	64	75
Is there access to an early discharge scheme?	44	60
Is there a HDU available for COPD patients?	NA	61
Is NIV available when required?	NA	89
Is self-management advice given at discharge?	NA	44
Is there a local patient support group?	NA	72
Do your patients have access to palliative care?	NA	73
Does your unit provide an ambulatory oxygen service?	NA	39

S013 PATIENT VIEWS ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE SERVICES: A FOCUS GROUP STUDY

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Introduction: The RCP/BTS/BLF NCROP study aims to improve chronic obstructive pulmonary disease (COPD) services in the three key areas of NIV provision in acute respiratory failure, early discharge from hospital and pulmonary rehabilitation. In preparation the views of patients about these services were sought in order to inform future plans to develop optimum care for COPD patients.
Method: Four focus groups organised by the BLF were run in Scotland, England (2), and Wales involving a total of 36 COPD patients and each facilitated by two trained researchers. Each followed a set framework in which participants were asked their views on the patient perspective of the optimum service provision in the three areas identified above for improvement. The 2 hour long sessions were tape recorded with consent and transcribed later for analysis identifying emergent grouped themes.
Results: *NIV*: few patients understood the term, or the concept or had personal experience of this treatment. Those with experience reported insufficient information provision for them to make informed choices and this at a time when vulnerable and not physically or mentally supported to make such decisions themselves. Patients generally reported hospital admissions as times of severe fear and anxiety. There was a general suggestion that all hospitalised COPD patients should be told about this form of treatment at a time of relative stability and the options that may be offered at subsequent admissions. *Pulmonary rehabilitation*: In contrast to NIV, all participants were conversant with rehab. It was strongly advocated. Specifically it gave hope and support to patients and was felt a bridge between hospital and home. Suggestions were for ongoing programmes and not time limited ones. Separate COPD classes were preferred over general public gym sessions and the presence of nurses or physiotherapists were seen as important in providing reassurance. *Early discharge*: Just under a third of the group members had been through an EDS. Most rated them highly. Just over 50% of the remainder had not heard of the term at all. Of these some expressed concerns over discharge to free beds rather than to improve care and were worried about lack of community support. Once more there was a general suggestion that more information was needed for all patients so they might adjust to the concept before it was applied to them during an admission. *Other concerns*: patients expressed worry over care provided by non specialists when acutely ill and gave examples of less than optimum experiences. A more holistic approach to care including the psychological effects of COPD was requested and, again, more information about their condition and the treatments.
Conclusion: patients want more information about medical interventions before they are applied. These are best provided during periods of stable health.

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

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

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

Non-compliance with medication	35/51 (70%)
Side effects led to cessation	8/51 (16%)
Increased symptoms	4/51 (8%)
Exacerbated	2/51 (4%)
Letter not acted on	1/51 (2%)
Unknown	1/51 (2%)

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

Letter not acted upon	23/43 (53%)
Repeat script not changed	7/43 (16%)
Instruction to patient	4/43 (9%)
Increasing symptoms	4/43 (9%)
Side effects	3/43 (7%)
Unknown	2/43 (5%)

Abstract S014 Table 3 Were specific medication changes ineffective

Medication (top 7)	Total	Change not effective	Primary care event	Patient event	Main reason
Tiotropium	41	10 (24%)	3 (33%)	7 (66%)	Stopped: 3
Antibiotic	38	18 (47%)	14 (77%)	4 (23%)	Letter: 13
Symbicort	32	10 (31%)	2 (20%)	8 (80%)	Stopped: 8
Salbutamol	28	14 (50%)	4 (29%)	10 (71%)	Stopped :8
Prednisolone	27	9 (33%)	5 (55%)	4 (45%)	Stopped: 3
Seretide	26	8 (35%)	4 (50%)	4 (50%)	Nil clear
Combivent	24	7 (29%)	3 (43%)	4 (57%)	Stopped: 13
Aminoph	3	3 (100%)	2	1	Intolerance 3

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

S015 ARE EVALUATED RESPIRATORY SERVICE DEVELOPMENTS IMPLEMENTED INTO CLINICAL PRACTICE?

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Background: In respiratory medicine there has recently been a growing interest in evaluating how best we deliver respiratory healthcare. This has led to a number of publications regarding service developments (or similar) which have been evaluated in key centres. However, it is not clear whether all such service developments subsequently become normal practice, even in the originating institution
Methods: Methodical search and review of potential service development studies in 4 respiratory journals over a 4 year period. A questionnaire was then sent to the corresponding authors regarding implementation of the study findings into clinical practice.
Results: 3281 papers were identified in the four journals during the 4 year period, of which 121 had a title or key word which suggested the possibility that they were reports of a respiratory service development. Following review of the actual papers 85 of these were rejected because they contained negative results (n = 17), were not true service developments (n = 50) or were audits or systematic reviews (n = 13). The questionnaire was sent to the authors of the remaining 36 papers and 30/36 (83.3%) replied. 10 reports concerned evaluation of the sharing of care with nursing colleagues and 5 more concerned use of physiotherapists, pharmacists, peer group educators, practice assistants and smoking counsellors. The remainder of the studies involved new technologies, use of the telephone, patient information sheets, mailing patients, education and guideline implementation. 15/30 respondents have put the researched service development into practice; 11 of the 15 doing so immediately after the research ended. Delays in implementation of 12–60 months were due to staffing and organisational issues in 3 cases and the institution not being prepared to pick up costs in 1 case. For those 15/30 (50%) studies which have not been put into practice, 2 might be implemented and in 2 cases the benefits were perceived to have been rather marginal. 10 studies will not be put into practice. One study was completed 9 years ago and although initally implemented is no longer used. Out of the 10 studies not implemented the commonest single reason was due to the key person leaving (n = 5)
Conclusions: While it is encouraging that half of all reports of the evaluation of service developments are able to be continued, it is disappointing that many innovations were not implemented even in the reporting institution. These were equally distributed between studies of the use of different healthcare professionals and new technologies, but process changes were particularly unlikely to be continued. In a couple of cases reflection suggested the benefit of the reported intervention was not large, and in the remainder, costs or loss of key personnel were the explanation for non continuation of the service development.

S016 ESTABLISHMENT OF A COMMUNITY RESPIRATORY ASSESSMENT UNIT

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Respiratory disease is common. There are many types and symptoms are shared with disorders of other systems. Spirometry is one tool which can enhance diagnostic accuracy; previous studies have shown that without its use mistaken diagnoses occur in primary care. Hospitalisation rates for asthma and COPD within Hammersmith & Fulham PCT are among the highest in London. In 2004 the Hammersmith & Fulham PCT with the support of the Strategic Health Authority, Hammersmith Hospitals NHS Trust and Imperial College established a Community Respiratory Assessment Unit (CRAU) with three intentions: to improve the diagnosis of respiratory conditions, to empower patients, and to encourage implementation of national respiratory guidelines. The service was developed and run by two specialist nurses. Significant time was spent on the logistics of patient referral to the service, the development of a protocolised approach to patients, and to the development of a semi-standardised reporting system. Where a diagnosis was obvious, self management advice and checking of inhaler techniques, SaO_2 and breath CO measurements were also undertaken. Educational materials for different respiratory scenarios were included with the report to GPs and these were designed to be of use for all patients not just those attending CRAU. Of the 33 primary care facilities in Hammersmith and Fulham PCT, 16 were given access to the service initially and the remaining 17 six months later. Prescribing data from GP practices were collected before and after implementation of CRAU. The service was based at Charing Cross Hospital and a peripatetic service was offered to practices furthest away. As part of the referral process GPs stated reasons for referral and what they would have done if the service had not been available. 364 patients were referred over the first 12 months and we have full details on the 330 who attended (148M 182F, mean age 70 year (SD 14.9), 107 smokers 123 ex-smokers). 57% of all referrals related to definite/suspected COPD and definite/suspected asthma accounted for 28% of referrals. When asked what they would have done in the absence of the service, 57% of GPs would have referred patients to a hospital clinic and 54% would have instituted a trial of therapy (98/140 short acting beta-agonist; 74/140 inhaled corticosteroid). Definite or suspected COPD, was the most common reason for referral (189/330) but airway narrowing was only demonstrated in 110/189 (58%) of these. GP satisfaction with the service was extremely high and 97% rated the education materials which accompanied the report as being helpful or very helpful. A community orientated respiratory diagnosis assessment service, offering more than spirometry alone, has the potential to improve the accuracy of respiratory diagnosis in primary care and potentially to lead to savings associated with delayed diagnosis and inappropriate trials of therapy.

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

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As part of the ''Connecting for Health'' (CfH) project, it is the intention of the Department of Health to introduce the picture archiving and communications system (PACS) throughout NHS trust hospitals as a more efficient imaging process than film. A postal questionnaire on PACS was sent to 782 respiratory consultants (BTS database) in the first quarter of 2006 to make assessments of (1) current availability, (2) involvement of respiratory consultants in implementation, (3) clinical acceptability of the system, and (4) anticipated timing of introduction in hospitals which do not currently use PACS.
Response rate: The institutional response rate was 95% (276/290) with an individual response rate of 72% (561/782).
Hospitals with PACS: 45% of hospitals (124/276) had undergone either a complete (88/276) or a partial (36/276) transition to PACS; however 33% of these hospitals had not involved their respiratory consultants in discussions leading up to its implementation.
Perceived benefits following introduction of PACS: The majority (percentages in parentheses) of consultants were positive in response to questions concerning ability to manipulate images (83%), speed of access (77%), fewer lost images (71%), its use as a teaching or research tool (67%), its ability to reduce clerical time (64%) and to improve clinical interaction between colleagues within the same institution (61%).
Perceived problems following introduction of PACS: 48% of respondents had experienced difficulty transferring images to other hospitals and 68% recorded no benefit in clinical interaction nationwide. Further difficulties had been experienced: (1) in obtaining good quality images in the outpatient clinic (36%) or wards (48%), (2) with delay in displaying images on screen (52%), (3) in obtaining archived images (33%), (4) with IT training/backup (27%).
Hospitals without PACS: Of the 55% of hospitals with no PACS (152/276), 47% of these hospitals were expected by respondents to have PACS within the next year, 31% within 2 years, 8% in longer than this, the remaining respondents being uncertain.

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

Cellular mechanisms in asthma

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

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Introduction: Asthma is a disease characterised by both chronic inflammation and structural airway changes associated with alterations in the extracellular matrix composition. The fibroblast is pivotal in maintaining the balance between production and breakdown of the ECM in the healthy lung. However fibroblasts in the asthmatic lung may deposit increased levels of ECM proteins, which contribute to the remodelling of the airways observed in asthma.
Methods: Primary cultures of fibroblasts were grown from endobronchial biopsies taken from healthy and asthmatic volunteers. Broncho-alveolar lavage (BAL) fluid from healthy or asthmatic donors, 10 ng/ml tumour necrosis factor (TNF)-α and 1 ng/ml transforming growth factor (TGF)-β1 were applied to the fibroblasts for 24 hours and TaqMan real-time PCR was used to quantify gene expression. Four genes were analysed; connective tissue growth factor (CTGF), interleukin-8 (IL-8), Collagen III and alpha smooth muscle actin (α-SMA). The RNA was extracted with Tri-reagent.
Results: Mild asthmatic BAL (n=7) and moderate/severe asthmatic BAL (n=7) was shown to significantly increase Collagen III, α-SMA, and CTGF mRNA expression from asthmatic fibroblasts compared to healthy fibroblasts ($p \leqslant 0.008$). Asthmatic fibroblasts also exhibited a significant increase in CTGF and IL-8 (both $p \leqslant 0.0001$) mRNA expression compared to healthy fibroblasts after challenge with healthy BAL and moderate/severe asthmatic BAL respectively. 1 ng/ml TGF-β1 and 10 ng/ml TNF-α also caused a significant increase in Collagen III ($p \leqslant 0.0001$) mRNA expression in asthmatic fibroblasts compared to healthy cells. Healthy fibroblasts were shown to express significantly higher levels of CTGF mRNA than asthmatic fibroblasts after challenge with 1 ng/ml TGF-β1 and 10 ng/ml TNF-α ($p \leqslant 0.002$), and also α-SMA ($p=0.001$) mRNA after challenge with healthy BAL (n=7).
Discussion: These data indicate that BAL fluids from asthmatic subjects contain factors that stimulate asthmatic fibroblasts to express genes for ECM proteins such as Collagen III, and that fibroblasts from asthmatic donors may have increased potential to generate ECM. Identification of factors responsible for activating fibroblasts in asthma may help to generate new targets for therapeutic intervention to reduce the severity of lung remodelling in chronic asthma.

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

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Background: Mast cell microlocalisation to the airway smooth muscle (ASM) bundle is a feature of asthma and the number of mast cells in the ASM-bundle are correlated to the degree of airway hyper-responsiveness. Mast cells in the ASM-bundle express IL-4 and IL-13. In a recent study comparing the immunopathology and clinical response to corticosteroids of eosinophilic (sputum eosinophilia >3%) and non-eosinophilic asthma we found that mast cell infiltration of the ASM-bundle was a consistent feature of asthma, but that a favourable response to corticosteroids was reserved to the eosinophilic group. We hypothesised that this differential response to corticosteroids may be associated with different cytokine expression by the mast cells in the ASM.
Method: We recruited subjects with mild eosinophilic and non-eosinophilic asthma and age matched healthy controls. Subjects underwent bronchoscopy and endobrochial biposies. Biopsies with assessable ASM (area>0.1 mm^2) were available from 7 subjects in each group. We enumerated inflammatory cells and IL-13+ cells in the ASM using immunohistochemistry.
Results: The number of IL-13+ cells in the ASM was increased in eosinophilic asthma compared to all the other groups ($p<0.001$; table). The number of mast cells in the ASM was increased in the subjects with asthma compared to healthy controls ($p<0.001$; table).
Conclusion: Mast cells in the ASM are a feature of eosinophilic and non-eosinophilic asthma. The mast cell activation was different between the asthma phenotypes with increased IL-13 expression from mast cells in those with eosinophilic asthma. This difference in the nature of the mast cell activation between the asthma phenotypes may provide a possible explanation for the differential response to corticosteroids.
Supported by Asthma UK and DoH Clinician Scientist Award.

Abstract S019

ASM	Mild EA	Mild NEA	Normal control
IL-13+/mm^2	2.2 (1.7)*	0 (0)	0 (0)
Mast cells/mm^2	11.3 (3.4)*	7.5 (5.8)*	0 (0)

Median (IQR) cells/mm^2 airway smooth muscle *$p<0.001$ (Kruskal Wallis across groups and Mann Whitney between groups).

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

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Respiratory infections trigger inflammatory responses, leading to leukocyte recruitment, epithelial damage, mucus hypersecretion, and bronchoconstriction. This has the potential to exacerbate many airway diseases, for example asthma, by sensitising the tissue micro-environment to allergen. Toll-like receptors (TLRs) 3, 7, and 8 have been described as sensors of viral infection, with TLR3 recognising the double-stranded RNA produced during viral replication, while TLRs 7 and 8 detect single-stranded viral RNA. Thus, TLRs may provide a dynamic system for host defence against pathogenic respiratory viruses if present and functional in the airway. Our results reveal TLR3 is expressed intracellularly in primary human airway smooth muscle cells (HASMCs) and confirm TLR3 expression (extra- and intra-cellularly) on the BEAS-2B human airway epithelial cell line. Stimulation of both cell types with polyI:C, a dsDNA mimic which acts via TLR3, caused the release of a repertoire of pro-inflammatory cytokines (CXCL8, CXCL10, IL-6, and CCL5) and upregulated ICAM-1 expression, an adhesion molecule utilised by some respiratory viruses to gain access to tissue cells. These responses were significantly enhanced by coincubation with the proinflammatory cytokines IL-1b or TNFa. Peripheral blood mononuclear cells (PBMCs) defend against infection and modulate immune responses in the lung, thus their role as mediators of lung antiviral responses was investigated using an in vitro coculture system. We have previously shown that PBMCs are necessary for LPS-induced cytokine release from HASMCs (Morris *et al. AJRCCM* 2005;**171**:814–22), here we report that PBMCs also enhance LPS-induced cytokine release from BEAS-2B cells, and were required for tissue cell responses to agonists of TLR7/8. Exposure to multiple TLR agonists may also occur at inflammatory sites, we therefore stimulated cocultures of PBMCs with either BEAS-2B cells or HASMCs, with agonists of both TLR4 (acting principally on the monocyte) and TLR3 (acting principally on the tissue cell) and observed cooperative responses leading to a synergystic enhancement of cytokine generation from the cocultured PBMCs and tissue cells. These data indicate that the inflammatory response is regulated by cooperative networks that can be modelled in vitro with primary human cells, furthermore it suggests these will be of more importance than the response of an individual cell when examining the processes of acute TLR-driven inflammation.
Some of the data have previously been presented at Toll2006: Recent advances in Pattern Recognition, Salvador, Brazil.

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

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Malfunctioning of the bronchial epithelium is a recognised feature of both acute infections and chronic inflammatory disorders of the airways as seen in severe asthma,[1] and this may contribute to enhanced neutrophil responsiveness. We set out to determine the modulatory role of the repairing human bronchial epithelium by studying the way the bronchial epithelial cell line, 16HBE 14o- impacts on neutrophil activation and its downstream signalling pathways. Culture conditioned medium (CM) was collected from subconfluent 16HBE cells (16HBE-CM) and to mimic the phenotype of the repairing asthmatic epithelium, 16HBE cells were treated with EGF (10 ng/ml). While EGF itself was not

chemotactic, CM derived from EGF-treated cells promoted greater chemotaxis than 16HBE-CM alone. ELISAs detected basal secretion of TNF-α, GM-CSF, and IL-8 in 16HBE-CM, and these levels rose significantly following EGF treatment of epithelial cells. Complete abrogation of EGF-treated 16HBE-CM-mediated chemotaxis was achieved with the combination of anti-GM-CSF mAb with SB-225002 (CXCR2 antagonist) or CP-105696 (BLT1 antagonist), providing evidence for a synergistic role for these mediators. Neutrophil activation was also assessed by flow cytometry investigating expression of cell surface markers. Relative to the 16HBE-CM response, treatment of neutrophils with EGF-treated 16HBE-CM caused greater upregulation of CD11b and CD66b expression, paralleled by a marked downregulation of CD62L. Such changes in expression elicited by EGF-treated 16HBE-CM reflected an increase in the degranulation capacity of neutrophils. The migratory response involved PI3-kinase signalling as it was prevented by the PI3-kinase inhibitor (wortmannin, 100 nM). Western blotting of whole-cell lysates showed that neutrophils express Akt, and EGF-treated 16HBE-CM induced increased Akt phosphorylation when compared with 16HBE-CM alone. Application of an Akt-specific inhibitor, HIMO (10 mM) reduced the migratory response evoked by EGF-treated 16HBE-CM. Where the non-selective protein kinase C inhibitor, staurosporine (100 nM) only partially prevented the effects of EGF-treated 16HBE-CM-mediated chemotaxis, rottlerin (a selective PKC delta inhibitor) did abrogate the response in a dose-dependent manner (10 nM-10 mM). These data demonstrate a marked capacity for the repairing bronchial epithelium to modulate the effector functions of neutrophils through an increased release of chemotactic factors *via* a PI3-kinase/Akt/PKC d-dependent pathway. We speculate that these processes may be involved in the activation and recruitment of neutrophils during airways inflammation in conditions, such as severe asthma or acute bronchitis, where epithelial damage and repair are common features.

1. **Davies DE**. *Curr Allergy Asthma Rep* 2001;**1**:127–33.

S022 VASCULAR REMODELLING IS A FEATURE OF ASTHMA AND NON-ASTHMATIC EOSINOPHILIC BRONCHITIS

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Background: Increased vascularity and expression of vascular endothelial growth factor (VEGF) are recognised features of the asthmatic airway. Vascular remodelling in asthma is inversely related to airflow obstruction. Few studies have examined the association of vascular remodelling with airway hyper-responsiveness (AHR). Non-asthmatic eosinophilic bronchitis (EB) is a powerful disease control model to study potential mechanisms of AHR. We hypothesised that vascular remodelling does occur in EB and asthma, relates to airflow obstruction and may be related to FEV_1 decline.
Methods: *COHORT 1*- 16 asthmatics (GINA1-2 n=8, GINA 3-4 n=7), 10 patients with EB and 11 healthy matched controls were recruited. Prospective longitudinal FEV1 data were available for the EB subjects to assess FEV1 decline. Expression of the endothelial marker EN4 was assessed in bronchial biopsy samples. Vessels were counted using the validated mean chalkley count (MCC) by a blinded observer. In brief, a 25-point chalkley eyepiece graticule was applied to 4 subjectively predetermined, non-overlapping vascular hotspots at ×200 magnification and the MCC derived. *COHORT 2*- A second independent cohort of 31 asthmatics (GINA1-2 n=11, GINA 3-4 n=20), 14 patients with EB and 15 matched controls were recruited.

Induced sputum supernatant VEGF was measured by ELISA (R&D).
Results: The MCC and sputum VEGF were increased in those subjects with GINA 3-4 asthma and EB (table). 12 subjects met ATS criteria for refractory asthma and in these subjects the sputum VEGF was increased (6007 (1545) pg/g) compared to the other asthmatics and healthy controls ($p<0.01$). In asthma there was a significant correlation between the post-bronchodilator FEV1% predicted and MCC ($r^2=0.28$; $p<0.05$), and sputum VEGF ($r^2=0.18$; $p<0.05$). In EB there was a significant correlation between FEV1 decline and MCC ($r^2=0.6$; $p=0.03$). The mean (range) duration of follow up of EB subjects was 2.8 (0.7–6.7) years. There was no significant correlation between MCC or sputum VEGF and AHR or sputum eosinophilia.
Conclusions: Vascular remodelling is not associated with AHR, is inversely associated with the post bronchodilator FEV1 in asthma and FEV1 decline in EB.

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Abstract S022

	Control	Asthma (GINA 1-2)	Asthma (GINA 3-4)	EB
MCC	3.5 (0.5)	4.1 (0.5)	5.3 (0.5)*	5.1 (0.2)*
VEGF (pg/g sputum)	1612 (445)	2622 (1066)	4445 (1090)*	6287 (1117)*

Mean (SEM), *$p<0.05$ compared with control

The role of TGF-β in lung disease

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

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Idiopathic pulmonary arterial hypertension (PAH) is an often fatal disease characterised by proliferation of endothelial and smooth muscle cells in small pulmonary arteries. Approximately 70% of familial PAH cases are due to heterozygous germline mutations in the gene encoding the bone morphogenetic protein type II receptor (BMPR-II), a receptor for the transforming growth factor-β (TGF-β) superfamily. Dysfunctional BMP signaling is now emerging as a feature of diverse forms of PAH. We questioned whether dysfunctional BMP/TGF-β signaling was a feature of two commonly used models of PAH: the chronically hypoxic and the monocrotaline treated rat models. Male Sprague-Dawley rats received a single intraperitoneal injection (60 mg/kg) of the pyrrolizidine alkaloid monocrotaline (M) or were exposed to normobaric hypoxia (FiO_2 10%) (H) for 3 weeks. Control rats were maintained in room air. After three weeks the M and H rats had a significant increase in pulmonary arterial pressure, right ventricular hypertrophy and vascular remodeling, compared with control rats. In both experimental groups there was a reduction in the lung expression of both BMPR1A and BMPR-II mRNA (~60%) as determined by real-time RT-PCR. In addition there was a reduction in the expression of the inhibitory Smad6, a transcriptional target of BMP signaling. In the M rats western blot analysis of lung protein revealed that there was a trend for a reduction in the expression of phospho-Smad 1/5, a downstream target of BMP signaling. In addition, there was a significant increase ($p<0.05$) in the expression of phospho-Smad 3, a downstream target of TGF-β signaling. Expression of collagen was also increased in H and M lungs. These findings demonstrate that downregulation of BMP receptors is a feature of two widely used rat models of pulmonary arterial hypertension. In addition they provide evidence for increased TGF-β signaling. Further studies are required to determine whether reduced BMP receptor expression plays a causal role in the development of PAH in these animal models.

*These authors contributed equally.

S024 ANALYSIS OF THE HHT3 LOCUS ON CHROMOSOME 5, ENCODING A NEW GENE FOR HEREDITARY HAEMORRHAGIC TELANGIECTASIA

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The majority of patients with pulmonary arteriovenous malformations (PAVMs) have underlying hereditary haemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome) in which abnormal vascular structures develop throughout life. HHT is inherited as an autosomal dominant trait and is genetically heterogeneous. Three disease genes have been identified to date, resulting in HHT type 1 (*endoglin*), HHT type 2 (*ALK-1*), or HHT-JP, an HHT-juvenile polyposis overlap syndrome (*Smad4*). PAVMs occur in all

types of HHT, most commonly in HHT type 1 due to *endoglin* mutations. HHT type 2 patients with *ALK-1* mutations are also at risk of HHT-associated pulmonary hypertension. *Endoglin* and *ALK-1* encode proteins expressed on vascular endothelial cells, and all three gene products modulate or transmit transforming growth factor (TGF)-β signals.

We recently identified a new locus for HHT on chromosome 5 (Cole SG, Begbie ME, Wallace GMF, Shovlin CL. *J Med Genet* 2005;**42**:577–82). First we demonstrated that the HHT gene in a Hammersmith PAVM/HHT family was unlinked to the known HHT genes *endoglin*, *ALK-1*, or *Smad4*. The 3 known HHT genes were also sequenced, and no mutations were identified. A genome-wide linkage study was used to identify the *HHT3* locus on chromosome 5 where a single haplotype was inherited by all affected members of the pedigree (Zmax 3.45, q = 0, fully informative markers). The remainder of the genome was excluded to a 2–5 cM resolution. Fine mapping narrowed the interval to a 5.4 cM/6 Mb region that contains 28 genes including 10 novel genes (http://www.ensembl.org).

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

This work is supported by the British Heart Foundation.

S025 ACTIVATION OF PROTEINASE ACTIVATED RECEPTOR-1 ON MESOTHELIAL CELLS INDUCES ACTIVATION OF TRANSFORMING GROWTH FACTOR-BETA VIA UPREGULATION OF THROMBOSPONDIN-1

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Rationale: TGFβ is a potent pro-fibrotic cytokine with immunomodulating actions, known to be important in human pleural diseases. We have previously shown that intra-serosal thrombin levels are elevated in pleural disease, and that thrombin stimulates release of TGFβ from mesothelial cells via activation of (PAR)-1. TGFβ is mainly secreted in a latent form, and its activity is tightly regulated by post-translational activation. The aims of this study are to establish (1) the presence and (2) the significance of activators of latent TGFβ on mesothelial cells.
Methods: (1) Expression of known activators of TGFβ - thrombospondin (TSP)-1 and αvβ6 and β8 integrins - at mRNA and protein levels was determined using RT-PCR, FACS and immuno-precipitation in cultured mesothelial and mesothelioma cells. (2) Mesothelial cells (MeT5A) were exposed to thrombin or TFLLR-NH2 (a PAR-1 agonist peptide) and the expression of the activators of latent TGFβ was measured by real-time RT-PCR. Effect of TSP-1 on activation of latent TGFβ was investigated using LSKL, a competitive inhibitor of TSP-1 mediated TGFβ activation. Active TGFβ levels were measured using a modified mink lung epithelial cell bioassay. Total TGFβ levels were measured by heat treating the samples before assay.
Results: (1) TSP-1 and αvβ6 and αvβ8 integrins are expressed by all six benign and malignant mesothelial cell lines tested. TSP-1 expression was further confirmed by RT-PCR in human pleural tissue samples (n = 15) of various benign and malignant aetiologies. (2) Thrombin stimulated a time- and dose-dependent increase in active and total TGFβ released from mesothelial cells ($p<0.01$ both). This was accompanied by a time-dependent upregulation of TSP-1 expression (up to sevenfold *v* control, $p<0.001$), but not that of αv, β6 or β8 integrin subunits in mesothelial cells. The addition of LSKL, (but not the scrambled control peptide SLLK) reduced the basal level of active TGFβ by 24%, and both the thrombin and the TFLLR induced increase in active TGFβ by over 70% (all $p<0.05$).
Summary: Mesothelial cells express all the known potent activators of latent TGFβ. Activation of PAR-1 induces significant increases in active TGFβ by increasing the release of total TGFβ and by upregulating TSP-1.

S026 FALIURE OF BONE MORPHOGENETIC PROTEIN RECEPTOR TRAFFICKING IN PULMONARY ARTERIAL HYPERTENSION: POTENTIAL FOR RESCUE?

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

S027 EPITHELIAL MESENCYMAL TRANSITION OCCURS IN PRIMARY AIRWAY EPITHELIAL CELLS IN RESPONSE TO TRANSFORMING GROWTH FACTOR-BETA AND EPIDERMAL GROWTH FACTOR

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Introduction: Epithelial to mesenchymal transition (EMT) is a process by which an epithelial cell changes its phenotype to that of a fibroblast or myofibroblast. EMT is believed to play a significant role in epithelial loss and fibrogenesis in chronic kidney and liver diseases yet data on its role in chronic lung disease is much more limited. During EMT cells loose their epithelial properties, such as ability to form tight junctions and gain features of a mesenchymal cell such as invasiveness and collagen production. We have recently shown a marker of EMT in airway biopsies from lung transplant recipients (Ward *et al*, *Thorax* 2005) suggesting this phenomenon could play a role in the airway remodeling seen after lung transplantation.
Aims: This study investigated whether the growth factors, TGFβ and EGF, could induce in airway epithelial cells the typical phenotype change and the changes in protein expression characterisitc of EMT.
Methods: Primary human small airway epithelial cells (Cambrex) were grown to ~50% confluence on vitrogen and were then stimulated with TGF-β (10 ng/ml) and EGF (200 ng/ml). The phenotype of the cells was monitored by phase contrast microscopy, After 72 hours some cells were fixed and expression of the tight function, E-cadherin, and Collagen I was assessed by confocal microscopy. The remaining cells were harvested for western blotting and probed for E-cadherin and Collagen I expression.
Results: In the absence of exogenous stimulus, control cells showed a uniform epithelial morphology with a high level of E-cadherin expression and no expression of collagen I. Stimulation with TGFβ and EGF for 72 hours induced numerous cells to adopt a biopolar phenotype characteristic of (myo)fibroblasts. There was a significant downregulation of E-cadherin expression of 90% together with a 10-fold increase in expression of the mesenchymal marker collagen I. TGFβ treatment of the airway epithelial cells induced a rapid phosphorylation of the intracellular signaling molecules SMAD 2/3 and translocation to the nucleus within 30 minutes and signaling persisted for at least 72 hours.
Conclusion: This study demonstrates that TGFβ and EGF can drive EMT in primary airway epithelial cells and that this is associated with rapid activation of the SMAD signalling pathway. EMT may play a role in airway fibrogenesis and additional studies are needed to assess the clinical relevance of these observations to chronic airway diseases associated with remodelling.

AJF is supported by a GSK Clinical Fellowship.

S028 TALC INDUCES RELEASE OF TRANSFORMING GROWTH FACTOR-BETA FROM MESOTHELIAL CELLS IN VITRO AND SEROSAL ADHESION FORMATION IN VIVO

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Background: Talc is widely used to induce pleural adhesion formation during therapeutic pleurodesis. The mechanism by which talc induces pleurodesis is unclear. Transforming growth factor-beta (TGFβ) is a potent pro-fibrotic cytokine: its direct injection can induce pleurodesis promptly in animals. The role of TGFβ in talc pleurodesis has not been explored.
Methods: Commercially available human grade talc (Novatech, France) with median particle size of 20 mm was used. (A) In vitro, human pleural mesothelial cells were cultured with increasing doses of talc for 24 hours. Active TGFβ levels were measured using a modified mink lung epithelial cell assay. Total TGFβ levels were quantified by heating the samples before assay. (B) In vivo, C57BL/6 mice (n = 5–7 in each group) were given a single intraperitoneal injection of talc slurry (0, 25, 50 mg) in saline. On day 5, a peritoneal lavage was performed and the differential leucocyte count and TGFβ levels measured. The intra-abdominal adhesions were quantified macroscopically. Tissue thickening was quantified microscopically on H&E stained sections by taking the average measurement of 10 high power fields for each sample, by a blinded investigator.
Results: (A) In vitro, talc induced a dose-dependent increase in total TGFβ levels from cultured pleural mesothelial cells: up to 1.9-fold, over media-only controls ($p<0.05$) with 0.15μg/cm^2 of talc. (B) In vivo, talc potently induced serosal adhesions in a dose dependent manner with a macroscopic score of 0 ± 0, 0.8 ± 0.5, and 2.4 ± 0.6 for mice receiving 0, 25, and 50 mg of talc respectively. This was mirrored by a corresponding increase in a semi-quantitative score of microscopic thickening of 7.1-fold ($p<0.05$) for mice receiving 50 mg talc over saline controls. Trichrome staining showed that the thickening was predominantly a result of increased extracellular matrix deposition. TGFβ levels increased in a dose-related fashion, with a fold increase of 1.33 and 2.59 ($p<0.05$) in mice given 25 and 50 mg of talc over saline controls. Talc also induced a significant dose-dependent increase in neutrophil influx ($\times10^5$/ml lavage fluid) in the serosal cavity: 2.6 ± 1.2 (saline) *v* 17.5 ± 10.7 (25 mg talc) *v* 115.1 ± 18.7 (50 mg talc). These results were reproduced using another talc preparation (Sigma).
Summary: Talc induces the release of total TGFβ from mesothelial cells in vitro. In vivo, talc induces a dose-dependent increase in active TGFβ levels, proliferation and thickening of mesothelial cell layer, collagen deposition, and formation of adhesions.

Pathomechanisms of COPD

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

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Background: Scotland has recently introduced a legislative ban on smoking in confined public places. We sought to investigate the impact of this ban on the health of bar-workers.
Methods: A prospective observational study was undertaken in non-smoking bar workers from Tayside, Scotland. Data on exposure to environmental smoke, symptoms, pulmonary function, and airway and systemic inflammation were gathered one month before then one and two months after the introduction of the ban.
Findings: The percentage of bar-workers with respiratory or sensory symptoms fell by 26% (95% CI −13.8 to −38.1) and 32.5% (−19.8 to −45.2) at one and two months respectively ($p<0001$). FEV1 increased by 8.2% (3.9 to 8.0) and 5.1% (2.1 to 8.0) of predicted ($p<0.005$) at one and two months, with significant changes in both asthmatic and non-asthmatic workers. Serum cotinine levels fell by 1.93 ng/ml (−2.83 to −1.03) and 2.23 ng/ml (−3.10 to −1.34) at one and two months ($p<0.001$). The total white cell and neutrophil count was reduced by 630 cells/μl (−1010–−260, $p=0.002$) and 410 cells/μl (−740 to −90, $p=0.028$) respectively at two months. Compared with baseline, asthmatic and rhinitic bar-workers also had less airway inflammation at one month with a 0.8-fold reduction (0.67 to 0.96, $p=0.036$) in exhaled nitric oxide, and better Juniper quality of life scores by 7.3 points (0.1 to 14.6, $p=0.049$).
Interpretation: Banning smoking in public places resulted in significant early improvements in symptoms, pulmonary function, and circulating neutrophils in non-smoking bar-workers. Asthmatics also had reduced airway inflammation and improved quality of life.

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

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Background: Systemic inflammation may be related to reduced pulmonary function. We tested the hypothesis that small increases in C-reactive protein (CRP), within the ''normal'' range, were associated with reduced forced expiratory volume in one second (FEV1) in apparently healthy middle-aged men in Northern Ireland.
Methods: 10600 French and Northern Irish men aged 50 to 59 years were recruited mainly at their place of work from 1991 to 1994 as part of the Prospective Epidemiological Study of Myocardial Infarction (PRIME); of the Northern Irish participants, 2010 of the 2745 men were rescreened at 10 years. This involved a questionnaire and physical measurements including lung function by spirometry. Aliquots of plasma were frozen immediately at −80°C for later high sensitivity CRP analysis. We present a cross sectional analysis of the 1273 rescreened men for whom a high-sensitivity CRP measurement and a valid spirometry trace had been obtained.
Results: The men had a mean age of 64 years and 42% had never smoked. The table shows a significant reduction in the mean percentage predicted FEV1 (FEV1%) with increasing CRP ($p<0.001$). After adjustment for confounders (including smoking status, education, BMI, alcohol intake, waist-hip ratio, age, height, and social status), this association remained ($p<0.001$). Specifically, after adjustment, individuals with a CRP over 264 μg/dl had a reduced FEV1% of on average 8.7 compared with individuals with CRP below 102 μg/dl.
Conclusions: There is a strong negative relationship between high sensitivity C-reactive protein and percent predicted FEV1 in middle-aged men in Northern Ireland. This association suggests a link between systemic inflammation and reduced FEV1.

Abstract S030 Percentage predicted FEV1 by CRP (in fourths)

CRP (μg/dl)	n	FEV1.0% Mean (SD)	Adjusted effect* (95% CI)
<102	318	94.1 (15.9)	0 ref cat
102.1–153.8	318	90.5 (18.4)	−1.9 (−4.4 to 0.7)
153.9–264.5	319	88.6 (15.6)	−2.7 (−5.3 to −0.6)
>264.6	318	80.9 (17.7)	−8.7 (−11.3 to −6.0)
		p<0.001	p<0.001

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

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

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Circulating interleukin-6 (IL-6) increases with low intensity exercise in adults with cystic fibrosis. We hypothesised a similar increase after whole body and inspiratory muscle exercise (IME) in patients with chronic obstructive pulmonary disease (COPD). Patients (22) mean (SD) age 70.4 (6.7) years and 12 age matched healthy subjects (HS) performed cycle ergometry and resistive IME on different days. Cycling

Abstract S031

IL-6 pg/ml	Start	End	Increment
IME HS	1.1 (0.1)	1.01 (0.10	0.08 (0.01)
IME patients	2.86 (1.9)	3.23 (1.86)*	0.37 (0.07)
Cycling HS	1.17 (0.15)	1.12 (0.15)	0.04 (0.007)
Cycling patients	2.7 (1.0)	3.07 (1.6)**	0.44 (0.3)

started with 3 min unloaded pedalling at 60 rpm, then increments of 5–10 watts/min at 60 rpm until voluntary exhaustion. During IME forced inspiratory effort at 75% of maximum inspiratory pressure (MIP) was maintained with progressively shorter recovery time between repeat manoeuvres. Plasma IL-6 and TNFa sr I and II were measured at start, end of exercise and 15, 30, 60, and 120 minutes later. FEV1/FVC for patients was 55.7 (9.0)%, BMI and fat free mass were in the healthy range. No patient was hypoxaemic at rest. The power achieved during cycling (80–100 watts) was similar to activities of daily living. IL-6 and TNFa sr I and II were greater for patients than HS at all time points ($p<0.05$). IL-6 increased with cycling and IME for patients, but not in HS. Neither TNFa sr I nor II changed after cycling or IME. In nutritionally replete patients with moderate severity COPD cycling or IME were associated with increased circulating IL-6. This effect during activities of daily living could add to the persistent systemic inflammation in COPD. (geometric means, *$p=0.016$, **$p<0.01$)

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

S032 THE EFFECTS OF CANNABIS ON PULMONARY STRUCTURE, FUNCTION AND SYMPTOMS

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Background: Cannabis is the most widely used illegal drug worldwide. Long term use of cannabis is known to cause chronic bronchitis and airflow obstruction, however the frequency of macroscopic emphysema, the dose-response relationship and the dose equivalence of cannabis with tobacco has not been determined.
Methods: A convenience sample of adults from the Greater Wellington Region was recruited into four smoking groups; cannabis only, tobacco only, combined cannabis and tobacco and non-smokers of either substance. Their respiratory status was assessed using high resolution CT scanning, pulmonary function tests and a respiratory and smoking questionnaire. Associations between respiratory status and cannabis use were examined by analysis of covariance and logistic regression.
Results: A total of 339 subjects were recruited into the four groups. A dose-response relationship was found between cannabis smoking and reduced FEV1/FVC and sGaw, and increased TLC. For adverse respiratory effects one cannabis joint was equivalent to between 2.5 and 6 tobacco cigarettes, depending on the lung function variable measured. Cannabis smoking was associated with decreased lung density on HRCT scans. Macroscopic emphysema was detected in 1/75 (1.3%), 15/92 (16.3%), 17/91 (18.9%) and 0/81 subjects in the cannabis only, combined cannabis and tobacco, tobacco alone and non-smoking groups respectively.
Conclusions: Smoking cannabis is associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. The 1:2.5 to 6 dose equivalence between cannabis and tobacco cigarettes for adverse effects on lung function is of major public health significance.

S033 SERUM GAMMA-GLUTAMYL TRANSFERASE IN LUNG DISEASE

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Introduction: Serum gamma-glutamyl-transferase (GGT) is elevated in 26.6% of patients with alpha-1-antitrypsin deficiency (AATD), independent of the presence of previous liver disease (Stockley. ATS 2006). GGT regulates transport and synthesis of the antioxidant glutathione. Its expression is increased in rat lung epithelial cells in response to oxidative stress (Liu. *Am J Physiol* 274:l330) and serum GGT correlates with CRP as a systemic marker of inflammation in humans (Lee. *Atherosclerosis* 178:327). We hypothesised therefore, that serum GGT may be related to lung disease and its severity in AATD.
Method: The database for the UK AATD registry was searched to find baseline lung function, smoking information and clinical features regarding sputum production and colour, along with exacerbation data for 338 subjects. Any relationship between these factors and baseline serum GGT were was then assessed.
Results: Serum GGT correlated negatively with forced expiratory volume in 1 second (FEV1)% predicted. ($r=-0.158$, $p=0.002$). Mean serum GGT increased as the GOLD stage increased from 33.4 iU/l (SE 2.91) in stage 0 to 49.2 iU/l (SE 4.29) in stage 4 ($p=0.002$). Mean serum GGT was significantly higher in patients who had chronic bronchitis (49.3 iU/l SE 3.96) compared to those who did not (39.1 iU/l SE 2.51) ($p=0.002$), suggesting a relationship to bronchial inflammation. There was, however, no significant difference between mean serum GGT for subjects who produced sputum of various colour categories as defined by a sputum colour chart. ($p=0.966$) Nor was there a relationship between serum GGT and the numbers of exacerbations over the previous 1 year. A difference in mean GGT was, however observed for never smokers (37.1 iU/l SE 4.29) compared to ex- (45 iU/l SE 2.73) and current smokers (44.8 iU/l SE 6.62) ($p=0.002$). Nevertheless serum GGT was not shown to be significantly correlated with pack years ($r=0.092$, $p=0.073$).
Conclusion: Serum GGT is related to the severity of airflow obstruction (GOLD stage) in AATD, smoking status and chronic bronchitis. The relationship to this regulator of glutathione is consistent with an anti-inflammatory role of this systemic biomarker.

S034 OXIDATIVE STRESS INDUCES EPITHELIAL TO MESENCHYMAL TRANSITION IN BRONCHIAL EPITHELIAL CELLS: A POSSIBLE ROLE IN AIRWAY REMODELLING

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Introduction: Excessive oxidative stress may play a role in airway injury and contribute to airway remodelling seen in chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or post-transplant obliterative bronchiolitis. The mechanism by which oxidative stress may contribute to airway remodelling is poorly understood. We hypothesised that oxidative stress may induce epithelial to mesenchymal transition (EMT) in airway epithelial cells. EMT is a process by which an epithelial cell loses epithelial properties such as forming tight junctions and develops a myofibroblast phenotype with increased expression of collagen and mesenchymal markers. Recently markers of EMT have been demonstrated in airway biopsies from lung transplant recipients (Ward *et al*, *Thorax* 2005).
Aims: To investigate the effect of an environment high in oxidative stress on cell morphology and expression of epithelial and mesenchymal markers in human bronchial epithelial cells.
Methods: Human bronchial epithelial cells (16HBE14o-) were exposed to low dose hydrogen peroxide, at concentrations between 0 and 25μM, or to 40% hyperoxia for 7 and 14 days. The production 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. At the end of treatment cells were either fixed for confocal microscopy or harvested and protein expression was assessed by Western blotting.
Results: In the absence of oxidative stress, 16HBE14o- cells show a uniform epithelial morphology with high level expression of the tight junction protein, E-cadherin. Levels of the mesenchymal markers S100A4, alpha-smooth muscle actin (α-SMA), and collagens type I/III were very low or undetectable. Treatment with hydrogen peroxide or 40% hyperoxic resulted in significantly increased expression of the mesenchymal marker: S100A4 (250% increase) after only 7 days. After 14 days in hyperoxia levels of α-SMA, collagen type I and collagen type III were increased (200%, 100%, 150% respectively) and E-cadherin expression was decreased by 46%. Co-incubation with the anti-oxidant N-acetylcysteine (NAC) almost completely inhibited collagen type III expression in 16HBE14o- cells in response to hydrogen peroxide.
Conclusions: Oxidative stress can induce EMT in bronchial epithelial cells and provides a potential mechanism for increased fibrogenesis in the airway microenviroment and may contribute to airway remodelling.

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Diagnostic procedures in lung cancer

S035 THE ROLE OF TRANSBRONCHIAL NEEDLE ASPIRATION IN AN INTEGRATED CARE PATHWAY FOR ASSESSMENT OF PATIENTS WITH SUSPECTED LUNG CANCER

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Introduction: Transbronchial needle aspiration (TBNA) is a safe, simple yet underutilised sampling modality for patients with suspected lung cancer and mediastinal lymphadenopathy. It may be the sole diagnostic test, or as a staging modality to prevent unnecessary mediastinoscopic biopsies.
Methods: We prospectively evaluated the value of TBNA in patients with suspected lung cancer and mediastinal lymphadenopathy. Patients attending the linked Rapid Access Chest clinics of the two hospitals between December 1999 and June 2003, who underwent bronchoscopy as part of an integrated care pathway were included. Standard methods for bronchoscopy and TBNA and were used. Particular care was taken to prevent contamination of TBNA samples from the distal airway secretions, thus minimising false positive results. Two dedicated respiratory cytopathologists assessed TBNA samples for adequacy of sample, presence of lymphocytes representing a lymph node aspirate, and the presence or absence of malignant cells. Patients without a positive TBNA result proceeded to positron emission tomography (PET) and/or mediastinoscopy. In patients with a negative TBNA and no further investigations due to clinical confidence of non-malignancy, a true negative TBNA was only assigned after 18 months follow up without evidence of malignancy. An additional analysis, the number needed to diagnose (NND) was calculated in the same way as number needed to treat. It represents the number of TBNAs needed to be performed to provide a positive result, and is calculated as 1/[sensitivity – (1-specificity)].
Results: Of 827 patients referred for which prospective data were collected, 561 had a final diagnosis of malignancy, with pathological confirmation in 502 (89%) patients. The initial CT scan provided information for a non-bronchoscopic diagnostic investigation in 128 patients. 433 patients underwent bronchoscopy. Of these, 129 (30%) patients had TBNA at the time of their diagnostic bronchoscopy. TBNA was the sole diagnostic modality in 30 (23%) patients, and provided staging information in 63 (49%) patients. In nodes >10 mm, for which TBNA was undertaken, the number of pts needing a TBNA to diagnose one malignancy (NND) was 1.47 patients. The sensitivity of TBNA was 69% and specificity of 100%. Diagnostic accuracy was 78%. 71% of TBNA were sampled adequately with the right paratracheal node being most frequently sampled. There were 29 false negatives, of which 16 underwent mediastinoscopy and 10 were unsuitable for surgery. There were 3 lymphomas diagnosed. There were no serious adverse events from TBNA.
Conclusion: TBNA can be easily, safely and cheaply incorporated into a lung cancer diagnostic pathway with a high success rate, reducing unwanted mediastinoscopies in 49% of patients.[1]

1. **Shah PL**, Singh S, Bower M, *et al. JTO* 2006;**4**:1–5.

S036 STENTING IN SUPERIOR VENA CAVAL OBSTRUCTION: A FIVE YEAR EXPERIENCE WITH LUNG CANCER

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Introduction: Superior vena caval obstruction (SVCO) causes significant morbidity in lung cancer with distressing symptoms and shortened survival. The aim of this study, was to evaluate the efficacy and report our experience with metallic stents in SVCO at our hospital. Data gathering was done by retrospective review of case notes and hospital information systems.
Methods: Twenty nine patients aged between 47 and 91 (mean 70.7) years underwent stenting as primary treatment for clinical and/or radiological SVCO between Jan 2001–Dec 2005.The diagnoses of lung cancer was established in 69%(n = 20); non small cell lung cancer 34.5% (n = 10), small cell lung cancer 27.5% (n = 8), and mesothelioma 6.9% (n = 2) and tissue diagnosis could not be ascertained in 9 (31%) cases. Obstruction to the superior vena cava was found to be due to stricture and/or thrombus in all patients (n = 29).
Results: Immediate response to treatment was measured radiologically by the following three parameters; while central venous pressure (CVP) recorded in 48.3% (n = 14) cases demonstrated a mean fall in pressure 6.48 (1.41) mm Hg, establishment of free flow to the right atrium and disappearance of collaterals were reported in 51.7% (n = 15) and 10.3% (n = 3) subjects respectively. Clinical improvement in breathlessness and/or facial swelling was noted in 10.3% (n = 3) patients immediately after stenting. Long term stent patency was achieved in all cases. We encountered four minor and one major complication. Minor problems occurred in 4 (13.8%) patients, one each had shoulder pain, groin haematoma, stent thrombus and contrast leak. One patient had major complication of pulmonary embolism within 48 hours of stenting requiring anti coagulant therapy. More than a third of patients 37.9%(n = 11) had chemotherapy and/or radiotherapy. Mean stent survival was 87.7 (3 to 340) days with one patient surviving more than two years to date.
Conclusions: Our study provides further evidence on the role of stent placement in malignant vena caval obstruction (SVCO) in accordance with NICE guidance on this subject. With locally available expertise, our practice was found to be safe and effective in providing rapid symptom palliation in advanced lung cancer.

S037 A COMPARISON OF AUTOFLUORESCENCE BRONCHOSCOPY AND VIDEOBRONCHOSCOPY FOR THE DETECTION OF PRE-INVASIVE LESIONS IN PATIENTS WITH POSSIBLE LUNG CANCER

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Introduction: Autofluorescence bronchoscopy has been developed to detect the pre-invasive precursors to squamous cell carcinoma of the lung. Various autofluorescence (AF) systems have been tested but their role in the assessment of suspected lung cancer remains uncertain due to a high false positive rate. Distinguishing inflammation from pre-invasive lesions has been difficult (Lam *et al Chest* 1998;**113**:696–702). Olympus Tokyo developed a new integrated high resolution videobronchoscope with fluorescence capacity. This system is designed to distinguish inflammatory tissue (blue) from intra-epithelial neoplasia (pink). We assessed this AF system as a diagnostic test for detecting cancer and pre-invasive lesions in comparison to the white light mode (WL).
Methods: Data were collected from 49 patients having a bronchoscopy for suspected lung cancer or haemoptysis. Under WL any mucosal changes seen were classified as inflammatory or suspicious. This was repeated under AF. Biopsies were taken from any abnormal areas and control biopsies were taken from two random normal areas. The pathologist, blinded to the bronchoscopic appearances, graded the biopsies according to the WHO criteria (Kerr *J Clin Pathol* 2001;**54**:257–71). Pre-invasive lesions were defined as moderate dysplasia or worse.
Results: Eighty one areas were biopsied. 11 (14%) were invasive carcinoma and 5 (6%) pre-invasive. The AF system did not detect any pre-invasive lesions not detected under WL. One abnormal area was missed by both modes. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy are shown in the table.

Abstract S037

%	Sensitivity	Specificity	PPV	NPV	Accuracy
WL	94	92	75	98	93
WL then AF	93	82	54	98	84

Conclusion: The new videobronchoscope is superior as a diagnostic tool compared to older scopes and we presume this is a function of the clarity of the on-screen image. The AF mode performed well but false positives were still a problem. There was no added diagnostic benefit from the AF mode, perhaps because the white light images were so clear. Another reason may be the low incidence of pre-invasive lesions in this patient population, less highly selected than in other studies (Chiyo *et al. Lung Cancer* 2005;**48**:307–13). The optimum design and use of autofluorescence systems continues to be refined.

S038 IMPROVING THE DIAGNOSTIC YIELD FROM BRONCHOSCOPY WHERE THERE IS NO VISIBLE ENDOBRONCHIAL LESION

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Introduction: Patients with lung cancer often have no visible endobronchial lesion, despite the presence of centrally based pathology on radiological examination of the chest. In these cases, the clinician may be prompted to obtain a histological diagnosis via another route, potentially delaying the patient journey and increasing the resource requirements. To circumvent this, we have adopted a policy of fine needle aspiration (FNA), bronchial brushings (BBr), blind bronchial biopsy (BBB), and bronchial lavage (BAL) via the original bronchoscopy. We report the additional diagnostic yield using this approach.
Method: We looked at all patients attending our large cancer unit over an 18 month period who had the above investigations performed when no endobronchial cancer was seen. Demographic and radiological data were collected, and the diagnostic yield and any further investigations performed were noted.
Results: Thirty one patients (mean age 69 years, mean FEV1 1.71 litres, WHO PS mean 0.95 (range 0–2), 17 male), fulfilled the criteria. All had pre-bronchoscopy staging CT scans with evidence of mediastinal lymphadenopathy (subcarinal (13), hilar (7), pre/paratracheal (13)). 24 patients had lung masses and 1 pleural thickening/RML atelectasis. All patients had FNA (carina (20), trachea (3), main/lobar bronchus (8)), by an SpR in 23 cases (74%). FNA was positive in 10 (32%) (9 malignancy, 1 sarcoidosis); in only 3 cases was insufficient tissue obtained. Consultants had a higher success rate (50% *v* 26%), and the yield was greatest through the bronchial route (62% *v* 25%). 9 patients underwent BBB which was positive in 3 (33%). BAL (25 cases) and BBr (13) were positive in 1 case each. Overall, the combination of these procedures produced a diagnostic yield in 15 cases (48%). No complications were recorded. The remaining patients underwent mediastinoscopy (4), percutaneous needle biopsy (3), VATS (1), and ultrasound guided biopsy (1). Despite this, 7 patients ultimately had a clinical diagnosis of malignancy.
Conclusion: The addition of these sampling methods at bronchoscopy increased the yield in this selected group of patients who had no visible endobronchial lesion, obviating the need for further invasive and resource intensive investigations in up to half of them. Other clinicians may wish to consider adding these simple to perform diagnostic tests to their routine bronchoscopy practice.

S039 MINIMISING INTERVENTIONS IN THE DIAGNOSIS AND STAGING OF LUNG CANCER THROUGH BIOPSY OF METASTASES AND MEDIASTINAL NODES AS AN INITIAL PROCEDURE

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Introduction: Rapid assessment of suspected lung cancer is important for patients to minimise uncertainty and to ensure treatment is commenced as soon as reasonably possible. The aim is to diagnose and stage with the minimum number of interventions and ideally the safest and least costly test. Our local practice is to biopsy mediastinal nodes or liver, bone, and adrenal metastases where present, thereby diagnosing and staging the patient in one investigation, with reduced morbidity in patients who often have poor lung function and poor performance status.
Methods: The case notes of patients diagnosed with lung cancer between October 2003 and 2005 were identified from the MDT and reviewed. In each case, the procedures undergone, modality by which diagnosis was obtained and stage were recorded.

Abstract S039

Procedure	Number	% diagnostic for malignancy
Bronchoscopy	40 (33%)	63%
CT/USS guided lung biopsy	46 (38%)	89%
CT/USS guided pleural biopsy	9 (7%)	89%
Metastatic biopsy	24 (20%)	100%
Pleural fluid	8 (6%)	37%
Sputum	7 (5%)	40%
Thoracoscpy	1 (<1%)	(100%)

Results: 151 patients were identified; 24 were excluded (diagnosis not lung malignancy or still under investigation). Notes were unavailable on a further 5, leaving 122 for analysis. 72% were non-small cell lung cancer, 8% small cell, 10% mesothelioma and 1% carcinoid (diagnosed on surgical excision). 9% had a clinical or radiological diagnosis of lung cancer with no formal tissue type identified. 11% of patients, but only one patient from the metastatic biopsy group, underwent more than one procedure to establish a tissue diagnosis.
Discussion: These data for image guided lung biopsy give diagnostic rates comparable to that in the literature (Schreiber *et al. Chest* 2003;**123**:115S–128S). In this series, a fifth of patients with lung cancer underwent metastatic biopsy with a superior diagnostic rate to other interventions, with the additional benefit of having undergone a single diagnostic and staging procedure, and the potential for reduced morbidity and time to first treatment. There may be a role for increased use of this modality in the investigation of lung cancer.

Paediatric respiratory disease: bench to bedside

S040 CONGENITAL HEART DISEASE AND OTHER HETEROTAXIC DEFECTS IN A LARGE COHORT OF PATIENTS WITH PRIMARY CILIARY DYSKINESIA

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Background: Primary ciliary dyskinesia (PCD), a recessive genetic disorder with a prevalence of 1/12–17 000, is characterised by sino-pulmonary disease and reflects abnormal ciliary structure and function. Situs inversus totalis (SI) occurs in ~50% of PCD patients (Kartagener's syndrome), and there are a few reports of PCD with heterotaxy (situs ambiguus), including cardiovascular anomalies. Advances in diagnosis of PCD, including genetic testing, allow the systematic investigation of this association.
Methods and Results: The prevalence of heterotaxic defects was determined in a cohort of 326 PCD patients by reviewing clinical and radiographic data. Phenotypic markers included anomalies of cardiac, vascular, pulmonary, splenic, gastrointestinal and hepatic anatomy. Situs solitus was identified in 45% and situs inversus totalis in 49% of 328 PCD patients. A substantial fraction (20/326) of PCD patients had heterotaxic defects (6%). Half the patients with heterotaxy had cardiovascular defects (10/20) and most (7/10) had complex congenital heart disease (CHD) requiring surgery. Polysplenia was also prominent (11/20). Genetic analyses in 12 patients with heterotaxy revealed that 7 carried at least one mutation in *DNAH5* or *DNAI1* and 5 patients had biallelic mutations in *DNAH5* (n = 3) or *DNAI1* (n = 2).
Conclusions: At least 6% of 326 patients with PCD have heterotaxy, and half of these have cardiovascular abnormalities. The prevalence of CHD with heterotaxy is 200 fold higher in PCD than in the general population (1:50 *v* 1:10 000). Mutations in genes causing defective cilia are a significant cause of heterotaxy and CHD, and screening for PCD should be undertaken in these patients, particularly if there is concomitant sino-pulmonary disease.

S041 TRENDS IN PNEUMONIA AND EMPYEMA IN SCOTTISH CHILDREN IN THE PAST 25 YEARS

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Introduction: Empyema thoracis is a complication of pneumonia. The incidence of empyema in children has increased in UK and North America over the last 10 years and this increase is most marked in the 1–4 year group; reasons for this increase are unclear, but could include an increase in the incidence of pneumonia. We report on the number of children admitted to hospital in Scotland for empyema over the past 25 years in the context of pneumonia admissions over the same period.
Methods: Admissions for children <15 years with empyema and pneumonia were analysed using ICD-9 and ICD-10 coding obtained from the Scottish Information Services Division. The period of interest was between 1 January 1981 and 31 December 2005 and changes in

the total population over this period were considered in the analysis. Data was divided by age (groupings <1 year, 1–4 years, 5–9 years, and 10–14 years).
Results: There were 24,312 admissions for pneumonia in children (11 299 between 1 and 4 years) and 217 for empyema (76 between 1 and 4 years). Empyema admissions increased from <10 per annum up to 1999 to reach a peak of 33 in 2005. Among the 1–4 year age group empyema admissions rose from <2/year 1981–85 to 7.4/year between 2001–05. When all children were considered, annual admission rates for pneumonia remained unchanged. However among 1–4 year olds, admissions/year rose progressively during the early nineties reaching a plateau by 2000 (mean admissions/year (SD) between 1981–85 were 394 (47.7) compared with 520 (40) between 2001–05).
Discussion: Our whole population study shows that the incidence of childhood empyema has risen recently in Scotland and continues to rise. The incidence of pneumonia in young children has also risen over the last 25 years and this preceded the rise in empyema by approximately 10 years. Our observations suggest that the rise in empyema is unlikely to be related to an increase in pneumonia. Changes in bacterial pathogenicity and/or host susceptibility could be important.

S042 DO ESTIMATIONS OF HABITUAL ACTIVITY IN CHILDREN WITH CYSTIC FIBROSIS PREDICT AEROBIC FITNESS?

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

We studied 17 children with cystic fibrosis (mean age 12.5 (3.5)), and obtained estimates of habitual activity in three ways. Each child wore an accelerometer (Actiwatch, Cambridge Neurotechnology Ltd, UK) on non-dominant wrist, and a heart rate monitor (Polar Heart Rate monitor, Polar Electro Oy, Finland) for a period of 4 days (2 school days and 2 weekend days), and completed an activity questionnaire (HAES) for one typical weekday and weekend day. Actiwatch counts were converted to levels of energy expenditure (Puyau *et al. Med Sci Sports Exerc* 2004;**36:**1625–31). ''Awake time'' was counted as all epochs with count >0, and ''active'' as epochs with counts >700. For heart rate data, activity was calculated as proportion time spent >50% above resting heart rate (PAHR-50) (Logan *et al. Med Sci Sports Exerc* 2000;**32**:162–6). Aerobic fitness was assessed using an incremental ramp protocol with breath by breath analysis and expressed as peak oxygen consumption ($V'O_2$peak).

Mean (SD) percentage of awake time spent active as reported by HAES was 47.5 (15.7) and as measured by Actiwatch was 28.2 (8.4); PAHR-50 was 28.1 (12.6). Mean (SD) $V'O_2$peak was 39.2 $ml.kg^{-1}.min^{-1}$ (9.2). The correlations between these three estimates of activity and $V'O_2$peak were assessed.

The measures of regular activity all correlated to some degree with aerobic fitness, but this relationship was strongest for the heart rate estimate. The HAES questionnaire correlated rather weakly with direct measures of activity, particularly PAHR-50. Ambulatory heart rate monitoring appears to be useful in assessing levels of activity which influence aerobic fitness; questionnaire data may not be sufficiently reliable.

Abstract S042

$V'O_2$peak and HAES	$r=0.33$	PAHR-50 and Actiwatch	$r=0.49$
$V'O_2$peak and Actiwatch	$r=0.29$	Actiwatch and HAES	$r=0.35$
$V'O_2$peak and PAHR-50	$r=0.71$	PAHR-50 and HAES	$r=0.1$

S043 SMAD SIGNALLING AND MAP KINASE ACTIVITY IN EXPERIMENTAL CONGENITAL DIAPHRAGMATIC HERNIA

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Background/Aim: Up to 70% of patients with familial pulmonary hypertension (PHT) have bone morphogenetic protein (BMP) receptor 2 gene mutations (*Am J Hum Genet* 2001;**68**:92). Downstream of BMP signalling, mitogen activated protein kinases (MAPK) and SMAD activity are abnormal in adult human PHT (*Circ Res* 2005;**96**:1053). We test if similar dysregulation of SMAD and MAPKs contributes to lethal PHT in congenital diaphragmatic hernia (CDH).
Methods: CDH was created in offspring of Sprague-Dawley rats by administration of nitrofen at e9.5 (term 22 days). Left lungs were harvested from normal and nitrofen left CDH (LCDH) fetuses at e17.5, e18.5, e20.5, and e21.5 and postnatal pups sacrificed at 15–45 minutes following caesarean delivery. In addition, control lungs were harvested from 12 hour, 1 week old and adult rats. Total lung protein was extracted and concentration normalised. Samples were analysed for phospho SMAD 1/5/8, phospho p44/42 (MAPKs) and actin expression by Western blot. Normalised relative band densities were compared by Mann-Whitney U test and reported as medians and interquartile ranges.
Results: Phospho (activated) SMAD 1/5/8 protein levels (normalised band density relative to actin) in control lung decline in late gestation ($n\geq5$ all groups) from 1.7 (1.2–2.4) at e18.5 to 0.76 (0.46–0.82) at e21.5 ($p<0.05$ *v* e18.5) before a significant rise to 1.9 (1.1–2.4) at 1 week of age ($p<0.05$ *v* e21.5). Phospho p44/42 levels are steady throughout early gestation ($n\geq4$ all groups). However levels rise significantly from 0.12 (0.060–0.21) immediately after birth to 0.75 (0.24–1.7) at 1 week of age ($p<0.05$) before falling to 0.18 (0.048–0.38) in adult lung ($p<0.05$). Normal and nitrofen-exposed CDH lung had similar expression of phospho-SMAD 1/5/8 and phospho-p44/42 pre- and postnatally ($p>0.05$).
Conclusions: SMAD 1/5/8 are developmentally regulated, especially around the time of birth suggesting a potential role in normal lung development and perinatal pulmonary vascular adaption. These data indicate that PHT of CDH has a different mechanism to familial PHT and may therefore require distinct therapeutic strategies.

S044 THE ROLES OF ANGOIPOIETIN-1 AND TIE-2 IN LUNG ADAPTION AT BIRTH AND PULMONARY HYPERTENSION IN CONGENITAL DIAPHRAGMATIC HERNIA

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Background/Aim: Angiopoietin-1 (Ang-1)/Tie-2 upregulation is observed in adult pulmonary hypertension (PHT) and is suggested to cause accompanying vascular remodelling (NEJM 2003 348;6). Pulmonary vascular pressure is high prenatally, falling dramatically at birth. We test whether Ang-1/Tie-2 regulate transitional physiology at birth and contribute to development of PHT in congenital diaphragmatic hernia (CDH).
Methods: CDH was created in offspring of Sprague-Dawley rats by administration of nitrofen at e9.5 (term 22 days). Left lungs were harvested from normal and nitrofen left CDH (LCDH) fetuses at e17.5, e18.5, e20.5, e21.5 and from postnatal pups sacrificed at 15–45 minutes following caesarean delivery. In addition, control lungs were harvested from 12 hour, 1 week old and adult rats. Total lung protein was extracted and concentration normalised. Phospho-protein immunoprecipitates and normalised extracts were analysed for Ang-1, Tie-2 and actin by Western blot. Normalised relative band densities were compared by Mann-Whitney U test and reported as medians and interquartile ranges.
Results: Ang-1 protein levels (normalised band density relative to actin) in control lung fall significantly during fetal development ($n\geq5$ all groups), from 1.5 (1.1–2.2) at e17.5 to 0.58 (0.49–0.79) at e21.5 ($p<0.05$ *v* e17.5) before a significant rise to 1.3 (0.91–2.1) by 12 h after birth ($p<0.05$ vs e21.5). Adult lung has significantly less Ang-1 0.14 (0.077–0.95) than fetal lung ($p<0.05$ *v* e17.5–e20.5). Tie-2 protein levels in control fetal lung ($n\geq5$ all groups) rise significantly from 0.57 (0.42–0.94) at e17.5 to 1.3 (1.2–1.9) at e21.5 ($p<0.05$ *v* e17.5) before increasing further to 2.2 (1.2–2.8) immediately after birth ($p<0.05$ *v* e17.5). Tie-2 rises significantly in adulthood to 2.6 (2.2–3.6) ($p<0.05$ *v* all prenatal). Normal and LCDH lung had similar expression of Ang-1 and Tie-2 pre- and postnatally. Phospho (activated) Tie-2 levels

at e20.5 (n = 6) and e21.5 (n = 3) were also equivalent between the groups.
Conclusions: Pulmonary Ang-1 and Tie-2 are developmentally regulated during perinatal transition suggesting a key role in adaption at birth. However pulmonary vasculopathy in fetal CDH is not associated with Ang-1/Tie-2 upregulation: therefore their hyperactivation may be the consequence rather than cause of pulmonary vascular remodelling in adult human PHT.

S045 NATIONAL SURVEY OF CHILDREN WITH POST-INFECTIOUS OBLITERATIVE BRONCHIOLITIS: A PROGRESS REPORT

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Introduction: Obliterative bronchiolitis (OB) is reported to be relatively common in some developing countries, but has previously been thought to be rare in developed countries. Increased suspicion and improving diagnostic methods now identify many more paediatric cases in the UK. Little is known about the true incidence of this problem and so a national study began in October 2005 with the aim of ascertaining all cases diagnosed in the last 10 years. The study will describe the epidemiology of OB including causative organism, degree of diagnostic delay, overall severity of disease, mortality and quality of life of patients and their families.
Methods: Four sources of ascertainment are being used: (1) all consultant general paediatricians; (2) respiratory paediatricians in regional centres; (3) British Paediatric Orphan Lung Disease Registry; (4) mortality data from the Office for National Statistics. Radiological findings will be assessed by two pairs of blinded radiologists, and this component of the study will provide a unique consensus on HRCT diagnostic criteria. Cases will be reassessed 5 years after completion of the initial study.
Results: Over 1700 consultants were mailed and to date 52% have replied. 290 cases have been reported There are large regional variations, but estimated overall incidence of disease is 2.5 per million children per year aged 0–15 years. The number of cases notified by region is shown in the table.
Conclusions: Further data are awaited, but this is already by far the largest series of children ever reported. This condition is not nearly as rare as previously thought in the UK, and claims that this is primarily a condition seen in developing countries now need to be revised. OB now needs to be recognised as a significant cause of chronic respiratory morbidity in UK children.

Abstract S045

Region	Cases
North East	56
North West	53
Yorks/Humber	9
East Midlands	4
West Midlands	35
East	6
South East	72
South West	18
Scotland	11
Northern Ireland	12
Wales	14

Occupational asthma

S046 IS FEV1 DECLINE SLOWER IN WORKERS WITH OCCUPATIONAL ASTHMA WITH NORMAL EXHALED NO?

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We have found two phenotypes of occupational asthma separated on exhaled breath Nitric Oxide (FE_{NO}). We postulate that the rate of FEV1 decline during continued exposure is less in those with normal FE_{NO} compared to those with raised FE_{NO}. Fifty one consecutive workers, presenting at an occupational lung disease clinic, had measurements of exhaled breath NO and induced sputum whilst exposed to the causative agent. They were followed with regular FEV1 measurements until complete removal from the causative agent. All were advised to avoid continuing exposure at diagnosis. They were divided into those with normal and raised FE_{NO} (+/−9.6 ppb with the Logan meter, flow rate 200 l/min, corresponding to induced sputum eosinophilia +/−2.2%). The rate of FEV1 decline was computed by linear regression using all measurements made over a follow up period of at least 1 year. Thirty eight workers had a normal FE_{NO}; of these, 32 completed >1 year before complete removal from exposure. This group had $DFEV_1$ of 6.86 ml/year (SEM = 17), only 5/32 had an annual FEV1 decline of >60 ml/year. In the raised FE_{NO} group only 7/13 workers remained exposed for >1 year before complete removal from exposure; making $DFEV_1$ assessment unreliable. Our previous work showed $DFEV_1$ 100.9 ml/year (SEM 17.7) in 90 workers with occupational asthma and continuing exposure (not phenotyped by FE_{NO}) who were followed-up over a mean of 2.9 years *(Thorax online first 10.1136/thx.2005.054080)*. Therefore, those with normal FE_{NO} at presentation may be a group with a better prognosis despite continuing exposure to the causative agent.

S047 BAKERS' KNOWLEDGE OF THE HEALTH RISKS POSED BY FLOUR DUST IN RELATION TO WORK RELATED RESPIRATORY SYMPTOMS

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Background: The Health and Safety Executive of the United Kingdom is committed to reducing occupational asthma by 30% by 2010, as part of the public service agreement targets. Many initiatives are currently being undertaken to effect this change in the UK, but central to these is the realisation by workers that agents in the workplace may be hazardous, and have potential health risks associated with inhalation.
Aims and Methods: We studied 264 bakers as part of a cross sectional workplace study to assess the relationship between flour dust exposure, allergic sensitisation, respiratory symptoms and awareness of the health risks associated with flour dust exposure.
Results: 200 workers (76%) reported regular flour dust exposure. Work related nasal or lower respiratory symptoms were reported by 25%, while 16% were sensitised to flour or alpha-amylase. In addition, 11% of workers showed evidence of airflow obstruction by spirometry (that is, FEV_1:FVC ratio <0.7). Only 40% of workers were warned on starting employment about the health implications of breathing in flour dust, while only 29% had received training on how to keep flour dust levels down. In addition, despite being regarded as good practice, only 56% were enrolled on a health surveillance programme. Those workers reporting flour exposure that had been warned of the health implications of breathing in flour dust reported significantly lower prevalences of work related lower respiratory symptoms compared with those who had not: 13% versus 26% ($p<0.05$). In addition, significantly fewer workers who reported being enrolled on a health surveillance programme on starting employment showed evidence of airflow obstruction by spirometry: 8% versus 18% ($p<0.05$).
Conclusions: This study shows that education aimed at workers and employers is needed to ensure hazard and risk identification in flour exposed workplaces and such education may be effective in reducing work related ill health.

S048 ASTHMA AMONG SCOTTISH FARMERS MAY BE DETERMINED MORE BY OCCUPATIONAL RATHER THAN COMMON ALLERGENS

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Symptoms were recorded, and blood taken from 119 mixed dairy farmers in a rural general practice in Lanarkshire, Scotland, and categorised likely asthma or hypersensitivity pneumonitis (HP) according to the profile.

The region has a recognised high rainfall and requires indoor animal husbandry during the winter months. Most were asymptomatic, 20 had symptoms of asthma (7 non smokers) which was significantly related to IgE level ($p<0.007$), and 13 of HP (10 M faeni precipitin positive, 11 non-smokers).

Respirable dust (mainly from stored and then crushed barley feed mix) concentrations varied between 2.0–45 mg/m^3 in barns which were all poorly ventilated. Skin tests indicated that storage mite (Lepidoglyphus destructor) sensitivity was most common (33/119, 15/20 $p<0.001$), with lesser reactions to grain (33/119, 12/20), animal dander (31/119, 10/20). Grass pollen sensitivity was less than expected (9/119, 3/20 p=NS) when compared with non-farming background atopic asthma in the practice.

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

S049 OCCUPATIONAL ASTHMA CAUSED BY *ARABIDOPSIS THALIANA*

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A 36 year old never-smoker with an 8 year history of hay fever but no past history of asthma undertook a 3 year research project involving the plant *Arabidopsis thaliana* (wall cress). He was based in a small laboratory with an attached growing room that was maintained at 22–24˚C and 30–55% humidity. The laboratory and growing room did not have specific ventilation but there was no obvious damp or mould. After 2 years research he began to develop breathlessness within 5–10 minutes of entering the laboratory. Initial investigations confirmed asthma with airflow obstruction (FEV1/FVC 3.01/4.75 litres: predicted values 3.67/4.43 litres) and increased airway responsiveness (PD20 22 μg methacholine: asthma range <200 μg). Skin prick tests showed positive responses to mixed grass pollen (4 mm), rape pollen (4 mm) and house dust mite (4 mm) with 7 mm positive and 0 mm negative controls. Serial PEF measurements showed a work related pattern with an OASYS score of 4 (asthma likely with scores >2.5). A supervised workplace challenge test led to a fall in FEV1 from the baseline value of 3.10 litres to 2.55 litres within 5 minutes of entering the laboratory. There was a further fall over the next 10 minutes to 1.95 litres and the test was terminated. Skin prick solutions were prepared from Arabidopsis leaves and flower heads. There were positive 4 mm responses to the flower heads (pollen) but no response to the leaves or to a genetically modified plant. A control subject did not show positive skin responses.

Arabidopsis is a member of the *Brassicaceae* (mustard) family. It is related to ragweed, rape and birch. It is used extensively in plant biology research as its genome is small, has been fully sequenced and is easily manipulated. Previous studies have identified its lipid transfer protein 1 as a potential allergen (*Int Arch Allergy Immunol* 2003;**131**:85–90).

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

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Introduction: Sodium metabisulphite (SMBS) is widely used in the fishing industry as a preservative, antioxidant and bleaching agent. At sea its use may be poorly controlled resulting in high exposure among fishermen. It has been described as causing occupational asthma and dermatitis in workers.[1–3]
Aim: To investigate the lung function response of two patients with suspected occupational asthma exposed to sodium metabisulphite.
Methods: Both patients provided serial peak expiratory flow readings. Blood samples were taken for total IgE and RAST. Methacholine challenge testing was performed before and two days after specific challenge testing with (1) seawater and (2) sodium metabisulphite in an exposure challenge chamber. Sodium metabisulphite handling tasks were simulated for 5, 10, 15, and 60 minutes for one patient with measurement of SO_2 concentration.
Results: Both patients showed a work related pattern in peak flow changes. Total IgE was negative in one and moderately elevated in the other; RAST levels for shrimps were negative in both patients. Methacholine challenge testing in one patient showed no response before and a 10% decline in FEV1 two days post specific exposure. Specific exposure to sodium metabisulphite resulted in a 23% decrement in FEV1 at the highest exposure concentration, accompanied with symptoms of wheezing, chest tightness and itching of the scalp. The SO_2 concentration in the exposure chamber reached 40 ppm after only 15 minutes. In the second patient the work related respiratory symptoms disappeared after SMBS was substituted by another preservative agent.
Conclusion: Sodium metabisulphite is widely used in the food industry and occupational exposure may occur in fish processing. We report two cases of sodium metabisulphite induced occupational asthma. Further research is needed to explore the prevalence of respiratory symptoms in this working population.

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This paper was previously presented at the SOM ASM 2006 in Solihull.

S051 PREVALENCE OF ASTHMA RELATED TO EMPLOYMENT IN THE UK: A NATIONAL SURVEY THROUGH GENERAL PRACTICE

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Asthma induced by an occupational exposure is one of the very few forms of the disease that can be ''cured''; it is also readily amenable to prevention. Current estimates suggest that the population attributable risk for occupational exposures in adult asthma is about 15%. Very few of the data for these estimates come from UK populations. In any case there is likely to be considerable intra-national geographical variation due to regional workforce differences; this has not been explored previously. Furthermore, there is evidence of reporting bias by asthmatics of occupational exposures.

In order to overcome these deficiencies we have embarked on a large study of asthma and occupation located in UK general practices recruited through Education for Health. Here we present the protocol and early findings of the study. 9000 adults with registered asthma will be invited to complete a brief postal questionnaire enquiring into their work histories and the date of onset (or worsening) of their disease. Up to two reminders will be sent. Occupations will be classified using both standard and JEM categories; we will also explore a post hoc ''high risk'' categorisation. Cases will be defined as those whose asthma started or deteriorated within two years of starting new employment; we will explore variations in this lag period. Case-referent and case-crossover analyses will allow the estimation of age, sex, and occupation specific risks and regional, population attributable fractions.

Basic mechanisms in pulmonary vascular disease

S052 INTERACTION BETWEEN SMAD AND MITOGEN-ACTIVATED PROTEIN KINASE SIGNALLING IN FAMILIAL PULMONARY ARTERIAL HYPERTENSION

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Familial pulmonary arterial hypertension (FPAH) is known to be caused by heterozygous germline mutations in the gene encoding the bone morphogenetic protein type II receptor (BMPR-II). Mutations in BMPR-II reduce the activity of downstream signaling via Smad proteins, specifically Smads 1, 5, and 8, leading to a failure of antiproliferative effects of BMPs in pulmonary artery smooth muscle cells (PASMCs). However, the penetrance of FPAH is less than 50%, indicating that

additional genetic or environmental factors are necessary for disease manifestation. Since mitogen-activated protein kinase (MAPK) pathways are essential for cell proliferation and have been reported to inhibit Smad signaling we determined the importance of this interaction in PASMCs isolated from small pulmonary arteries (<3 mm external diameter). In initial experiments we confirmed that BMP2 and 6 led to concentration dependent phosphorylation of Smad1, and extracellular signal-related kinase 1/2 (ERK1/2) in PASMCs by immunoblotting. Inhibition of ERK1/2 with the selective inhibitor, U0126, increased phosphorylation of Smad1 following BMP stimulation, increased nuclear translocation of Smad1 and increased activation of a BMP responsive luciferase reporter gene.

Activation of ERK1/2 by exogenous platelet-derived growth factor-BB (PDGF-BB) also antagonised BMP-stimulated Smad1 phosphorylation in PASMCs. Using phospho-specific antibodies we determined that PDGF stimulation increased phosphorylation of the serine 206 residue of the linker region of Smad1, and not the c-terminus serine typically responsible for BMP transcriptional responses. In PASMCs harbouring mutations in the kinase domain of BMPR-II, BMP stimulation was associated with reduced c-terminus Smad1 phosphorylation and reduced activation of Ras/ERK pathways. We conclude that phosphorylation of the Smad1 linker region by ERK1/2 inhibits c-terminus Smad1 phosphorylation, nuclear import and BMP dependent gene transcription in PASMCs. Activation of ERK1/2 pathways by growth factors implicated in the pathogenesis of pulmonary hypertension, such as PDGF, may contribute to the defect in BMP signaling and have a permissive effect on disease manifestation in FPAH.

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

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Introduction: Endothelin-1 (ET-1) has been implicated in pulmonary vascular remodeling and the development of pulmonary arterial hypertension (PAH). Vascular smooth muscle is also an important source of ET-1, although the mechanisms controlling its synthesis and release are poorly understood. We have previously reported a synergistic release of ET-1 by human pulmonary artery smooth muscle (HPASM) cells when stimulated with the inflammatory cytokines, tumour necrosis factor (TNF) α and interferon (IFN) γ. We sought to determine possible mechanisms.
Methods: HPASM cells were grown from explanted vessels taken at lung surgery, under local ethical approval. Cultured cells were treated with either 10% fetal calf serum (FCS), 10% FCS plus TNF-α (10 ng/ml), 10% FCS plus IFN-γ (10 ng/ml) or 10% FCS and a combination of the cytokines, for 18 hours. Complementary DNA was produced and real-time quantitative PCR performed using primers for the pre-pro ET-1 gene. In further experiments, chromatin immunoprecipitation (ChIP) was performed using an antibody against acetylated histone H4, on HPASM cells treated under the same conditions for 2 hours (previously optimised by time course experiments). DNA/histone interactions were fixed with formaldehyde. To investigate transcriptional activity at putative nuclear factor (NF)-κB and interferon regulatory factor (IRF)-1 binding sites on the pre-pro ET-1 promoter, primers were designed and real-time quantitative PCR performed on the acetyl-histone H4/DNA pull-downs.
Results: We show that the combination of TNF-α and IFN-γ induced synergistic transcription of prepro-ET-1 mRNA as determined by real-time PCR, compared to the cytokines alone (ET-1/GAPDH copy number ratio: control, 0.003 (0.00077); IFN, 0.007 (0.00214); TNF, 0.0025 (0.00108); TNF/IFN, 0.0213 (0.0049), p = 0.0041). Furthermore, using ChIP we have demonstrated that there is enhanced acetylation of histone H4 at the NF-kB sites positioned at 891, 1214, 2093, and 2424 bp from the start codon. Interestingly, there was no difference in the acetylation of histone H4 at a single IRF-1 site with the different cytokine combinations, and several of the remaining NF-κB sites appeared redundant.
Conclusions: The enhanced synthesis of ET-1 by the combination of TNF-α and IFN-γ in HPASM involves synergy at the level of transcription of the prepro-ET-1 gene. During this process there is enhanced acetylation of histone H4 at several NF-κB binding sites. As far as we are aware, this is the first report of epigenetic control of ET-1 synthesis, and the use of ChIP in primary human cells to investigate such mechanisms. Understanding such mechanisms may lead to novel therapies directed against PAH.

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

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Background: Excessive pulmonary vascular cell proliferation is a key aspect in the development of severe pulmonary hypertension. Exploring the differential effects of any proposed antiproliferative treatment on the cell types resident to the pulmonary artery is important if we are to learn how best to exploit these drugs. Statin drugs have antiproliferative effects and reverse pulmonary hypertension in animal models. In particular, we have reported fluvastatin inhibition of hypoxia-induced pulmonary adventitial fibroblast (PAF) proliferation (Carlin *et al*, BTS, 2005). It is unknown whether statins would be effective in the treatment of pulmonary hypertension in humans at standard doses or which statin would be best suited to this indication. Also unknown is whether established or novel therapies would complement or simply duplicate the effects of statins and whether we should expect all forms of pulmonary hypertension to respond similarly. To address some of these questions we studied proliferative responses of PAFs, pulmonary artery smooth muscle cells (PASMCs) and systemic adventitial fibroblasts (SAFs) to incremental doses of serum, platelet-derived growth factor and acute hypoxia (5%). We studied the effects of different statins across a range of doses. The cellular mechanisms in the PAF-hypoxia model were assessed by studying effects of statins, prenyl intermediates and related inhibitors on proliferation and MAP kinase activation.
Methods: Proliferation of vascular cells was assessed by [3H] thymidine uptake and cell counting. MAP kinase activation was assessed by Western blot analysis.
Results: Fluvastatin at pharmacological doses inhibited hypoxic proliferation and p38 MAP kinase phosphorylation in PAFs. This effect was reversed by the prenyl compound geranylgeranyl pyrophosphate and mimicked by a geranylgeranyl transferase inhibitor, suggesting that hypoxia-induced p38 phosphorylation is mediated via a GTPase protein such as RhoA or Rac1. The Rho kinase inhibitor hydroxyfasudil had no effect. PASMCs and SAFs showed no increased proliferation in acute hypoxia. Serum and PDGF-induced proliferation of PAFs, PASMCs, and SAFs was only influenced by fluvastatin at doses 10–100 fold higher than achieved in vivo, with no evidence of a circulation specific effect. Simvastatin and atorvastatin had similar effects to fluvastatin, but in contrast to fluvastatin the doses of these required are much greater than those achieved in vivo, in humans.
Conclusion: An important hypoxic signaling pathway in RPAFs has been identified and it is selectively inhibited by fluvastatin at pharmacological dosage. Fluvastatin would seem to have specific potential for hypoxia-associated pulmonary hypertension.

S055 TRANSFORMING GROWTH FACTOR β1 REGULATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN PULMONARY ARTERY SMOOTH MUSCLE CELLS

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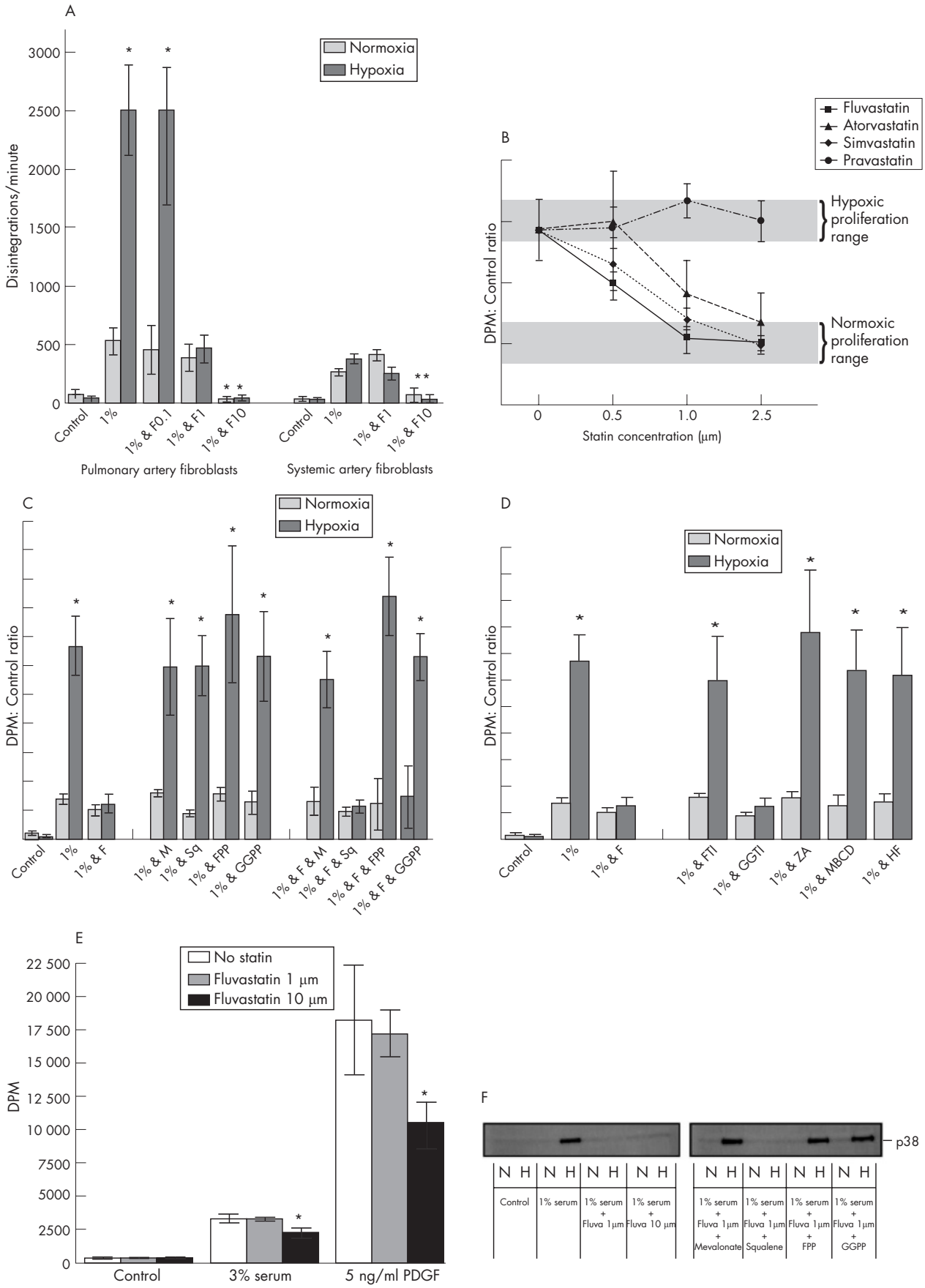
Background: Pulmonary hypertension (PH) is a rare disorder of the pulmonary vasculature characterised by abnormal vasoconstriction and remodelling of the pulmonary arteries. It is widely that agreed pulmonary artery smooth muscle cells (PASMC) proliferation leads to the remodelling that underlies severe PH. Interest in vascular endothelial growth factor (VEGF) in respect to PH arose through two observations. (1) The lumen of small and medium precapillary pulmonary arteries of PH patients contain plexiform lesions which have been described as ''dynamic angiogenic lesions'' as they express angiogenic molecules including VEGF and VEGF receptor 2. (2) Numerous animal studies have shown the introduction of increased VEGF by various methods to alleviate PH. The aim of this research was to study the regulation of VEGF in PASMCs. From the cytokines and growth factors tested ($TGF\beta_1$, bradykinin, interleukin-1β, prostaglandin E_2, tumour necrosis factor α and endothelin-1), only $TGF\beta_1$ caused a significant increase in VEGF protein and, therefore, became the focus of the project. This has added interest due to the past discovery of the BMPR2 mutation (a receptor in the TGFβ superfamily) in familial PH and the emerging concept of aberrant BMPR2 signaling having a positive impact on $TGF\beta_1$ signalling.
Methods: Studies were performed in PASMCs at passage 6. VEGF protein production was measured by ELISA. Transcriptional regulation was assessed by transient transfection of promoter reporter constructs using either Lipofectamine 2000 or Fugene 6 according to



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

manufacturer's protocol. Serum starved confluent PASMCs were used for inhibitor studies.
Results: PASMCs constitutively produce VEGF protein and TGFβ_1 caused a significant, concentration (0.01, 0.1, 1, and 10 ng/ml) and time (0, 2, 4, 8, 16, 24 hours) dependent increase in VEGF protein (peak 2.4-fold at 24 hours with 1 ng/ml TGFβ_1). Use of mitogen activated protein kinase (MAPK) inhibitors showed the increase to be independent of P44/42, P38 MAP kinases and c-Jun N-terminal kinase (JNK). TGFβ_1 induced activity of a wild type VEGF luciferase reporter construct (1.6-fold after 3.5 hour 10 ng/ml TGFβ_1 stimulation). Serial deletion of fragments of the wild type reporter down to 318 bp had no effect on luciferase activity whereas at 135 bp the activity was lost. As the sequence between 318 and 135 bp contains SP-1, AP-2, p53, and TCF binding sites, we determined whether these transcription factors were activated by TGFβ_1 using reporters linked to multiple transcription factor recognition sequences. TGFβ_1 did not increase SP-1, AP-2, or p53 reporter activity. However an increase in TCF reporter activity (2.1-fold after 24 hour 10 ng/ml TGFβ_1 stimulation) was seen suggesting TCF involvement.
Conclusions: TGFβ_1 stimulates VEGF protein production by PASMCs independently of P44/42, P38 MAP kinase and JNK. This is regulated transcriptionally and future work will concentrate on confirming the involvement of TCF transcription factor.

S056 BMPRII DYSFUNCTION IN PULMONARY ARTERY SMOOTH MUSCLE CELLS CAUSES ABNORMAL GROWTH RESPONSE TO TGF-β

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Introduction: Pulmonary arterial hypertension (PAH) is characterised by increased growth of pulmonary vascular endothelial and smooth muscle cells. The familial variant of this condition (FPAH) is mainly caused by mutations in the bone morphogenetic protein type II receptor (BMPRII), a receptor in the TGF-β/BMP superfamily. Although mechanisms underlying this dysregulated cell growth are not yet fully understood, our previous results have implicated TGF-β. Here we characterise more comprehensively the abnormal growth response to TGF-β in cells harbouring disrupted BMPRII.
Methods: Pulmonary arterial smooth muscle cells (PASMC) were harvested from explanted lungs from patients undergoing lung transplantation for FPAH as well as from lobectomy tissue in non-PAH control patients. Cells were maintained under standard tissue culture conditions. Cells from 3 control and 3 mutant cell lines were seeded at 1.5×10^3 cells/well and quiesced for 24 hours. Cells were then incubated in DMEM/10% FBS in the absence or presence of TGF-β_1 (10 ng/ml), treatments being replenished every 48 hours. Cells were counted on alternate days and viability assessed by trypan blue exclusion. Similar studies were also performed on cells harvested from mice heterozygous for a null allele BMPRII as well as human control cells in which BMPRII was knocked down by transfection with siRNA for BMPRII.
Results: The growth of control cells, both human (table) and mouse, was significantly inhibited when treated with TGF-β_1. However, cells harbouring a BMPRII mutation or with reduced expression of BMPRII receptors, due either to a null allele or as a result of transfection with siRNA for BMPRII, were not susceptible to the growth inhibitory effect of TGF-β_1 Western blot analysis of protein from cells transfected with BMPR-II siRNA, has demonstrated that this TGF-β_1 mediated effect is not due to increased activation of the TGF-β signaling intermediaries, Smad 2 or 3.
Conclusions: These results show that BMPRII dysfunction is central to the abnormal growth response to TGF-β. Although the mechanism of this response remains to be defined our initial results suggest a Smad-independent mechanism.

Abstract S056 Absolute cell counts at day 6 (SEM)

	10% FBS	10% FBS + TGF-β
Control human PASMC	38.4×10^3 (0.77)	22.9×10^3 (2.11)*
BMPRII mutant human PASMC	42.3×10^3 (12.6)	54.0×10^3 (16.24)

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

S057 IMAGE ANALYSIS OF ELASTIN CHANGES IN PULMONARY VASCULAR REMODELLING IN SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE SHOWS LOSS OF MEDIAL FIBRE ORGANISATION

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Introduction: Degradation of the elastic microstructure is a histological feature of a number of chronic lung diseases including chronic obstructive pulmonary disease (COPD). Although there is accumulating evidence of vascular remodelling in COPD, the morphology of elastic fibre changes has not been well studied. Using tissue specimens from a severe COPD patient cohort, we have developed an image analysis system to objectively assess and quantify these changes.
Methods: Tissue samples were randomly selected from archival material, the only criteria being the presence of bronchovascular pairs. Tissue samples were received with ethical consent from 6 patients undergoing lung volume reduction surgery. Serial sections were stained with H&E and Miller's elastic van Gieson (EVG). Vessels were examined on H&E (n = 215) and severity of medial remodelling scored according to our

Abstract S057

Remodelling score	Mild	Median	Severe
Media score	2 (0–3)	5 (5–5)	10 (8–11)
Total vessel score	5.5 (3–8)	9 (9–11)	16 (11–19)
Hue	199 (182–220)	202 (188–223)	207.5 (186–225)
Saturation	101 (86–129)	97 (80–118)	92 (79–119)
Intensity	183 (167–213)	191 (173–208)	194.5 (174–216)

previously described grading system (BTS Winter Meeting 2005). Three groups, each comprising 20 vessels were chosen based upon the scores achieved (lowest (mild), median and highest (severe) media score). The elastic tissue within these vessels was analysed on EVG sections using Leica Qwin. An arbitrary score (maximum = 255) for hue (purity of red/green/blue colour), saturation (shade of colour) and intensity (brightness) was recorded.
Results: Expressed as median (range). No significant difference between groups was found with hue or intensity measurements, implying uniformity of EVG staining. Within the vessel population, saturation inversely correlates with both media score ($r = -0.344$, $p = 0.012$) and total vessel score ($r = -0.391$, $p = 0.004$). Saturation was significantly less in the severely remodelled group compared with the mildly remodelled group ($p = 0.04$), as highlighted in the table.
Conclusions: Saturation data strongly suggest decreasing fibre density with increasing severity of medial pathology. This implies increased fragmentation or redistribution of the elastin fibres. The effects of oedema may be confounding, however, this will be mitigated by the largely area-independent saturation analysis. Further work is in progress to investigate elastin fibre degradation as opposed to fibre redistribution.

Abstract S059

Time	Group A (n = 113)	Group B (n = 115)	Group C (n = 116)	p Value (Fisher's exact)
Week 1	100%	100%	100%	NS
Week 4	–	49%	51%	NS
3 months	5% (n = 101)	4% (n = 98)	15% (n = 95)	0.01
6 months	1% (n = 76)	4% (n = 78)	4% (n = 70)	NS

Smoking cessation

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

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Introduction: Smoking cessation is one of the most important aspects of managing patients with chronic obstructive pulmonary disease (COPD), as it slows the rate of decline of lung function and benefits patients in terms of symptom progression and survival. Smoking cessation intervention is associated with a variable short and long term quit rates.
Aim: To assess the effectiveness of smoking cessation advice given during and after an acute exacerbation of COPD in the community by ROS in the Hull and East Yorkshire area.
Methods: Smoking cessation intervention was provided by a trained nurse as a part of a respiratory outreach service (ROS) to patients during an acute exacerbation in the hospital followed up in the community, in the form of support, verbal advice and nicotine replacement therapy. They were followed up in 1, 3, 6, and 12 months.
Results: Over a period of 18 months, 91 patients were qualified, 12 (13%) patients died and in the remaining 79 patients (39 women) mean age was 65 (51–87) years. Smoking history was 62.2 pack years with a range of 10 to 228 pack years. After inervention, 41 (51%) patients managed to stop smoking in 4 weeks. At 3 months 33% and at 6 months 30% managed to stop smoking. However 17 started smoking again. At 18 months 20 (25%) of them managed to stop smoking.
Conclusion: The national COPD audit conveys a high mortality rate following an acute exacerbation. Smoking intervention has a high success rate at 4 weeks following an acute exacerbation, which was maintained at the end of 18 months. We suggest a routine smoking cessation intervention during an acute exacerbation and as a part of hospital at home service and might emphasis similarity with pulmonary rehabilitationregarding effectiveness of early intervention following exacerbation.

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

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Background: Most smoking cessation programmes are based either in secondary care or primary care/community. We tested a model where hospitalised smokers are first counselled in secondary care and then referred to the community service for ongoing support and relapse prevention. To validate quitters, they must first attend.
Methods: Open-label, randomised, controlled, intervention trial. Smokers attending two hospitals, who wanted to quit, were randomised to (A) single session and generic advice from the Stop Smoking Counsellor (SSC) +/−NRT and then advised to contact the community smoking cessation service on a provided leaflet, (B) 4 weeks' support by the SSC, +/− NRT and then advised to contact the community service, (C) 4 weeks' support by the SSC, +/− NRT and then given a specific appointment with the community service before leaving the SSC office. Non-attenders were sent a reminder letter and were phoned once. Those with active psychiatric illness, substance misuse, were pregnant or who were housebound were not recruited. We compared attendance at each time point between the three groups.
Results: We present interim data on 344 patients. The three groups did not differ significantly on age, gender, pack-years, comorbidity, self-reported daily consumption, comorbidity, number of outpatients, and baseline modified Fagerstrom score. The table shows % attendance (from number eligible to attend at each time point).
Conclusions: Despite good attendance within secondary care, later attendance to the community service is very poor, even when specific appointments are made and smokers are individually reminded. Although there is an 11% difference in attendance rates at 3 months between groups B and C, by 6 months this difference has disappeared.

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

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Introduction: Smoking is the greatest preventable cause of respiratory disease in the developed world. A smoking history should be taken from all patients, and smokers advised to stop and given support.[1] We have previously reported on smoking history and cessation support in acute medical admissions to our hospital, and the effect of a clerking proforma;[2] this is a follow up study after the introduction of a smoking cessation strategy and service.
Methods: We obtained a sample of casenotes of patients admitted as medical emergencies in January 2006, after the introduction of a smoking cessation strategy (including guidelines for support and pharmacotherapy, and training for all health professionals). We collected demographic and diagnostic information, the documented smoking history and cessation advice given. We carried out descriptive and univariate analysis (using smoking history and cessation as outcomes), and compared results with those of our previous study using STATA 8.
Results: We reviewed casenotes of 99 patients, mean age 59 years, 55 (56%) male, 47 (49%) with smoking-related diagnoses. 82 (83%) had a smoking history recorded. Of the 30 current smokers identified, only 6 (20%) were given advice to stop, although those with smoking-related diseases were more likely to be given advice compared to unrelated conditions (33% *v* 7%, χ^2 3.0, $p = 0.08$). Smoking history was significantly better compared to results from 2004 (recorded in 83% *v* 61%, χ^2 11.2, $p = 0.001$), before the introduction of the smoking cessation strategy and service, although the proportion of smokers given smoking cessation advice was no different (20% *v* 16%, χ^2 0.016, $p = 0.90$).
Conclusions: Although we have shown a significant improvement in smoking history in acute medical admissions, smoking cessation advice remained poor despite the introduction of a smoking cessation strategy and service. This study highlights the continued need for education of medical staff in smoking cessation.

1. **West R**, *et al*. Smoking cessation guidelines for health professionals. *Thorax* 2000.
2. **Baker JG**, Molyneux AW. Smoking history and cessation in acute medical admissions. *ERJ* 2005;**26**:5s.

S061 SMOKERS ADMITTED TO HOSPITAL: ROLE OF JUNIOR DOCTORS, SMOKING CESSATION SERVICES, AND SMOKE-FREE HOSPITAL

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Background: Intensive intervention with inpatients who smoke improves smoking cessation rates. Smoking cessation (SC) services for inpatients started at the Whittington Hospital in July 2004 and in July 2005 the premises became ''smoke free''. However, junior doctors need to know what SC advice to give and prioritise giving it for SC services to be used. Over a 16 month period we measured smoking rates in inpatients, documentation of smoking status and provision of SC advice by junior doctors.
Method: Three cross sectional surveys of all adult medical and surgical inpatients were carried out on single days in October 2004, June 2005, and January 2006. Patients were interviewed by medical house officers using a standardised anonymous questionnaire. Questions included current smoking status, whether smokers had smoked since admission, and whether smokers had received SC advice during their admission. Documentation in the medical record of smoking status and SC plan was also recorded. Junior doctor education on SC was provided with audit feedback after each survey. After the first survey, the investigators added a prompt to the admission proforma reminding junior doctors to discuss SC and giving details of how to refer patients to SC services.
Results: A total of 616 in-patients were interviewed. The response rate for each survey was 74.3 (1.4)% (mean (SEM)). The percentage of inpatients who were smokers did not change at 19.6 (1.4)%, consistently lower than the community smoking prevalence of ~35%. Smoking status was well-documented (84%–91% of patients). In October 2004 only 15/45 (30%) of smokers were advised about SC. This increased significantly to 26/46 (57%) in January 2006 ($p<0.05$). SC plan was documented for only 3/45 (7%) smokers initially, but increased significantly over the period ($p<0.05$), although only to 10/46 (22%). There was no significant trend for patients smoking during their admission; 21/45 (47%) admitted to smoking in hospital in October 2004 and 14/46 (30%) were still smoking during their admission in January 2006 despite being on ''smoke-free'' premises.
Conclusions: Approximately one in five inpatients smoke. Only 30% of patients were given SC advice initially, despite having a SC service. Our data suggest that SC education and feedback for junior doctors had a significant impact on increasing provision, and documentation, of SC advice. This is important for SC services to be used optimally. More still needs to be done as only 60% of smokers were given advice and this is still poorly recorded. Of concern, despite the premises being smoke free, 30% of patients continue to smoke during admission. More training of junior doctors as well as inpatient SC advisors are needed to help inpatients quit.

S062 THE NHS STOP SMOKING SERVICES: HOSPITAL STAFF AWARENESS AND THE PATTERN OF REFERRAL TO THE LOCAL (BASILDON AND THURROCK) SERVICES

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Introduction: Smoking cessation services (SCS) have a quit rate of between 13–19% (abstinence for six months or longer) when compared to 5% following GP advice alone and 2–3% if no advice is given.[1] The effort of SCS has largely focused on primary care practices. However close links with the secondary care is important for delivery of more effective services. Promotion and awareness schemes have been orchestrated in the past for the hospital setting. The aim is to audit and review what is needed to promote this further.
Objectives: (1) To assess the level of awareness of the local SCS among hospital medical and nursing staff in a 652-bedded District General Hospital. (2) To identify the pattern of referral to the SCS and to assess the effectiveness of our two local SCS (the Basildon and Thurrock services).
Methods: (1) A survey was undertaken among the staff at Basildon Hospital to assess awareness and frequency of referral to the SCS. (2) The database of the Basildon and Thurrock SCS was reviewed.
Results: Forty eight hospital staff participated in the survey (12 nurses, 12 junior doctors, 12 middle grade doctors, and 12 senior doctors). Thirty six participants (75%) reported that they were aware of the local SCS. Only 10 participants (21%) had referred patients to the local SCS. During the period April 2004 to March 2005, Basildon SCS received 776 referrals including 619 self referrals (79%), 157 GP referrals (20%) and 10 direct hospital referrals (1%). It is possible that some individuals who self-referred had done so following hospital staff advice. Of the 776 referrals to the Basildon SCS, 457 attended the SCS clinic at least once and 301 completed the whole program. The 12 month quit rate for this group was 27%. During the same period, the Thurrock SCS received 963 referrals including 643 self referrals (67%), 271 GP referrals (28%), 4 direct hospital referrals (0.4%) and 45 from other sources (4.6%). Out of the 963 referrals, 413 attended at least one clinic and 290 completed the program. No data are currently available for the 12 month quit rate for this group.
Conclusion: Although many hospital staff are aware of the presence of the local SCS, the pattern of referral suggests poor attempt from the hospital staff to use the service directly. Judging by the 12 months quit rate for Basildon SCS, the service has higher success rates relative to the expected figures of 13–19%. Increase awareness of SCS and encourage more collaboration between secondary care and SCS is recommended.

1. **West R**, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;**55**:987–99.

S063 KNOWLEDGE OF QUIT SMOKING SERVICES BY HOSPITAL PAEDIATRIC STAFF

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Aims: Parental smoking is associated with increased rates and severity of childhood respiratory illness.[1] Many parents want to quit smoking, but need professional support.[2] We questioned staff within the Paediatric Department to determine what level of knowledge they had about smoking cessation services available locally and how confident they felt to advise a parent about quitting smoking.
Methods: We sent an anonymous questionnaire to all the 237 nursing, medical and support staff in the Child Health department of our hospital.
Results: 167 (71%) responded, of whom 81% were nursing staff, 12% doctors, 7% clinical support workers and students. Staff identified passive smoking as being associated predominantly with respiratory problems particularly asthma (55%), otitis media (10%) and SIDS (9%). 59% of respondents were aware of a smoking cessation service within the Trust, but 37% of these were unable to clearly identify what was available or name the service. 49% of all respondents did not know how to refer a patient for smoking cessation support. 56% said that they did discuss the benefits of stopping smoking with the parents of patients, but 69% did not discuss quitting smoking with the children/young people. 71% of staff said they were not confident to advise a parent or patient about how to stop smoking and 73% of the staff would like to receive training in quit smoking interventions.
Conclusion: If attempts are to be made to help families achieve a non-smoking environment for their children, paediatric professionals need training in quit smoking interventions and be better informed of the services available.

1. **West R**, McNeill A, Kaw M, *et al*. A smoking cessation intervention for parents of children who are hospitalized for respiratory illness: The stop tobacco outreach program. *Pediatrics* 2003;**111**:140–5.
2. **Sheahan SL**, *et al*. Counseling parents to quit smoking. *Pediatr Nurs* 2005;**31**:98–109.

S063A MOTIVATIONAL EFFECTS OF SPIROMETRY ON SMOKING CESSATION

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Introduction: For many years clinicians have believed that demonstrating that smoking was damaging their lungs would help people to quit, but also worried that if smokers knew they had normal lung function they might be encouraged to continue. We investigated the effect of spirometry on motivation to quit smoking.
Methods: A cohort of smokers was recruited from patients >35 years old attending eight GP practices over one year. Opportunistic spirometry, performed by a trained nurse, was classified as obstructive (OLF) if predicted values were FEV1/FVC <85% or $FEF_{25–75\%}$ <55%, or normal (NLF). Restrictive changes were excluded (FVC <80% predicted). All smokers were given brief general quit advice plus a specific feedback message on spirometry: OLF group told ''Evidence of lung damage due to smoking'' and NLF group told ''No evidence of lung damage''. The effect of spirometry feedback on shift of stage in the Transtheoretical Model[1] (which describes five stages in the process of achieving

long-term smoking cessation) and sustained smoking cessation was assessed after 3 months by self-report.
Results: 328 participants (98% of eligible total) were recruited, 193 in NLF and 135 in OLF groups. Baseline nicotine dependence, cigarette consumption, stages of change distribution, quit confidence and perception scores (VAS) for health, lung damage and quit benefits were similar in both groups. Follow up was successful for 297 (91%). The increase in positive stage shift between OLF and NLF groups was not significant, 39 (31.2%) and 42 (24.4%) respectively (p=0.399). Negative stage shift was similar (12%) in both OLF and NLF groups. Using multinomial logistic regression, higher perception of health was a significant predictor for positive stage shift compared to negative shift (p=0.002) while a shorter smoking history ($\leqslant$20 *v* >20 pack years) was not quite significant (p=0.06). Seventeen participants quit, with 7-day point prevalence cessation rates in the OLF group 50% greater that in the NLF group, but not significantly different at 6.7% and 4.1% respectively (p=0.311). Successful quitting was associated with shorter smoking history (p=0.03), lower nicotine dependence (p=0.003), quit confidence above average (p=0.008), higher perception of health (p=0.011) and later stages of change for cessation. Association with category of feedback (OLF *v* NLF) was not significant (OR 1.65, p=0.315) but after adjusting for smoking history it was stronger (OR 2.436, p=0.087).
Conclusion: In unselected smokers in primary care, receiving feedback that spirometry showed damage due to smoking was associated with non-significant increases in short-term smoking cessation and positive shift of motivational stage. Feedback that there was no damage was not associated with any decrease in motivation. This is reassuring, as GP contract indicators for chronic obstructive pulmonary disease will increase use of spirometry in smokers in primary care.

1. **Prochaska JO**, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *J Consult Clin Psychol* 1983;**51**:390–5.

Pulmonary infections

S064 MICROBIOLOGY INVESTIGATIONS IN COMMUNITY ACQUIRED PNEUMONIA: WHAT IS AVAILABLE FROM ENGLAND AND WALES LABORATORIES?

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Aims: To assess the availability and usage of microbiological investigations in the diagnosis of community acquired pneumonia (CAP).
Methods: Postal questionnaire sent to 212 England and Wales microbiology laboratories. Questions related to the provision of Gram stain for sputum samples, and testing of urine specimens for legionella and pneumococcal antigens.
Results: 143 questionnaires returned (67%) with 133 datasets (10 centres reported jointly). *Gram stain on sputum specimens*: 52/133 labs (39%) do not provide this service and 81 (61%) labs do (48 (36%) on special request only). Of the 81 labs, 14 (17%) specify criteria to requesting clinicians and 14 (17%) specify minimal microscopy criteria before reporting specimens. 20 (25%) provide same-day reporting only within working hours. 46 (57%) also provide this out of hours. *Legionella urine antigen testing*: 131 (99%) labs offer this but 44 (34%) specify criteria to clinicians. 18 (14%) labs specify criteria based upon the 2004 Update to the BTS Management of CAP Guidelines (BTS2004CAP). 97 of these labs (74%) run the test on site, and 92 (93%) offer a routine service within 24 hours. 49 labs (50%) provide a result for urgent specimens within 6 hours during working hours; 44 (44%) offer this service out of hours. 61 (62%) of labs refer ''positives'' to the national reference lab. 43 (69%) refer to support national surveillance. 56 (92%) refer to confirm initial test results. 69 labs (53%) provided data on numbers of tests processed in 2004. The mean number of cases tested per lab was 170 (max 849). The mean number of positive cases per lab was 2.1 (1.2% of tests – total positive cases 145). *Pneumococcal urine antigen testing*: 71 (53%) labs offer this, and 10 (8%) plan to introduce the test within the next year. Of reporting labs, 23 (32%) specify criteria to requesting clinicians. Most labs (59–83%) provide the service on site, and 55 (93%) offer a routine service within 24 hours, 26 labs (44%) report urgent specimens within six hours (during working hours) and 28 (48%) offer this service out of hours. 33 labs (46%) provided data on the number of tests processed in 2004. The mean number of cases tested per lab was 74 (max 832). The mean number of positive cases per lab was 4.3 (5.8% of tests – total positive cases 304).
Comments: BTS2004CAP suggest the use of all these tests in severe CAP. Early microbiological diagnosis of severe CAP should facilitate optimum therapy. The results of this large survey show that sputum Gram stain is available in only 2/3 of labs of which half offer immediate results. Legionella urine antigen testing is almost universally available, but usually only in working hours. The diagnostic rate is low, perhaps because only 24% of labs specify criteria to requesting clinicians, as suggested by BTS2004CAP. Pneumococcal urine antigen testing is less widely available, but access is increasing. The positivity rate is encouraging.

S065 CLINICAL AND SPUTUM CHARACTERISTICS OF PATIENTS WITH BRONCHIECTASIS ATTENDING A LARGE UNIVERSITY TEACHING HOSPITAL

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Bronchiectasis remains a common respiratory disease, even in developed countries, yet little current research is available to improve treatment and none of the major respiratory societies has yet produced guidelines on this area. 215 sputum samples from 107 patients labelled as having bronchiectasis were received by the microbiology department of a large UK teaching hospital over a 6 month period in 2005. A random sample of 56/107 was selected for further study; 8 did not have bronchiectasis on inspection of the clinical notes, leaving 48. Mean (SD) age 65 (9.1) years, 21 (44%) male, mean time since diagnosis made 17 (range 0–67) years. Only 2 (4%) were current smokers, 26 ex-smokers and 19 lifelong non-smokers. Mean (SD) FEV1 % predicted 57% (24.0); 33 (69%) had airflow obstruction (FEV1/FVC ratio <70% and FEV1 <80% predicted). 41 patients had CT evidence of bronchiectasis, 1 had been diagnosed with a bronchogram; the diagnosis was made on clinical and CXR grounds in the remaining 6. 20 (42%) were classified as having primary bronchiectasis, and 27 (56%) secondary; 16 following childhood respiratory pneumonia or pertussis, 4 post tuberculosis, 1 rheumatoid arthritis, 1 AAT deficiency, 5 miscellaneous. 20/48 had immunoglobulin levels recorded and of these only 1 had a low IgG; none had further assessment of immune function. 12 had Aspergillus precipitans measured and of these 2 were positive. 35/48 (73%) had been taught home postural drainage and other physiotherapy techniques.

17 (35%) were inpatients at the time of the sputum sample collection. Sputum samples were positive in 32 (67%) samples and organisms grown were Pseudomonas species (12), Haemophilus influenzae (9), Coliform (5), Staphylococcus aureus (4), yeasts (2), Escherichia coli (1), Moraxella catarrhalis (1), MRSA (1) and Streptococcus pneumoniae (1). 4 samples were positive for 2 organisms. All pseudomonas species tested were sensitive to ceftazidime. There were no differences in demographics or clinical characteristics between those who grew Pseudomonas species and those who did not.

Diagnosis, investigation and management of bronchiectasis patients remains somewhat haphazard. The BTS guidelines, due to be published soon, will be a welcome measure towards improving the care of these patients.

S066 STAPHYLOCOCCUS AUREUS IN WEGENER'S GRANULOMATOSIS: COLONISATION OR CAUSATION?

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Introduction: Wegener's granulomatosis (WG) is a small vessel vasculitis characterised by anti-neutrophil cytoplasmic antibodies against PR3. It has been proposed that bacterial infection may have a role in the disease process. Nasal carriage of Staphylococcus aureus (SA) has been associated with an increased relapse rate. The lower airway is involved in approximately 90% of WG patients, however no detailed studies have looked for SA in the lower airways. It has previously been shown that the pro-inflammatory cytokines IL1β, IL1RA, IL6, and TNF have a biphasic role in bacterial growth, supporting growth at higher concentrations.
Study Aims: To determine the prevalence of lower airway *SA* infection in WG at presentation, remission and at relapse. To ascertain if the presence of *SA* influences cytokine levels. To investigate whether WG BALF promotes *SA* growth.
Methods: Forty four patients with WG, 31 with IPF and 11 normal controls underwent bronchoalveolar lavage (BAL) through the mouth. WG disease activity was defined using BVAS. A nasal swab was performed. Quantitative culture was performed on the BAL samples.

Abstract S066

Mean data pg/ml	IL1β	IL1RA	IL6	IL8	TNFα	GCSF
WG	161.7	14521.8	17.3	1795	30.91	101.8
WG *v* N *t* test p value	0.021	0.000	0.025	0.004	0.037	0.015
IPF	16.3	12457.0	13.1	797.8	14.9	73.8
Normal	12.9	323.1	0.5	120.1	12.6	20.3

Cytokines were measured by Luminex array and ELISA. A laboratory *SA* was incubated with filter sterilised BALF from WG, IPF, and normal controls. The number of colony forming units (CFU) were counted after 24 hours.
Results: Greater than 10^4 CFU were cultured from 26 (66%) WG patients and in 16 *SA* was grown. In IPF a pathogen was grown in 12 (39%) patients with one *SA*. No pathogens were grown in BALF from normal controls. *SA* was more likely to be grown in the WG relapse and remission compared to acute patients ($p=0.025$). BALF growth of *SA* is independent of nasal carriage in 15% of cases. IL1RA is elevated ($p=0.05$) and TNFα ($p=0.003$) is reduced, when SA is grown in WG BALF.

Incubating *SA* in BALF from WG patients resulted in higher numbers of CFU than IPF ($p=0.043$) or normal ($p=0.036$), an effect that is heat labile.
Conclusion: SA has a predilection for WG patients where the alveolar environment appears permissive for SA growth. Cytokines reported to stimulate SA growth are elevated in WG BALF compared with controls. Although TNFα is elevated compared with controls, within the WG group, patients that grow *SA* have lower levels of TNFα which is specifically required for neutrophil killing of *SA*. Defective clearance mechanisms and a promotive cytokine environment may encourage persistence of SA provoking inflammation and an increased relapse rate.

S067 C-REACTIVE PROTEIN IS AN INDEPENDENT MARKER PREDICTING SEVERITY IN COMMUNITY ACQUIRED PNEUMONIA

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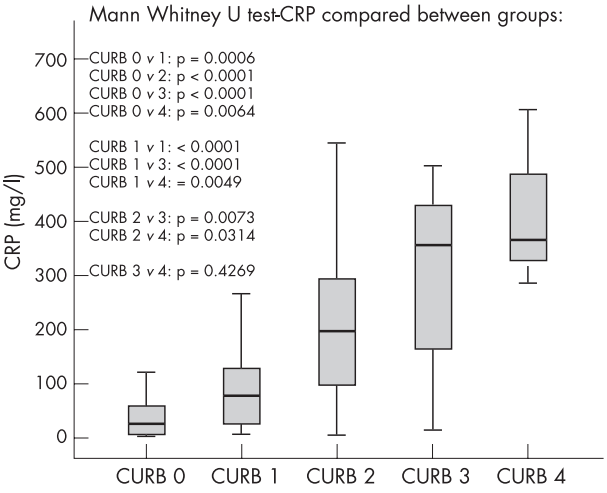
Introduction: National guidelines use CURB score (new mental confusion, urea >7 mmol/l, respiratory rate ≥30/minute, systolic blood pressure <90 mmHg and/or diastolic blood pressure ≤60 mmHg) for assessment of severity of community acquired pneumonia (CAP). A CURB score ≥2 is regarded as severe pneumonia. The aim of this study was to assess whether the acute phase C-reactive protein (CRP) was an independent marker of predicting severity of CAP.
Methods: We studied 187 adult patients admitted with CAP to the Royal Infirmary of Edinburgh between December 2005 and June 2006. Data are presented as median interquartile range (IQR). The Mann Whitney U test and Kruskal-Wallis test was used to compare groups. A p value less than 0.05 (two-tailed) was considered as statistically significant.
Results: CRP was an independent marker of severity of CAP: see figure 1. In addition, CRP correlated with patient placement (patients were all assessed in hospital but then were either discharged (hospital stay <24 hours), admitted to the Respiratory ward or were admitted to the high dependency (HDU) or intensive care unit (ITU)); see table.

The CRP normal range in our laboratory is from 0–10 mg/l. For CRP >10 mg/l, the positive predictive value for severe pneumonia (CURB ≥2) is 83.2% and the negative predictive value for exclusion of severe pneumonia for a CRP <10 mg/l is 95.7%.
Conclusion: CRP is an independent predictor of severity of CAP. CRP concentrations <10 mg/l effectively excludes severe CAP.



Abstract S067 Boxplot of CRP compared with CURB scores.

S068 NEUTROPHIL-MEDIATED IMMUNITY TO MYCOBACTERIUM TUBERCULOSIS INFECTION: ROLE OF LIPOCALIN 2

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Background: Some individuals exposed to infectious tuberculosis (TB) do not develop evidence of infection. We investigated the factors associated with this phenomenon in a group of TB contacts; independent risk factors for infection were identified with multivariate analysis.
Methods: We investigated correlates of host response to mycobacterial infection in 202 adult TB contacts in London, UK, using two whole blood assays, and evaluated the contribution of neutrophils to host response by neutrophil depletion. We determined serum concentrations of the neutrophil antimicrobial peptides HNP 1–3, LL-37 and lipocalin 2 by ELISA, investigated the effect of recombinant lipocalin 2 and iron-restriction on growth of *M tuberculosis* (MTB) in broth and identified regulators of lipocalin 2 secretion and gene expression in cell culture.
Results: We observed a strong and independent inverse relationship between peripheral blood neutrophil count and risk of latent TB infection (LTBI) as indicated by secretion of interferon gamma by whole blood stimulated with the MTB antigens ESAT-6 and CFP-10. The ability of

Abstract S067 Median (IQR) CRP levels is dependent on patient placement

Placement	Number	Median CRP (mg/l)IQR		p value (Kruskal-Wallis)
Discharge	12	28	12–49	p<0.0001
Respiratory ward	146	101	31–210	
HDU or ITU	29	216	85–370	

whole blood to restrict metabolic activity of the recombinant reporter mycobacterium BCG-*lux* was very significantly impaired by neutrophil depletion, and correlated with serum concentration of lipocalin 2, a neutrophil peptide which binds soluble siderophores of mycobacteria. Lipocalin 2 restricted growth of MTB in 7H9 broth; this effect was more marked in iron-depleted broth. Black African and south Asian TB contacts had lower serum lipocalin 2 levels, lower neutrophil counts and higher rates of vitamin D deficiency than whites. The active metabolite of vitamin D, 1α,25$(OH)_2$-vitamin D_3, induced secretion of lipocalin 2 in whole blood and induced lipocalin 2 gene expression in neutrophils in vitro.
Conclusions: High peripheral blood neutrophil count was independently associated with decreased risk of LTBI as diagnosed by a whole blood assay. The vitamin D-inducible peptide lipocalin 2 may contribute to neutrophil-mediated antituberculous activity. Vitamin D deficiency and ethnic neutropaenia may combine to enhance susceptibility to TB infection in south Asians and black Africans.

Paediatric asthma

S069 CHILDHOOD WHEEZE, PEAK FLOW, AND THE OXFORD TRANSPORT STRATEGY

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Background: Studies of the health effects of traffic interventions are rare. In June 1999 major changes were made to traffic flows in and around the city centre of Oxford. In this analysis we report the impact of the Oxford Transport Strategy (OTS) on peak expiratory flow (PEF) and respiratory symptoms among schoolchildren in the city.
Methods: Using a before-and-after design between 1998 and 2000, 1389 children aged 6–10 years were visited two to three times a year for five-day periods. On each day of each visit, we measured their PEF and enquired about respiratory symptoms including wheeze. At recruitment, parents completed a questionnaire enquiring into their children's history of asthma and potential exposures in the home. Exposure to road traffic before and after the implementation of OTS was estimated by modeled traffic flows on the street nearest each child's home.
Results: Regression analyses adjusting for potential confounders showed a statistically significant improvement in PEF (beta = 5.71 l/min, 95% CI (3.28 to 8.18)) and wheeze (OR = 0.80, 95% CI (0.69 to 0.92)) post-OTS. Children living near roads where traffic decreased post-OTS experienced a greater improvement in PEF than children living on streets where there had been an increase. This association was limited to children currently receiving treatment for asthma and to those in socioeconomic classes III-V.
Conclusion: Our findings suggest that traffic management can lead to localised improvements in childhood respiratory health but that such benefits are especially pertinent to children with pre-existing respiratory problems and those from less affluent backgrounds.

S070 INCIDENCE OF ADRENAL SUPPRESSION IN CHILDREN ON HIGH DOSE INHALED STEROIDS

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Children on high dose inhaled steroids are at potential risk of secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. There appears to be a greater risk of altered adrenal function with higher doses of steroids, but the large degree of inter-individual variability makes it difficult to predict which patients will suffer from this side effect. The British Thoracic Society and Scottish Intercollegiate Guidelines on the management of asthma do not give specific advice to clinicians on which children to screen for possible adrenal suppression.[1] However, clinical adrenal insufficiency has been reported at doses of inhaled fluticasone propionate (FP) >400 μg per day.

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

Abstract S070

	500–1000 μg FP/day	>1000 μg FP/day
Normal short synacthen test	29	27
Abnormal short synacthen test	0	4

These results indicate that a significant proportion of children on extremely high dose inhaled steroids are likely to have clinically important, yet undetected, adrenal suppression. Recent reports in the literature have detected even higher levels of impaired adrenal response in children on high dose FP.[2] Routine screening of adrenal function may be indicated in this group of children.

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

1. British guidelines on the management of asthma. *Thorax* 2003;**58**(Suppl).
2. **Paton JY**, Jardine E, McNeill E, *et al. Arch Dis Child*, 2006 (published online 23/03/06).

S071 BODY MASS INDEX, PHYSICAL ACTIVITY, AND BELIEFS ABOUT EXERCISE IN CHILDREN WITH ASTHMA

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Background and Aims: Children with asthma frequently cite exercise as a trigger and this has implications for weight management and mental health. This study aims to investigate the impact of asthma on children's customary activity. It is hypothesised that children with asthma will have higher BMI and lower levels of physical activity than children without asthma.
Design and Methods: A controlled, cross sectional study of children aged 7–14 attending hospital outpatient clinics, either for asthma (n = 56), or for ENT or dermatological conditions (n = 61). Outcome measures were BMI, International Task Force classification of obesity, Strengths and Difficulties Questionnaire (SDQ) scores and Physical Activity Questionnaire (PAQ) scores.
Results: The groups were well matched for demographic variables. The asthma group had higher BMI (p = 0.008) and 21.4% were obese compared to 6.6% in the non-asthma group (OR 3.89, 95% CI 1.17 to 12.88). Children with asthma reported fewer physical activities in the previous 24 hours (p = 0.002) but comparable levels of sedentary activities. Obese children were less active (p = 0.008) but regression analysis showed asthma was the strongest predictor of lower activity scores, followed by younger age (adjusted $r^2 = 0.104$). The asthma group had higher levels of emotional difficulties (p = 0.05) and, within this group, PAQ scores negatively correlated with SDQ scores indicating that more active children had better mental health (p = 0.009). More parents (60.7%) and children (66.1%) in the asthma group identified the child's health as a barrier to exercise compared to the non-asthma group (p<0.001).
Conclusions: Interventions to promote physical activity in children with asthma may reduce the risk of obesity and improve mental health.

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

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Introduction: The accuracy of parental reported wheeze in their preschool children has been questioned. The aim of the present study was to compare outcomes at five year of age in children with reported

wheeze at two years of age where wheeze was characterised by parents as rattling, purring, or whistling.
Methods: Participants were part of a whole-population birth cohort study designed to relate early dietary exposures to asthma outcome in later life. At two years of age, parents completed a respiratory questionnaire including the question ''Has your child wheezed in the previous year?'' Wheeze was then categorised as having one of the following characteristics: rattling, purring, whistling, or other. The five year assessment of this cohort included a respiratory questionnaire and a representative proportion also attended for spirometry and skin prick testing. Atopy was defined as at least one positive skin prick test. Spirometry was expressed as a z score adjusting for gender, weight and height.
Results: At two years of age, respiratory questionnaire data were available for 1371 of the original 1924 children and 207 had reported wheeze (24 whistle, 49 purr, 124 rattle, and 10 other). The proportion with rattling, purring or whistling did not differ by gender, maternal asthma or maternal smoking. At five years of age, questionnaire data were available in 157 children with reported wheeze at two years of age of whom skin prick reactivity and spirometry were assessed in 95 and 80 respectively. Current wheeze at five years was reported for 74% with previous whistling, 39% with previous purring and 34% with previous rattling ($p=0.015$), the respective proportions receiving treatment for asthma also differed (40%, 18%, and 11%, $p=0.017$). The proportion with atopy was higher (67%) among the six children with whistling at 2 years and lower for the 20 with purring (25%) and the 65 with rattling (22%), $p=0.051$; 25% of the whole population were atopic. The mean $FEV_{0.5}$ z scores at five years of age for previous whistling, purring, and rattling were −1.30, −0.22, and −0.09 (ANOVA $p=0.036$) and respective values for $FEF_{25–75}$ were −1.16, 0.01, and −0.15 (ANOVA $p=0.028$).
Conclusions: In this population, wheeze at two years of age categorised as a rattling or purring accounted for the majority of all reported wheeze and tended to resolve. Wheeze with a whistling quality at two years of age persisted in the majority of cases and was associated with an asthma phenotype at five years of age. Parents can characterise wheeze in young children, the presence of a whistling quality may indicate ''true'' wheeze and may also help identify those destined to develop asthma.

S073 CHANGES IN EXHALED NITRIC OXIDE AFTER DEFINITE SYSTEMIC STEROIDS IN CHILDREN WITH DIFFICULT ASTHMA

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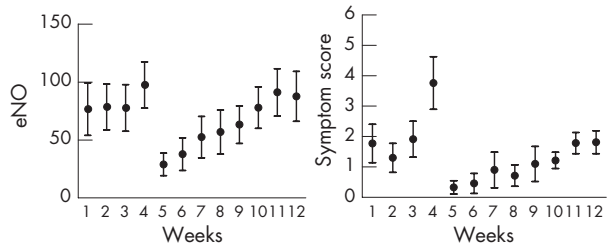
Background: In our difficult asthma clinic protocol, children to be considered for intramuscular (IM) steroid therapy (triamcinolone, TAM) must have regular assessment of exhaled nitric oxide (eNO) and symptoms.
Aim: To describe the pattern of change in eNO during systemic corticosteroid therapy and its correlation to symptoms, when the possibility of poor compliance is no longer an issue.
Methods: eNO (ppb) and symptom score in children (n=7) with difficult to control asthma (n=7) were monitored for 4 weeks before (week 1 to 4) and 8 weeks after (week 5 to 12) a single dose of 60 mg of IM-TAM. Data are summarised as mean (SEM).
Results: eNO was suppressed into the normal range (<25 ppb) during the week following IM-TAM, and profound suppression continued for 4 weeks (fig). Symptom scores were suppressed for 6 weeks, and in 6 children, the increase in symptoms was preceded by an increase in eNO by at least 2 weeks.



Abstract S073.

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

S074 ADRENOCEPTOR GENOTYPE PREDISPOSES TO EXACERBATIONS IN YOUNG ASTHMATICS ON SALMETEROL

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Background: In the airway, the presence of the homozygous Arg/Arg genotype (about 15% of patients with asthma in the US and UK) confers relative protection against downregulation by endogenous catecholamines and reverses the benefits from the regular use of short and long acting β_2–agonists in adults. The presence of the Arg-16 polymorphism (either Arg/Arg or Arg/Gly) confers bronchoprotective subsensitivity to methacholine and adenosine monophosphate challenge in steroid treated adults with asthma treated with formoterol and salmeterol. However, the consequences of real-life prescribing of long acting β_2 agonists, as an add-on medication to inhaled steroids, in Arg/Arg and Arg/Gly individuals with asthma, have not been explored.
Method: The study was cross-sectional, involving the collection of information through direct interviews, and the determination of position 16 and 27 of the *ADRB2* gene in DNA from mouthwash samples for 546 children and young asthmatics attending paediatric and young adult asthma clinics in Tayside, Scotland over 2004–05. Exacerbations of asthma over the previous 6 months constituted the primary outcome measure for the study.
Results: There was an increased risk of asthma exacerbations across all treatment steps of the British Thoracic Society asthma guidelines, when comparing the homozygous genotypes Arg/Arg *v* Gly/Gly (OR 2.05, 95% CI 1.19 to 3.53, $p=0.010$). This genotype-determined risk was largely in the salmeterol-treated patients. There was a major difference in risk when comparing Arg/Arg16 versus Gly/Gly16 (OR = 3.40, 95% CI 1.19 to 9.40, $p=0.022$) in these patients. The Glu27Gln polymorphism had no significant effect on asthma exacerbations in any treatment group.
Conclusions: The arginine 16 genotype of *ADRB2* predisposes to exacerbations in children and young adults with asthma. The effect is particularly important in those treated with regular inhaled salmeterol. This may be explained by genotype-selective salmeterol induced downregulation and impaired receptor coupling, and associated subsensitivity of response.

Characterisation of the COPD exacerbation

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

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Introduction: Chronic obstructive pulmonary disease (COPD) exacerbations represent a major burden to healthcare services. This study aims to characterise COPD patients with respect to exacerbation frequency.
Methods: A cross sectional cohort of 62 stable COPD patients, were analysed according to exacerbation frequency for clinical characteristics, including body mass index (BMI), airflow obstruction, dyspnoea and exercise capacity (BODE) index, white cell count (WCC) and health-related quality-of-life (HRQL).
Results: Compared to infrequent exacerbators (≤ 2 exacerbations/year, n=40), frequent exacerbators (≥ 3 exacerbations/year, n=22) had higher BODE index (frequent *v* infrequent; 5 (2–9) *v* 2.5 (0–8), $p<0.0005$), lower percentage predicted forced expiratory volume in one second (33.5 (18–72)% *v* 52 (18–83)%, $p<0.0005$), worse dyspnoea (Medical Research Council score 3.5 (2–5) *v* 2 (1–4),

p<0.0005), shorter 6-minute walking distance (295±116 *v* 376±90, p=0.007) and worse HRQL (St George's Respiratory Questionnaire total: 60.46±13.45 *v* 41.77±17.13, p<0.0005). Compared to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, BODE index quartiles better correlated with exacerbation frequency (BODE: *r*=0.586, p<0.0005; GOLD: *r*=0.487, p<0.0005) and HRQL (BODE: *r*=0.704, p<0.0005; GOLD: *r*=0.517, p=0.001). BMI and differential WCC were not associated with exacerbation frequency.
Conclusions: Frequent exacerbations are associated with severe COPD, high BODE index and poor HRQL. The multidimensional BODE index better predicts exacerbation frequency and HRQL than GOLD stage.

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

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Background: Respiratory virus infection is associated with ~50% of acute exacerbations of chronic obstructive pulmonary disease (COPD) (AECOPD) but a causal role is not proven and little is known about the mechanisms of virus-induced exacerbations. We hypothesised that experimental infection of COPD patients with rhinovirus (RV) would induce features of an AECOPD and could be used to develop an experimental model to permit study of mechanisms.
Subjects and Methods: 21 subjects (10 COPD and 11 age and smoking matched controls) were studied at baseline and then experimentally inoculated with RV16. Subjects kept daily diary cards of upper and lower respiratory tract symptoms. Lung function, blood, and sputum leukocyte counts were assessed prior to inoculation and during the infection phase. Nasal lavage was collected for detection of RV by RT-PCR.
Results: Following inoculation 2 subjects did not develop colds and were excluded from analysis. 19 subjects: 8 COPD (mean FEV1 70% predicted) and 11 controls (mean FEV1 108% predicted) developed symptomatic colds. These were accompanied by lower respiratory tract symptoms of breathlessness, cough, wheeze, increased sputum quantity and change in sputum quality. There were significant increases in total lower respiratory tract score in both groups. Cough and sputum scores increased in both groups but breathlessness increased significantly in the COPD group only (p=0.0313). PEF fell by 23.5 ml in the controls (p=NS) and by 50.5 ml in the COPD group (p<0.05). Kco fell significantly in the COPD group compared to baseline but not in the controls.

Peripheral blood total leukocyte count increased from 6.85×10^9/l to 9.45×10^9/l in the controls (p<0.01) and from 7×10^9/ml to 9.65×10^9/ml in the COPD group (p<0.01). Peripheral neutrophil count increased significantly in both groups (controls from 4.15×10^9/l to 5.75×10^9/l (p<0.01), COPD from 3.4×10^9/l to 6.7×10^9/l (p<0.05)). The total sputum non-squamous cell count and neutrophil count did not change significantly after infection in the controls. The total sputum non-squamous cell count increased from 1.205×10^6/g to 4.445×10^6/g (p<0.05) in the COPD group, and sputum neutrophil number from 0.545×10^6/g to 3.18×10^6/g (p<0.01). RV was detected in nasal lavage fluid in all subjects. There were no adverse events.
Conclusion: Experimental RV infection in COPD results in symptoms, lung function changes and systemic and airway inflammation similar to that seen in naturally occurring exacerbations. These data support a causal relation between rhinovirus infection and COPD exacerbations. This model of AECOPD may be used to gain insight into the molecular and cellular mechanisms of AECOPD

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

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Introduction: A significant proportion of patients with chronic obstructive pulmonary disease (COPD) will have lower airway bacterial colonisation. Sputum culture has so far been the most important method for identifying bacteria, but there is a need for more sensitive methods for bacterial quantification, such as real-time quantitative polymerase chain reaction (RT-PCR).
Methods: To assess the usefulness of RT-PCR, 159 sputum samples collected from 48 COPD patients (54.1% male, FEV1 1.02 l (SD 0.38) and FEV1 % predicted 42.8% (SD 16.8)) at baseline, exacerbation onset and at 1, 2 and 5 weeks post exacerbation were examined for *S pneumoniae, H influenzae* and *M catarrhalis* by culture and by an in-house multiplex real-time PCR assay using primers and labelled probes for the *ply* gene of *S pneumoniae;* the *hel* gene of *H influenzae* and the *cop*B gene of *M catarrhalis*. The assays were performed using the Corbett Research RotorGene. Pilot experiments using samples spiked with known bacterial loads suggested a cut-off of 7.2×10^5 colony forming units (cfu)/ml for *S pneumoniae and M catarrhalis* and 2.6×10^3 cfu/ml for *H influenzae* for deciding upon the presence or absence of a specific bacteria.
Results: Isolation rates for matched samples were higher by RT-PCR than by culture, for *S pneumoniae* isolation rate was 35.8% *v* 5.5% (χ^2 test; p<0.001), for *M catarrhalis* 11.7% *v* 9.7% (p=0.569) and for *H influenzae* 24.8% *v* 22.1% (p=0.579). The percentage of samples, positive for any of the three bacteria, were 54.5% by RT-PCR and 31.7% by culture (p<0.001). At baseline (exacerbation-free), the number of patients with a positive sputum for any of the three bacteria was 8/18 (44.4%) by RT-PCR and 5/18 (27.8%) by culture. At exacerbation, these proportions were 19/34 (55.9%) by RT-PCR and 15/34 (44.1%) by culture (Both NS). However, for *S pneumoniae* at baseline, RT-PCR detected 6/18 (33.3%) compared to 0/18 (0%) by culture (p=0.007) and at exacerbation, 11/34 (32.3%) compared with 4/34 (11.8%) (p=0.041).
Conclusion: RT-PCR substantially increased the number of pathogenic organisms detected, especially *S pneumoniae,* in sputum samples from COPD patients at baseline and at exacerbation.

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

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Introduction: Community acquired pneumonia (CAP) is a recognised cause of acute exacerbation of chronic obstructive pulmonary disease (COPD) and can lead to 15% of acute exacerbation cases. Symptoms like increased cough, increased sputum and breathlessness which are used to define acute exacerbation of COPD are non specific and can be the manifestations of CAP. The choice of antibiotic for CAP varies as per its severity and different from acute exacerbation of COPD.The Mid Cheshire Hospital trust revised its antibiotic guidelines for the management of CAP and recommended the use of the modified CURB-65 score to assess severity. In a prospective study we evaluated the antibiotic use in pneumonic exacerbation of COPD and its impact on morbidity and mortality.
Methods: Patients with acute exacerbation admitted to Mid Cheshire Hospital trust on acute medical take were identified. Presence of new radiological consolidation was a prerequisite to define CAP. Severity of CAP was assessed using modified CURB 65 Score. CAP was classified as severe if the CURB 65 score was more than 3 without comorbidities or 2 with comorbidities. Datas were collected on a predefined proforma and statistical analysed with SPSS software.
Results: Fifty seven patients (32 males) with a mean age of 72 from January 2006 to July 2006 were studied. The overall mean length of stay was 6.8 days (range 1 to 26).The mean length of stay in pneumonic exacerbation of COPD and non-pneumonic exacerbation of COPD was 9.5 and 6.13 days. Twelve out of 57 (21%) met criteria for CAP leading to acute exacerbation. Five out of 12 (41%) had non-severe CAP and 59% had severe CAP. Five out of seven pneumonic exacerbations received appropriate IV antibiotics as per hospital antibiotic policy. Two out of seven received oral antibiotics appropriate for acute exacerbation of COPD. In-hospital mortality of patient with pneumonic exacerbation of COPD was 25% in comparison to 12% mortality in previous series. The difference in length of stay between pneumonic and non pneumonic exacerbation was statistically significant (p=0.039).
Conclusions: This study highlights that CAP is a significant cause of acute exacerbation of COPD and caries high mortality and morbidity. The choice of antibiotic should be the same as per the CAP guidelines. We recommend that patients admitted with acute exacerbation of COPD should be properly assessed for the presence of CAP and severity assessed using the modified CURB-65 score and treated appropriately with antibiotics as per CAP guidelines.

S079 SEASONALITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE EMERGENCY ADMISSIONS TO HOSPITAL, AND PREDICTABILITY USING SURVEILLANCE FOR INFLUENZA-LIKE ILLNESS

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Introduction: Treatment of chronic obstructive pulmonary disease (COPD) exacerbations is a major burden to the National Health Service. The Met Office has developed a winter service forecasting the risk of exacerbation resulting in hospital admission, combined with anticipatory care to try to reduce the risk and prevent admissions. There is biological evidence to suggest that viruses are important in triggering COPD exacerbations. This study aimed to quantify patterns in COPD admissions, and determine whether influenza surveillance data could be used to forecast risk of COPD exacerbations.
Methods: Daily COPD admissions (ICD10 J40-J44) were extracted for England and five regions from Hospital Episode Statistics for 1997/98–2003/04. Corresponding weekly surveillance data for influenza-like illness consultations (ILI, ICD9 487) in England and Wales were available from the Royal College of General Practitioners' Weekly Returns Service, by age band. Linear regression against date was used to test for trend. Seasonality was tested using *t* tests of monthly averages and Box-Ljung tests for autocorrelation. Relationships between weekly COPD and ILI indicators were tested using linear regression, year-round and winter only (November–March).
Results: COPD admissions were found to increase in all geographical regions, at rates ranging from 2½% to 9% pa ($p<0.01$). Seasonality in both COPD and ILI was found to be significant. Average daily COPD admissions were found to be highest in winter, and about twice as high in January as in July ($p<0.001$). COPD and ILI were well correlated, with higher correlations in winter than year-round owing to small numbers in non-winter months. ILI in the over 65s age-band gave the best fit to COPD, with COPD leading ILI by 1 week ($r^2=0.43$–0.62 across the regions).
Conclusions: Our data suggest that ILI surveillance could be used as a marker for COPD exacerbations and workload during winter. Availability of real time COPD data would strengthen this. The seasonal pattern in COPD admissions could be used as a simple forecast of risk of COPD exacerbation. Because ILI lags behind COPD, ILI forecasts rather than surveillance would be needed to forecast COPD.

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

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Objectives: To determine the effects of a nurse-led intermediate care programme in the management of patients who have been hospitalised with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).
Methods: A randomised controlled trial of 122 patients who had been previously admitted to Hammersmith Hospitals NHS Trust with a diagnosis of AECOPD.
Intervention: A care package incorporating initial pulmonary rehabilitation followed by provision of a COPD self management action plan, monthly telephone calls and three monthly home visits from a specialist nurse over a two year period.
Main Outcome Measures: Hospital re-admission rates, unscheduled visits to general practitioners, use of self management, quality of life, mortality.
Results: At the end of two years six (9.8%) patients in the intervention group (IG) had died (1 from COPD) and 12 (19.7%) in the control group (CG) had died (8 from COPD), with a statistically significant difference in COPD deaths (Pearson χ^2 $p=0.015$). The number of days alive and out of hospital in both arms were the same (IG, median 726.5 days; CG, median 730 days), as were the total number of admissions (IG, 54 admissions; CG, 37 admissions). Patients in the intervention group were more likely to self administer antibiotics and/or steroid tablet treatments (IG 152 events *v* CG 23 events) and had a higher total usage of antibiotics and oral steroids (IG 347 courses, median 4.5, range 0–29 *v* CG 262 courses, median 2, range 0–19), in short courses either self administered or initiated by a doctor or a nurse. At the end of two years, more patients in the intervention group were likely to be receiving regular therapy with inhaled steroids (IG 93% *v* CG 89.5%), a long acting beta agonist (IG 93% *v* CG 71%), and a long acting anticholinergic agent (IG 79.1% *v* CG 42.1%) than in the control group.
Conclusions: An intermediate care package is associated with a significant reduction in COPD death rate, but no alteration in hospital admission rates. Those in the intervention group were more likely to have self administered medication at the first sign of an exacerbation and either this or a greater optimisation of therapy in the intervention group may account for the improved survival rate.
Acknowledgement: This study was funded by The Health Foundation.
*Dr Sridhar died on the 29 June 2006.

Clinical studies in asthma pathogenesis

S081 LESSONS LEARNT SO FAR FROM THE CURRENT FOLLOW UP OF THE TASMANIAN ASTHMA SURVEY: A LONGITUDINAL STUDY OF RESPIRATORY HEALTH FROM AGE 7 TO 44 YEARS

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Background: Natural history and risk factors for longitudinal changes in chronic respiratory diseases (CRDs) have not been established. This is mainly attributed to the lack of large longitudinal studies.
Aim: To examine the longitudinal changes in CRDs and their risk factors.
Methods: The Tasmanian Asthma Survey is a longitudinal study on respiratory health in a population-based birth cohort of 8500 probands that has been conducted from age 7 to 44 years. Information on respiratory symptoms and risk factors was collected at age 7, 14, 21, 32, and 44 years either on the total or sub samples. This abstract presents the results of the analyses to date of the current full follow up at age 44 years. Multiple Logistic Regression analysis was used to identify the relevant associations.
Results: By age 7, 16% had asthma. By age 44, current asthma prevalence is 11.3% with a ''true'' lifetime ascertained prevalence of 38%. One in four people who had childhood asthma continue to have asthma and one in 10 of those who did not have childhood asthma developed asthma. At age 7 years, exclusively breastfed children with a maternal history of allergy had a marginally lesser risk of current asthma than those who were not exclusively breast fed (OR 0.8, 95% CI 0.6 to 1.0). However, after the age of 7 the risk reversed and exclusively breast fed children were at an increased risk of current asthma by age 44 (OR 1.48, CI 1.08 to 2.03). The prevalence of chronic bronchitis (CB) by age 44 was 8.8% (CI 8.1% to 9.6%). In non-smokers, wheeze at age 13 predicted CB at age 44 (OR 2.71, CI 1.32 to 1.76). Maternal smoking increased chance of asthma up to age 44 but only in current smokers (OR 1.43, CI 1.13 to 1.81). Childhood immunisation protected against asthma to age 44 in those with childhood asthma (OR 0.47, CI 0.25 to 0.9).
Conclusions: Most adult current asthmatics have developed their asthma later in life. The prevalence of chronic cough and phlegm is high among middle age adults, which can be predicted by adolescent current asthma among non-smokers. Influences which have significant effects on current adult asthma include breast feeding, immunisations and maternal smoking, but with strong and complex interactions with other phenotypic features.

S082 EXPOSURE TO HOUSE DUST MITE ALLERGEN IS ASSOCIATED WITH AN INCREASE IN BRONCHIAL HYPERRESPONSIVENESS OVER FOUR YEARS IN ASTHMA

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Background: The long term effects of allergen sensitisation and exposure in asthma are not known. We therefore conducted a prospective longitudinal study in a large group of asthmatics to investigate the effects of house dust mite allergen sensitisation and exposure on lung function and bronchial hyperresponsiveness.
Methods: Participants were recruited in 1997/98 and underwent spirometry, direct bronchial challenge and measurement of exhaled nitric oxide (eNO). House dust mite allergen (Der p 1) was measured in mattress dust samples by ELISA and high exposure defined as a level

greater that 2 μg/g. Subjects returned in 2001/02 for repeat measurements of lung function and eNO.
Results: Of the 200 subjects who completed both visits, mite allergen exposure was measured in 165 (mean (range) age 45 (10–67) years, FEV1 2.51 (0.71–4.91) l, 82% atopic). Subjects returned for follow up after mean 47 (range 25–68) months. Overall there was no change in spirometry or bronchial responsiveness over the follow-up period. There was a significant but small fall in eNO (geometric mean 1.4 ppb (95% CI 1.2 to 1.6 ppb, p<0.001)). There was no association between exposure to mite allergen and change in spirometry or eNO. However bronchial responsiveness over the four-year period deteriorated in subjects exposed to high mite allergen levels compared to those not exposed (mean (95% CI) doubling dose (DD) change in PD_{20} −0.44 (−1.07 to 0.19) *v* 0.82 (0.27 to 1.36); mean DD difference 1.26 (95% CI 0.44 to 2.08, p=0.003)). This difference was preserved in the multivariate model (p=0.001; confounders: age, inhaled steroid use and dose, smoking status, baseline PD_{20}, sensitisation to house dust mite). There was no effect of the interaction between house dust mite exposure and sensitisation on change in bronchial responsiveness (p=0.7).
Conclusion: In a large cohort of asthmatics followed prospectively over four years, exposure to high levels of house dust mite allergen at baseline was associated with a subsequent increase in bronchial hyperresponsiveness. This effect is independent of sensitisation to house dust mite.

S083 ADIPOSITY ASSOCIATES WITH ASTHMA, IGE, AND EOTAXIN LEVELS

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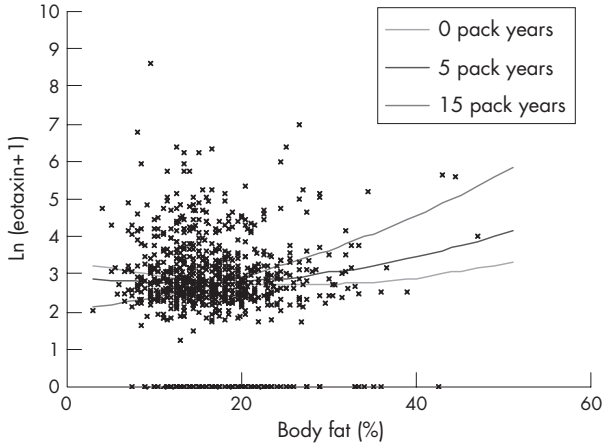
Background: Prospective studies suggest a possible causal link between obesity and asthma but the potential causative mechanisms are unclear. We examined the association between adiposity indices and both allergic and inflammatory factors and clinical outcomes in an unselected population.
Methods: Subjects comprised an unselected population of 1614 adults aged 18–30 years. Data included physician-diagnosed asthma, eczema, and hayfever (validated questionnaire). Anthropometric measures included waist circumference (WC), percentage body fat (%BF, bioelectrical impedance), and calculated body mass index (BMI) and waist/hip ratio (WHR). Total IgE, plasma eotaxin, and eosinophil counts were measured. Results were analysed by multiple logistic and linear regression, adjusting for relevant covariates.
Results: Adiposity indices associated with current asthma: for BMI, OR 1.08 for a unit change in BMI (CI 1.04 to 1.13, p<0.001). Body fat associated with current eczema (OR 1.03, 1.01 to 1.05, p=0.001). Total IgE and eosinophil counts (but not plasma eotaxin) were higher in current asthmatics (p<0.001). BMI, WC, and WHR associated with total IgE in females. The largest effect was seen for WHR (p<.05), equating to an IgE increase from 33 to 146 kU/l across the range of WHR (0.63–1.25). BMI and %BF associated with eotaxin in males only (p<0.01) and there was a significant interaction between %BF, eotaxin and smoking with a more marked relationship with increasing pack years (p=0.003) (fig). WC and WHR associated with eotaxin in the whole group (p<0.05). WC and WHR associated with eosinophil count with a significant interaction with current smoking such that the relationship was more marked for current smokers (p<0.05). For BMI, the positive association with eosinophil count was only seen in current smokers (p<0.05).
Conclusion: Associations were seen between adiposity and asthma and eczema. Adiposity indices associated with total IgE in females only and with eotaxin levels and eosinophil counts for males and females. These findings could partly explain the association between obesity and asthma and suggest that underlying mechanisms, including a proinflammatory state, may differ by gender and that smoking has modifying effects.



Abstract S083 Plots of ln(eotaxin+1) by percentage body fat for males according to smoking history of 0 *v* 5 v 15 pack years, obtained from fit of linear regression model. Eotaxin levels increase with percentage body fat with a more marked increase for individuals with a heavier smoking history.

S084 CHANGES IN AIRWAY WALL GEOMETRY OF THE APICAL SEGMENTAL BRONCHUS IN NON-EOSINOPHILIC ASTHMA

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Background: CT of the apical segmental bronchus (ASB) right upper lobe has been validated as a measure of airway wall remodeling in asthma and has demonstrated that airway wall thickening is a feature of severe disease. Airway inflammation is likely to be an important cause of airway wall thickening. The use of induced sputum to identify significant eosinophilic airway inflammation is an important target to direct corticosteroid therapy and reduce asthma exacerbations. We sought to identify whether there are differences in ASB wall geometry in eosinophilic (EA) versus non-eosinophilic asthma (NEA) in patients with refractory asthma.
Methods: All patients had a diagnosis of refractory asthma according to ATS criteria. NEA (n=8) was defined as the absence of a significant sputum eosinophilia (<1.9%) on serial measurements. We selected EA patients (n=7) that had a marked sputum eosinophilia (>20%) and were matched for age, disease duration, and mean daily corticosteroid dose. 11 healthy controls were recruited. All were non-smokers or ex-smokers with a smoking history of <5 pack years. In the asthmatics full thoracic HRCT scanning was performed using a siemens sensation 16 scanner at 120 KvP, 140 mAs, 16×1 mm collimation. The healthy controls had a limited CTscan (Aortic arch to 1 cm below carina: 120 kv, 50 mas, 16×0.75 mm collimation). HRCTs were reported as normal by our radiologists. Two observers measured ASB airway wall dimensions by ray casting using the full-width half-maximum method (Harvey Coxson, VA). Airway wall area (WA), luminal area (LA) and total area (TA) were corrected for body surface area.
Results: There was a good correlation between observers for ASB measurements (WA: r^2=0.93, p<0.0001). The WA was increased in asthma as a whole group compared to controls (table). However, there were marked differences in WA and TA in NEA versus EA (table).
Conclusion: NEA is associated with proximal airway dilatation, increased WA and TA. The mechanisms underlying changes in airway

Abstract S083

Adiposity measures	Outcome	p Value
BMI, WC, WHR	Total IgE	<0.05 for females
BMI, %BF	Eotaxin	<0.01 for males
WC, WHR	Eotaxin	<0.05
WC, WHR	Eosinophil count	<0.001
BMI	Eosinophil count	<0.05 for current smokers

Abstract S084

	Control	NEA	EA	Whole asthma group
Disease duration (years)	N/A	13 (6.6)	15.7 (6.4)	14.3 (3.7)
LA (mm^2/m^2)	7.3 (1.0)	17.5 (6.6)	6.4 (1.9)	12.3 (3.8)
WA (mm^2/m^2)*†	12.3 (1.0)	23.3 (3.0)	14.2 (2.0)	19.1 (2.2)
TA (mm^2/m^2)*†	19.6 (1.8)	40.8 (9.0)	20.6 (3.9)	31.4 (5.6)
%WA (mm^2/m^2)	63.6 (2.1)	65.6 (3.1)	71.7 (2.9)	68.5 (2.2)

Mean (SEM), *p<0.05 ANOVA, †p<0.05 EA *v* NEA *t* test.

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

S085 THE SIGNIFICANCE OF ACUTE EXERCISE INDUCED HYPERVENTIALTION IN PATIENTS WITH SEVERE ASTHMA

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Introduction: Hyperventilation and dysfunctional breathing have been linked with asthma[1] though the exact relationship between the two remains obscure. Patients with severe asthma have more symptoms which are more likely to be refractory to conventional asthma therapy. We hypothesised that patients with difficult asthma may have symptoms attributable to hyperventilation.
Methods: Patients with severe asthma as defined by the American Thoracic Society criteria[2] were recruited. Data on demographics, asthma history, respiratory questionnaires, spirometry, airway inflammatory markers, and objective exercise tolerance (incremental shuttle walk test) with concomitant end-tidal partial pressure for carbon dioxide ($P_{ET}CO_2$) were collected. Acute exercise induced hyperventilation (AEIH) was defined as any drop in $P_{ET}CO_2$ between rest and end-exercise.
Results: Twenty seven subjects were recruited. Five subjects (19%) showed evidence of AEIH. When the AEIH group was compared to remaining 22 subjects as a control group, the AEIH group was similar with FEV1 (72.9% *v* 72.3%), exhaled nitric oxide and sputum eosinophils. The AEIH group were prescribed more prednisolone (19 mg *v* 3.2 mg, p=0.01) and secondary asthma medications (1.4 *v* 0.7, p=0.036), had worse University of California Shortness of Breath Questionnaire scores (72.4 *v* 43.7, p=0.01) and Juniper Asthma Quality of Life scores (3.2 *v* 4.4 p=0.018). In addition, exercise tolerance was markedly reduced in the AEIH group (164 m *v* 548 m, p=0.001).
Discussion: AIEH is common in subjects with apparent severe asthma. Its presence is associated with higher medication use, worse symptomatology and reduced exercise tolerance. As such it may cause the true asthma severity to be overestimated. In patients with marked exertional limitation, AEIH may be the limiting factor rather than airflow obstruction.

1. **Demeter SL**, Cordasco EM. Hyperventilation syndrome and asthma. *Am J Med* 1986;**81**:989–94.
2. **American Thoracic Society**. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;**162**:2341–51.

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

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We have previously presented work using multivariate cluster analysis techniques to identify phenotypes of refractory asthma in a population of 270 patients attending our difficult asthma clinic. Our results suggested the presence of two cohorts in which there was discordance between the clinical expression of asthma and the extent of corresponding underlying eosinophilic airway inflammation. One group comprised an older male population with inflammation predominant disease and the other was a largely female, symptom predominant group. The clinical significance of these disease patterns is not known. We tested the hypothesis that these discordant refractory asthma phenotypes respond particularly well to inflammation guided therapy. Data from a recent 12 month prospective study of 73 patients with asthma performed at our centre (Green *et al. Lancet* 2002) was re-evaluated using cluster analysis techniques. Ward's hierarchical cluster analysis suggested the presence of 3 clusters. A k-means cluster algorithm predicting a 3-cluster model was then used to allocate individual cases to a cluster on the basis of the following baseline variables: demographic parameters, body mass index, atopic status, symptoms (modified Juniper asthma control score), bronchodilator reversibility and % sputum eosinophil count. Outcome measures investigated at 12 months were: change in total corticosteroid dose, number of hospital admissions for asthma and total number of severe asthma exacerbations requiring rescue oral corticosteroid therapy. The study cohort was stratified according to cluster membership and management protocol. Outcome measures were compared between subgroups within each cluster using the independent *t* test. The clusters identified in the study cohort resembled closely those described in our previous work. Cluster 1 (n=13) described a discordant symptom predominant (mean modified JACS 2.71, GM eos 0.4%) cohort with a high female preponderance (77%) and elevated BMI (mean 36, SD 5.63). Cluster 2 (n=27) was an inflammation predominant group (GM eos 5.13%, mean modified JACS 0.83) with a higher proportion of males (71%). Cluster 3 (n=12) was a mixed cohort with both symptoms and eosinophilic airway inflammation. Cluster 2 was the only group showing a significant difference in outcome between management strategies with a fall in exacerbation frequency in the sputum managed subgroup compared with the clinically managed subgroup (mean exacerbation rate per year 0.4 *v* 4.5, p=0.01). There was a trend towards requiring a lower dose of corticosteroids in cluster 1 for the sputum managed group (mean Δ steroid dose +842 μg *v* +6583 μg, p=0.07); this was not associated with a difference in other outcomes. We conclude that monitoring of airway inflammation is a particularly effective strategy in the management of patients cohorts presenting with evidence of discordance between clinical disease expression and underlying eosinophilic airway inflammation.

Clinical lung cancer highlights

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

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Background: Cannabis may have greater potential than tobacco to cause respiratory tract cancer.
Methods: A case-control study of respiratory tract cancer in adults ⩽55 years was conducted in eight district health boards in New Zealand. Cases were identified from hospital databases and the Cancer Registry. Controls were randomly selected from the electoral role with frequency matching to cases in 5 year age groups and district health boards. Interviewer administered questionnaires were used to assess possible risk factors including cannabis use. Logistic regression was used to estimate the relative risk of cancer for two anatomical subgroups: lung or laryngeal cancer, and head and neck cancer.
Results: There were 89 cases of lung and laryngeal cancer, 65 cases of head and neck cancer, and 324 controls. The relative risk of respiratory tract cancer was 3.47 (95% CI 1.13 to 10.7) for the highest tertile of cannabis use (>10.5 joint-years). The highest tertile of cannabis use was associated with an increased risk of lung or laryngeal cancer, (RR=4.56, 95% CI 1.35 to 15.5). For each joint-year of exposure, the risk of lung or laryngeal cancer increased 8% (95% CI 2 to 14%), equivalent to one pack-year of cigarette smoking. The association between cannabis use and head and neck cancer (RR=2.63, 95% CI 0.63 to 10.9) was not statistically significant.

Abstract S087 Cannabis use and risk of respiratory tract cancer

Joint-years	Cases	Controls	RR of respiratory tract cancer (95% CI)
None	117	285	1.00
1st tertile	5	19	0.40 (0.12–1.31)
2nd tertile	9	15	0.95 (0.38–2.40)
3rd tertile	19	5	3.47 (1.13–10.7)

*Adjusted for age, sex, ethnicity and family history and pack-years of tobacco use.

Conclusions: Long term cannabis use causes respiratory tract cancer in young adults, primarily due to an elevated risk of cancers in the lung and larynx.

S088 SURVIVAL SPECTRUM OF RESECTED NEUROENDOCRINE TUMOURS OF LUNG: A SINGLE CENTRE EXPERIENCE

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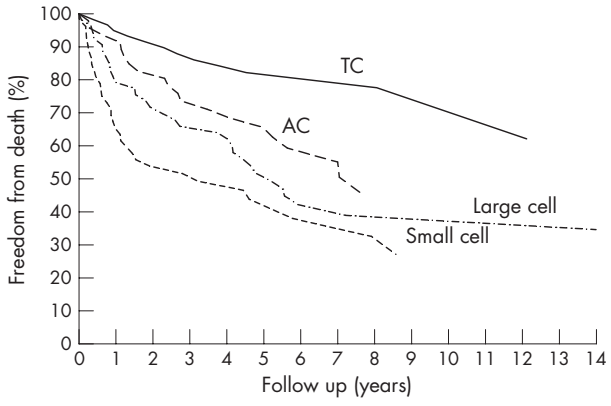
Introduction: Although lung tumours originating from neuroendocrine (NE) cells represent a spectrum of malignancy, from carcinoids (typical (TC), atypical (AC) or metastatic (MC)), large cell (LC) and small cell (SC) lung cancers, little is known about the survival prospects following resection. We therefore looked at the survival of patients post resection at our unit over a 17 year time period.
Method: The interrogated the comprehensive histology database present in our unit and tracked the survival of all patients who had undergone NE tumour resction between 1987 and 2004 until June 2006.
Results: Of 225 patients with resected NE tumours, 5 were excluded because of histological doubt. Some of the remaining 220 (mean age at resection 61 years (range 14–85), 107 male) had adjuvant chemotherapy. There were 46 (21%) AC, 59 (26.8%) TC, 9 (4%) MC, 53 (24.1%) LC, and 53 (24.1%) SC. Of these, 54 underwent pneumonectomy (36 left), 150 lobectomy and 16 wedge resection. At June 2006 114 were alive, 98 dead, and 8 lost to follow up. To date, median survival is 124 months (mean 128), with an overall 5 year survival of 63% (male 61%, female 65%; p=NS). Type specific 5 year survival was AC 65.6%, TC 85.1%, MC 88.9%, LC 51.8%, and SC 43.7%. At 10 years, overall survival fell to 50.6% and type specific survival 45.8%, 85.1%, 88.9%, 38.9%, and 27.1% respectively. There was significant difference in survival between AC and TC (p=0.01), LC (p=0.05), and SC (p=0.001) at five years which remained for TC and SC at 10 years. There was no significant difference in survival between LC and SC at any time period.
Conclusion: Survival in resected NE tumours varies with cell type. In our series there was significant difference in prognosis between typical carcinoids and the remainder. We also found that patients with even the most malignant variety (SC) can survive if the tumour is suitable for resection. This study shows the importance of histological distinction in this group of tumours, since it may have implications for survival.



Abstract S088

S089 NATIONAL LUNG CANCER AUDIT (LUCADA): HIGHLIGHTS FROM THE FIRST ANNUAL REPORT

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LUCADA (LUng CAncer DAta) is a long term audit of lung cancer care in England. The audit is now commissioned by the Healthcare Commission and managed within the information centre for Health and Social Care by the National Clinical Audit Support Programme (NCASP) in partnership with the Royal College of Physicians. LUCADA began collecting data in 2004 and as at 30.6.06 had 23 539 patient records in total. The first annual report will be published in Autumn 2006 and will contain data on all cases of lung cancer with an initial date of referral in 2005. This abstract describes that population. By the end June 2006 80% of the 151 eligible Trusts in England had submitted data and 10,920 cases of lung cancer diagnosed in 2005 had been registered. The median age was 72 (range 18–101), 6584 males:4336 females. The histological confirmation rate is a good surrogate marker of the standard of cancer care; 57% of cases had a histological and/or cytological diagnosis (interquartile range by cancer network 48%–73% median 63%). 78% of patients were reviewed by a multidisciplinary team (interquartile range by cancer network 70%–92% median 82%). This value is less than the national target of 100% and also of the ''greater than 95% discussed at MDT'' measure set by peer review. 8.6% had a surgical procedure (interquartile range by cancer network 4.4%–10.8% median 6.9%). 43% of patients received an active-cancer treatment (interquartile range by cancer network 35%–63% median 48%). These values are low by international standards and the data demonstrate significant regional variation across England, the reasons for which are still unclear. Some of this may be explained by incomplete data collection especially in networks where one hospital makes the diagnosis of lung cancer and then refers on to another centre for treatment. By collecting data on case-mix variables such as postcode, age, performance status, comorbidity and stage at presentation, LUCADA will be able to carry out risk-adjusted analyses which may start to explain some of these differences. The data from 2005 are unlikely to be of a high enough standard of completeness to allow for this and the aim for LUCADA must be to encourage more comprehensive data collection to make this possible.

No survival data are yet available from LUCADA. An automated link to death data is under development which will make this possible shortly. The National Lung Cancer Audit continues to recruit steadily and now is the largest audit of lung cancer ever. The continuing aim is to encourage participation with comprehensive data collection so that risk adjusted comparative data on activity, performance and outcomes becomes regularly available with the aim of improving outcomes for the future.

S090 FACTORS CONTRIBUTING TO BREACHES IN THE ''62 DAY WAIT'' TARGET FOR LUNG CANCER IN THE THE MERSEYSIDE AND CHESHIRE CANCER NETWORK

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Background: Nationally and within the Merseyside and Cheshire Cancer Network achieving 95% compliance with the ''62 day wait'' target has proved more challenging for lung cancer than other tumour sites. Lung cancer differs from other tumours because a proportion of patients may require interval CT imaging before the diagnosis is confirmed, and in others a series of investigations to achieve a histological diagnosis may be required depending upon the anatomical position of the tumour, thus lengthening the diagnostic pathway. However, avoidable delays reflecting lack of resources or suboptimal organisation of services (for example, poor access to CT and PET scans) may contribute. A Lung CNG audit was undertaken to quantify the

proportion of patients with lung cancer that require interval imaging before the diagnosis is confirmed, but also to analyse other factors that contribute to failures to meet the 62 day wait target.
Method: A retrospective casenote audit in the 7 Lung Cancer Units which make up the Merseyside and Cheshire Network, looking at the last 489 patients diagnosed with lung cancer.
Results: Of these 489 patients, 30% presented as inpatients, 43% as outpatients under the ''two week rule'' and the remaining 27% as outpatients by another route. Sixty nine per cent of patients had NSCLC, 23% SCC, and 8% mesothelioma. In total, 27 (9 inpatients and 18 outpatients) (6%) required an interval CT scan before the diagnosis of lung cancer was confirmed. Ninety five per cent of patients referred under the 2 week rule were compliant with the target and 97% patients began treatment within 31 days of decision to treat. However, 22% of patients failed to meet the 62 day wait target. Of the patients who failed the 62 day wait target, 2% had interval CT scans, 24% had CT and PET imaging, but 74% had CT scans and a histological or clinical diagnosis without PET. Forty seven of the 489 patients (10%) were referred for a PET scan, but had NICE guidelines for lung cancer been followed a further 77 patients should also have been referred. The median interval from PET request to PET scan was 28 days (range 12–197).
Discussion: Achieving the 62 day wait target for lung cancer with 95% compliance would be improved if the DoH agreed to temporarily ''suspend'' patients requiring interval CTs from monitoring. Delay in access to PET scanning in the Merseyside and Cheshire CNG contributes significantly to ''62 day rule breaches'' and would be exacerbated further if all patients who qualify for PET scans were referred. However, the majority of patients who breached the 62 day target had neither a PET or interval CT: a detailed analysis of factors contributing to these breaches will be presented.

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

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Malignant mesothelioma is an aggressive tumour associated with asbestos exposure. It has a latency of 30–40 years and in 90% arises in the pleura. The median survival with supportive treatment is 6 months.[1] In 2001 malignant mesothelioma was responsible for 1848 deaths in Britain and the incidence is expected to rise until 2015.[2] In the registration phase III trial, pemetrexed, a multi-targeted antifolate, combined with cisplatin, had a significant survival advantage compared to cisplatin alone, 12.1 versus 9.3 months in patients with malignant pleural mesothelioma.[1]

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

Patients were aged 46 to 86 years, 80% were male and 97% had pleural mesothelioma. A maximum of 6 cycles was given and the mean was 4.2 cycles. Median survival from diagnosis and from start of chemotherapy for all patients was 13.9 months and 10.6 months, respectively. In the registration phase III trial, eligible patients had pleural disease, a Karnofsky performance status ^{3} 70 and no prior chemotherapy or surgery. Comparable patients in our series with PS 0–1 had a median survival for CisP of 12.3 months (n = 27) and 11.4 months (n = 17) for CarbP. The difference between regimens was not significant. For comparable CisP and CarbP treated patients with PS 2 (n = 28), median survival was 10.1 months.

Grade 3 and 4 toxicity occurred in 59.5% of CarbP and 34.5% of CisP patients. Neutropenia (23% of patients), anaemia (12%) and leucopenia (14%) were the commonest toxicities, febrile neutropenia occurred in 3.5% of CisP and 5.4% of CarbP patients. There was one chemotherapy related death.

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

1. **Vogelzang NJ**, *et al. J Clin Oncol* 2003;**21**:2636–44.
2. **Hodgson JT**, *et al. Br J Cancer* 2005;**92**:587–93.

S092 SURVIVAL RATES FOR 705 HISTOLOGICALLY PROVEN NON-SMALL CELL LUNG CANCER DIAGNOSED BETWEEN NOVEMBER 1997 AND DECEMBER 2004 AND MANAGED BY A MULTIDISCIPLINARY TEAM

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Aims: In 1997 we established a lung cancer multidisciplinary team (MDT) and collected data prospectively. In 1999 a lung cancer specialist nurse was appointed and in 2001 we increased the Clinical Oncology sessions. The aim of this study was to see whether there has been any improvement in non-small cell lung cancer (NSCLC) survival since the implementation of this multidisciplinary approach.
Method: The database contained 726 histological proven NSCLC diagnosed between 19/11/97–22/12/04. Of these 14 were lost to follow up and 7 were diagnosed at postmortem. Survival for 705 patients was calculated from the date of presentation to 1/3/06. Survival was examined for each year (only 2 months of data were available for 1997 and therefore it was combined with 1998). Survival data were analysed using the Log-Rank (Mantel-Cox) method and Cox's regression model to adjust for the covariates of age and stage of disease.
Results: From 1998 to 2004 there were 129, 94, 97, 107, 101, 89 and 88 patients respectively. 644 (91.3%) of the patients were deceased. The median survival overall was 184 days (95% CI 161 to 207), One year 31.5%, 2 year 12.1%, three year 5.8% and 5 year 1.8%. Using Cox's regression model, it was found that survival was significantly related to age ($p<0.0005$), stage of disease ($p<0.0005$) as well as the year ($p = 0.007$). The median survival time for years 1998–2002 were similar (163, 158, 193, 157, 142 respectively) but seemed to improve in 2003–04 (238, 252 respectively). Using the Log Rank (Mantel-Cox) method for overall comparisons, the effect of year was highly significant ($p = 0.023$, $\chi^2 = 14.625$, $df = 6$).

Since it was clear that survival in 2003/04 was higher than previous years it was decided to group and compare years 1998–2002 and 2003/04.Using this classification, Cox's proportional hazard model was used to examine survival, allowing for the covariates age and stage of disease and it was found that the hazard (risk of death) was reduced by 27% (CI 11.0% to 40.4%, $p = 0.002$) in 2003–04 compared to 1998–2002.
Conclusion: From our data we have shown a highly significant 27% decrease in the risk of death in 2003–04 when compared to the previous 5 years. Short term survival rates have improved. These improvements may be attributed to a more aggressive approach from a very committed MDT, employing the full range of treatment modalities. However long term NSCLC survival rates have not shown any significant improvement

The spectrum of cystic fibrosis exacerbations

S093 CHARACTERISATION OF BACTERIAL DIVERSITY IN CYSTIC FIBROSIS SPUTUM

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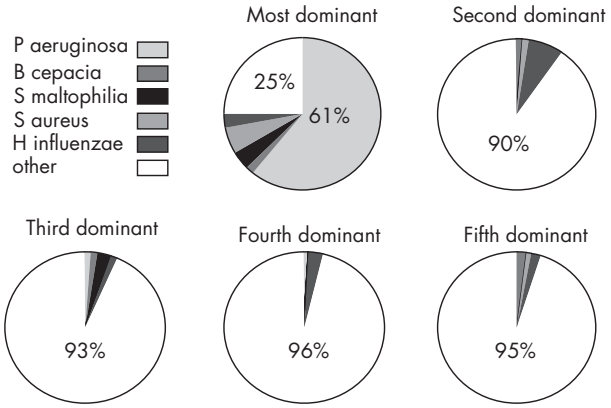
Introduction: 95% of mortality from cystic fibrosis (CF) is attributable to pulmonary infections and sepsis. Traditional diagnostic techniques for the identification of microbial organisms in CF sputum rely on sputum culture. Using these techniques a limited number of different organisms have been identified from CF sputum, dominated by Pseudomonas aeruginosa (PsA). However these techniques can only identify organisms that are culturable. A large number of organisms found in the natural world cannot be cultured. Terminal restriction fragment length polymorphism (T-RFLP) is a molecular technique which allows the differentiation of bacterial species on the basis of DNA sequence variation in phlogenetically-informative regions of the bacterial genome (Mersh T, *et al* 1999, Rogers G, *et al* 2003). Thus, T-RFLP can identify bacterial communities by avoiding many of the biases associated with culture based techniques.



Abstract S093

Aims: To identify total bacterial community present in CF sputum. To determine the prevalence of bacterial species not traditional associated with CF lung disease.
Methods: 102 whole sputum samples from 34 adult CF patients were analysed by T-RFLP using previously published techniques (Rogers GR, *et al* 2003, 2004, 2005). In brief, bacterial DNA was first extracted from the sputum samples. The DNA region of interest was then amplified, and cleaved using a restriction enzyme. The resulting segments of DNA were then separated by length using an automated DNA sequencer. This process generated profiles, comprised of different bands, each derived from a different individual bacterial species.
Results: 248 different bacterial species were identified, with a mean of 13.3 (7.9) species per sample. For each sample, bacterial species were ranked in order of relative prevalence within the sample (fig).
Discussion: With a mean of 13.3 species per sputum sample the bacterial diversity in CF sputum is higher than identified by traditional culture based techniques. Although PsA is the most dominant species in 61% of samples, species not traditionally associated with CF lung disease were the most dominant species in 25% of samples, and the second most dominant in 90% of samples. This would suggest that the bacterial community in CF sputum is more diverse than previously recognised, and that organisms not previously considered significant CF pathogens may have important roles to play in what appears to be a complex ecosystem.
Conclusion: Bacterial diversity in the CF lung, as identified by T-RFLP, is far greater than previously recognised. Although PsA is the most dominant species, non-CF organisms are more prevalent. The relative significance of each of organisms identified has yet to be determined.

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

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Introduction: *Burkholderia cepacia* complex (Bcc) pulmonary infection has been associated with a poor prognosis for patients with cystic fibrosis (CF). It has been demonstrated that clinical course after colonisation with cepacia can vary significantly between individuals. Previous researchers have tried to identify specific risk factors associated with a worse prognosis. The clinical outcome of 111 patients colonised with Bcc was assessed during a 15-year period.
Methods: Lung function, clinical features and microbiology were recorded for 111 patients until death or the end of follow up. The number of patients who progressed from initial to chronic infection were assessed as well as those who had multiresistant strains. The presence of diabetes and the use of antibiotics and steroids were also documented. Full data were not available in all patients.
Results: Age and sex were unrelated to outcome. Seventy five per cent (67/89) of patients infected with Bcc already had moderate to severe lung disease at diagnosis; 42% (34/81) had multi-resistant strains and 68% had persistent infection. The annual incidence was 0.3–3.8% and the prevalence 3.7–9.2%; 63 patients died. Compared with a previous study in our Unit,[1] the incidence has decreased over the last ten years, while prevalence and the number of deaths have decreased over the last six years. The mean survival was 49 months compared with 11 months in the previous study, however the present study is longer and with larger numbers of patients.
Conclusions: Advanced lung disease at acquisition confers a worse five-year clinical outcome ($p=0.001$); presence of multi-resistant strains as initial isolates ($p=0.043$) and previous use of steroids, ($p=0.007$) seem to be associated with a less favourable prognosis. Antibiotic prophylaxis does not lead to the emergence of multi-resistant strains. Patients with advanced CF, multi-resistant strains and persistent Bcc infection had a worse outcome. The incidence of Bcc appears to be declining.

1. **Taylor RFH**, Gaya H, Hodson ME. Pseudomonas cepacia pulmonary infection in patients with cystic fibrosis. *RespirMed* 1993;**87**:187–92.

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

M. France[1], M. E. Dodd[1], J. R. Govan[2], C. J. Doherty[2], A. K. Webb[1], A. M. Jones[1]. [1]*Manchester Adult Cystic Fibrosis Centre, UK;* [2]*Medical Microbiology, University of Edinburgh, UK*

Background: Early treatment of newly acquired *Pseudomonas aeruginosa* (*Pa*) infection has a success rate of approximately 80%. (UK CF Trust Infection Control Group. Suggestions for Prevention and Infection Control. CF Trust Guidelines 2004.) The CF Trust guidelines suggest the use of oral ciprofloxacin and nebulised colistin when *Pa* is first isolated. A policy of microbiological surveillance for clonal Pa strains (including the local Manchester clonal strain) was introduced within our centre in 2000. Our centre attempts to eradicate all new *Pa* infection.
Method: Patients with a clonal strain as their 1st isolate of *Pa* (2000–06) were selected (5) and the efficacy of eradication therapy assessed.
Results: All 5 patients identified failed to eradicate their clonal strain. The median FEV1 at acquisition was 2.8 (range 0.55–2.95) and the median FVC was 3.3 (range 0.9–3.95). Case 1: female; 32 y; 1st isolation of *Pa* in June 2000; prior colonisation with *Staphylococcus aureus (Sa)* only. Notably, she was 22 weeks pregnant at the time of acquisition. Ceftazidime and meropenem were in use at the time of acquisition and continued until after delivery in August 2000. Nebulised colistin was added. Case 2: male; 29 y; 1st isolation of *Pa* in August 2000; no previous pathogenic organisms. Oral ciprofloxacin and nebulised colistin were used for 1 month after acquisition. Ceftazidime, tobramycin and nebulised colistin were then used for a 14 day period for a moderate infective exacerbation. Case 3: female; 20 y; 1st isolation December 2000. Achromobacter xylosoxidans since1999. She delivered in July 2000 and was admitted peripartum for iv antibiotics. She was treated at the time of isolation of the Pa with 5 days of ceftazidime and gentamicin. She was subsequently continued on nebulised colistin. Case 4: female; 35 y; 1st isolation in June 2003; only *Sa* previously. After acquisition, admitted for 7 days of iv therapy, then ciproxin, rifampicin and nebulised colistin for 1 month. Nebulised TOBI was subsequently used for 1 month. Case 5: female; 43 y; 1st isolation of *Pa* in April 2004. No pathogenic organisms previously identified. 2 weeks of ceftazidime, meropenem and tobramycin for an infective exacerbation during March 2004. Continuous nebulised colistin was added at isolation. Ciprofloxacin was not tolerated.
Summary: In our experience, eradication therapy has failed in patients who have acquired the Manchester clonal strain of *Pa* as their 1st isolation of *Pa*. Thus the only effective infection control measure is the isolation of patients without *Pa* from those with a clonal strain. Two of the females acquired a clonal strain during pregnancy, raising the question of whether this is a time of increased susceptibility to clonal strains.

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

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

the monitoring of infective exacerbations in CF. Furthermore we have compared this to an accepted measurement of inflammation in CF sputum, interleukin 8 (IL8).
Methods: Twenty six patients attending the Scottish Adult CF centre were recruited at the time of an exacerbation requiring intravenous antibiotics. Sputum was collected at the start and end of antimicrobial therapy. Sputum Calprotectin and IL 8 levels were assayed with ELISA. Sputum was also assayed with SELDI TOF in tandem.
Findings: Sputum Calprotectin levels decreased significantly with antibiotic therapy from 661.9 (496–1039) μg/ml to 379.8 (206–640) (median (interquartile range)) at p=0.011. Sputum IL8 also decreased but this did not reach statistical significance 32.87 (19.70–54.86) pg/ml to 22.55 (10.74–60.46) at p=0.1. Protein profiles of Calgranulins A and B on SELDI TOF also changed accordingly with therapy.
Interpetation: These data suggest that Calprotectin levels in sputum reflect the underlying level of inflammation in the CF lung, and may be measured by ELISA as well as SELDI TOF. Proteomics identified sputum markers, such as Calprotectin have a potential application to the assessment of new therapies for CF lung disease. In this study group we demonstrate Calprotectin to be a more significant marker of change in lung inflammation during an exacerbation than IL8. Furthermore this study highlights the importance of longitudinal evaluation in the assessment of new biomarkers.

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

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

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

The aim of this study was to investigate levels of receptor activator of nuclear factor kB ligand (RANKL), osteoprotegerin (OPG) and bone turnover markers (osteocalcin and NTx) before (baseline), during (day 1 and 14) and after (day 42) in patients with CF during infective exacerbations treated with intravenous antibiotics.

Twenty-four patients (14 male, mean (SD) age 24.7 years (6.0), FEV1 48.8% of predicted, BMI 21.3 kg/m^2) were recruited. Patients were in a stable condition at the time of the baseline blood test. None of the patients had been prescribed oral corticosteroids for at least 3 months before the baseline visit and all patients were colonised with *Pseudomonas aeruginosa*.

Increased levels of serum NTx in CF patients were observed at day 1 (p=0.008) and day 14 (p=0.014) of exacerbation, with a decrease by day 42. Osteocalcin levels at baseline were lower than in controls ($p<0.05$), however they did not change significantly during infective exacerbation. Serum RANKL levels increased significantly by day 14 ($p<0.05$) and had decreased by day 42. OPG levels at baseline were lower than control levels ($p<0.05$) but increased by day 14 ($p<0.05$), but had decreased by day 42 to a level comparable to baseline.

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

Assessing effectiveness of pulmonary rehabilitation

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

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Aim: The deleterious effect of hospitalisation in patients with chronic obstructive pulmonary disease (COPD) has been well documented. Inpatient pulmonary rehabilitation (PR) may be able to prevent the observed physical decline. This pilot study evaluates the impact of an in-patient PR programme on the exercise capacity and quality of life, in patients during an acute exacerbation of their COPD.
Methods: Fifty patients with COPD were admitted for an acute exacerbation of their disease (27 male, mean (SD) FEV1 0.75 (0.25)l, % predicted FEV1 38 (12.1) %, age 69.9 (7.96) years) participated in an in-patient PR between May 2005 and May 2006. The programme consisted of educational talks 3 times a week and exercise sessions (endurance and strength) supervised 5 times a week in a gym located on an acute respiratory ward. Prior to commencing the programme patients completed the self reported Chronic Respiratory Questionnaire (CRQ-SR) and performed an incremental and endurance shuttle-walking test, these were repeated at time of discharge from hospital.
Results: The results of a paired *t* test are shown in the table below. These demonstrate a statistically significant improvement in all of the outcome measures, except the dyspnoea component of the CRQ-SR. The other components of the CRQ-SR exceeded the minimum clinically important difference. There were no adverse events during the exercise sessions.
Conclusions: Inpatient PR during acute exacerbation appears to have a significant benefit upon health status and exercise capacity. These pilot data suggest the PR in this population is safe and effective and warrants further investigation.

S099 PRIMARY CARE BASED PULMONARY REHABILITATION PROGRAMMES ARE EFFECTIVE AND MEET RECOGNISED EVIDENCED OUTCOME MEASURES: AN OBSERVATIONAL REPORT

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Background: Pulmonary rehabilitation is a well evidenced intervention in chronic obstructive pulmonary disease (COPD), however there is less evidence currently to support programmes in a community setting. It is recognised that across the UK, accessibility to Pulmonary Rehabilitation for all those who require it, is poor (~2%). Evidenced outcome measures include the Incremental Shuttle Walk Test (ISWT), Chronic Respiratory Diseases Questionnaire (CRQ) and the Hospital Anxiety and Depression Score (HADS).
Programme: From February 2005 the INSPIRE Team of East Lincolnshire Primary Care Trust implemented a Primary Care Based Pulmonary Rehabilitation Programme. This ran twice weekly for 8 weeks combining

Abstract S098

Mean (SD)	ESWT (secs)	ISWT (m)	CRQ - dyspnoea	CRQ - emotion	CRQ - fatigue	CRQ - mastery
Pre PR	58.4 (71.8)	34.6 (58.4)	1.97 (0.98)	3.47 (1.25)	2.48 (0.96)	3.13 (1.28)
Post PR	350.58 (267.2)	76.8 (74.7)	2.37 (1.50)	4.32 (1.12)	3.36 (1.13)	3.84 (1.08)
Mean change (95% CI)	292.18* (368.96–215.3)	42.2* (61–22)	0.39 (0.79–0.00)	0.84* (1.17–0.52)	0.88* (1.23–0.53)	0.71* (1.03–0.38)

*p<0.05.

Abstract S099

	Non COPD (n = 12)	Mild (n = 50)	Moderate (n = 72)	Severe (n = 49)
Performance				
Mean change in score (SD)	1.97 (1.12)	1.46 (1.58)	1.72 (1.64)	1.87 (1.84)
% showing improvement	92	86	81	88
% achieving MCIC	42	28	44	47
Satisfaction				
Mean change in score (SD)	3.33* (1.65)	2.22* (2.05)	2.16* (1.95)	2.75* (2.00)
% showing improvement	100	82	83	92
% achieving MCIC	75	54	51	61

*>MCIC.

exercise and education with a multi-disciplinary team. All patients with a formal diagnosis of COPD, on optimised therapy, and who present with functional disability related to breathlessness, were accepted onto the programme. 76 patients (mean age 69, 52 male) were offered a place on the programme after assessment. 75 accepted of which 60 completed with a mean FEV1 of 40.1% of predicted value.
Results: The mean improvement in ISWT was 50.5 m (−90–200). 80% of the group improved of which 67% improved beyond the Minimal Clinical Important Difference (MCID) of 50 m. Mean HADS for those who completed improved by 0.52 for Anxiety and 1.39 for Depression. The mean score for each domain of the CRQ also increased beyond the MCID of 0.5 for all those completing the programme (Dyspnoea 0.71, Mastery 0.67, Emotion 0.60, Fatigue 0.76). Interestingly, the patients not completing the course demonstrated lower mean scores in all domains of the CRQ compared with those that completed. Of those completing the programme and performing an Endurance Shuttle Walk Test, 42% (25/60) met the criteria for Ambulatory Oxygen Assessment.
Conclusion: Delivering a Primary Care Based Pulmonary Rehabiliation Programme has yielded in results that mirror those previously published for outpatient programmes (Withers *et al*, 1999; Williams *et al*, 2003). They can also improve accessibility for the patients, thus being congruent with the NHS Agenda to move services closer to patients, whilst ensuring effective results. The information on pulse oximetry post programme needs further studying as it is likely to have a profound effect on the prescribing and costing of oxygen, given the changes to the oxygen service and the ability for patients to receive ambulatory oxygen. The provision of ambulatory oxygen therapy to this group would lead to further study to review their outcomes post rehabilitation.

S100 FUNCTIONAL OUTCOME IN PULMONARY REHABILITATION USING THE CANADIAN OCCUPATIONAL PERFORMANCE MEASURE

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Introduction: On goal of pulmonary rehabilitation (PR) is to improve function. The Canadian Occupational Performance Measure (COPM) is a tool for recording self-perception of function and has been used in chronic obstructive pulmonary disease (COPD). A modified version of this tool was used for pragmatic reasons due to a period of restricted occupational therapy support to our programme. We are evaluating its sensitivity to change via our PR audit data and by NICE COPD severity categories.
Method: 196 patients were enrolled into one of our 3 PR programmes across North Surrey. Baseline % predicted FEV1 was used to classify severity of COPD according to the NICE guidelines. Patients were asked to rate (0–10) performance (P) and satisfaction (S), for three chosen tasks important to them, at baseline and reassessment post PR. The Minimal Clinically Important Change (MCIC) for COPM is 2.
Results: Change in COPM scores by disease category (n = 196)
Conclusion: Patients with every level of severity are reporting an improvement in function following PR. The greatest improvement in perceived performance and satisfaction with performance is in the Non-COPD and Severe categories. High percentages of patients show an improvement in P and S in all categories. Importantly, *satisfaction* in the way that patients manage activities of daily living improves as a result of PR.

S101 FACTORS AFFECTING COMPLETION OF PULMONARY REHABILITATION PROGRAMMES IN SOUTH EAST LONDON

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Introduction: Pulmonary rehabilitation (PR) is the most effective non-pharmacological intervention for chronic obstructive pulmonary disease (COPD). The physiological, psychological, and quality of life benefits of PR are well described (Troosters *et al. Am J Respir Crit Care Med*, 2005), but are limited by non-adherence rates of 30–40% (Garrod *et al. Eur Respir J*, 2006). Identification of risk factors for non-adherence, followed by appropriate support, is required to improve completion rates. Systematic recording of relevant variables at the time of initial assessment for PR at King's College Hospital (KCH) has provided a large dataset that is available for such analysis.
Methods: We carried out a retrospective analysis of all PR referrals to KCH and its four community PR sites between 01/05/04 and 31/03/06, classifying patients as ''completers'' (completed 8 sessions), or ''non-completers'' (assessed and attended <8 sessions). Associations between non-completion and pre-PR demographic (age, sex), physiological (FEV1 % predicted (FEV1 %), incremental shuttle walk distance (ISWD)), psychological (Hospital Anxiety and Depression Score (HADS)) and quality of life (Chronic Respiratory Questionnaire (CRQ)) variables were assessed by univariate, followed by multivariate, analysis.
Results: 327 patients started PR. 244 (74.6%) completed PR and 83 (25.4%) did not complete PR. Non-completers had worse exercise tolerance, higher levels of anxiety and depression, and poorer quality of life than completers in univariate analysis (table), and were more likely to have probable (HADS >10) anxiety (27.0% *v* 47.0%, p = 0.001) and depression (19.7% *v* 32.5%, p = 0.02). Only HADS depression score (p = 0.02) and CRQ dyspnoea (p = 0.03) were associated with non-completion in multivariate analysis.
Conclusion: The PR non-completion rate in South East London remains high, despite favourable comparison with other figures. Depression was a significant risk factor for non-completion and could be a target for intervention.

Abstract S101 Data presented as mean (SD)

	% male	Age (years)	FEV1 %	ISWD (m)	CRQ-D	CRQ-E	CRQ-F	CRQ-M	HADS-A	HADS-D
C	43.0	68.1 (10.1)	50.4 (21.0)	209.5 (135.2)	4.12 (3.77)	6.73 (8.04)	4.32 (3.37)	5.48 (4.08)	8.30 (4.42)	7.28 (3.90)
NC	42.2	65.0 (12.0)	48.5 (19.9)	180.3 (135.2)	2.93 (2.70)	4.85 (5.67)	3.38 (2.69)	4.20 (2.68)	9.75 (5.09)	8.71 (4.02)
p Value	0.89	0.41	0.56	0.03	0.001	0.01	0.001	0.001	0.03	0.004

C, completers; NC, non-completers; CRQ-D, CRQ dyspnoea; CRQ-E, CRQ emotion; CRQ-F, CRQ fatigue; CRQ-M, CRQ mastery; HADS-A, HADS anxiety; HADS-D, HADS depression.

S102 THE BRITISH LUNG FOUNDATION LUNG EXERCISE PILOT PROJECT: IS IT EFFECTIVE?

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Aim: The optimal strategy for maintaining the benefit of pulmonary rehabilitation has yet to be established. A community exercise scheme sponsored by the British Lung Foundation was developed in 10 different locations and the effectiveness assessed. The community exercise scheme was independent of health care professional input.
Methods: Two hundred and twenty five patients with chronic obstructive pulmonary disease (COPD) were recruited to participate (99 male, 96 females 29 missing data), mean age 68.4 (8.5) years, 26 patients were on LTOT. 107 patients had previously attended rehabilitation, mean time since graduation from a rehabilitation programme was 40 months. The programme consisted of weekly exercise sessions offered over 6 months. Sessions were supervised by local gym instructors. Prior to commencing the scheme patients completed the self reported Chronic Respiratory Questionnaire (CRQ-SR), Hospital Anxiety and Depression Score (HAD), and performed an incremental shuttle walking test. These were repeated at 8 weeks and 6 months.
Results: There were no adverse events during the exercise sessions. There was a small increase in SWT distance at 8 weeks from (mean, 95% confidence interval) 273.4 (243.8 to 302.9) m at baseline to 289.3 (263.3 to 315.3) m at eight weeks, this was not statistically significant. In those participants that completed the 6 month course the mean improvement from baseline was 68.2 (45.7 to 90.7) m (n = 85), this increased distance at 6 months was significantly higher than baseline and 8 weeks ($p = 0.005$). The HAD score showed a significant reduction at 8 weeks in both anxiety and depression ($p < 0.05$). At 6 months there were no further important improvements observed in either component. The CRQ-SR demonstrated a statistically significant improvement in dyspnoea, fatigue and emotion domain at 8 weeks ($p < 0.05$), but there were no further improvement at 6 months. The changes in the CRQ-SR did not exceed the minimum clinically important difference except in the dyspnoea domain.
Conclusions: The community exercise scheme supported by the British Lung Foundation appears very effective in not only maintaining but improving exercise performance. It appears that 6 months is required to maximise the effect of physical training. Changes in health status, anxiety and depression occur independently of changes in physical performance and appear to change early on in the programme. Overall this scheme appears to be worthwhile and warrants further support and investigation to establish the optimum maintenance regime.

Clinical and basic science of interstitial lung disease

S103 AUTOANTIBODY PROFILE RATHER THAN EXTENT OF SKIN DISEASE PREDICTS SEVERITY OF PULMONARY FIBROSIS IN SYSTEMIC SCLEROSIS

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Background: Pulmonary fibrosis in systemic sclerosis (SSc-PF) is associated with significant morbidity and mortality. It has been suggested that SSc-PF occurs predominantly in patients with diffuse cutaneous (dcSSc) rather than limited cutaneous (lcSSc) disease, and in patients carrying the anti-topoisomerase autoantibody (ATA, Scl70); screening in many centres is focused on these subgroups. In addition, the relationship between the extent of skin and pulmonary disease is unclear. In this study, we aimed to investigate the interplay between systemic and pulmonary disease in a large SSc cohort.
Methods: The records of 238 consecutive patients with SSc referred to the Royal Brompton Hospital Interstitial Lung Disease Unit between 1991–99 were reviewed. Data collected included: cutaneous disease subset, modified Rodnan skin scores (at the time of pulmonary evaluation), autoantibody subgroup including ATA, anti-RNA polymerase (ARA) and anti-centromere (ACA), and thoracic HRCT scans were graded using a semi-quantitative score of lung fibrosis extent and pattern, including the proportion of ground-glass attenuation.
Results: Ninety six patients had dcSSc, and 142 had lcSSc by conventional criteria. Skin scores ranged from 0–52 (lcSSc 0–22, dcSSc 3–52). 153 patients had SSc-specific serology (ACA, n = 29; ARA, n = 35; ATA, n = 89). HRCT disease extent ranged from 0–84%. SSc-PF was equally extensive in both dcSSc and lcSSc: the mean HRCT extent was 13.2 (12.6)% in lcSSc, versus 14.1 (16.4)% in dcSSc ($p = 0.63$). Stepwise regression analysis showed that Rodnan skin score did not predict the HRCT extent of SSc-PF, even if the analysis was limited to patients with dcSSc or ATA positivity (all $p > 0.1$), providing compelling evidence that the extent of skin and lung disease are not linked. ATA positivity was invariably associated with SSc-PF (87/89, 98%); SSc-PF was found in 14 of 29 (48%) with ACA and 20 of 35 (57%) with ARA. The mean SSc-PF extent in ACA was 6 (12)%, ARA 12 (20)%, compared with ATA-positive patients 20 (15)% ($p < 0.0001$). Thus, SSc-PF occurred in all groups, though was more extensive in ATA. Lastly, the pattern of HRCT disease, in particular the proportion of ''ground glass'' (when adjusted for disease extent), was not predicted by the autoantibody subset or skin score.
Conclusions: This study emphasises the high prevalence of SSc-PF in limited cutaneous SSc, and in non-ATA antibody subgroups, strengthening the case for regular screening in subsets previously thought to be minimally at risk. We have highlighted the central predictive role of ATA-positivity. Finally, we have shown that the extent of skin and lung disease appear unrelated in this cohort.

S104 THE COAGULATION CASCADE IN FIBROTIC LUNG DISEASE PROGRESSION: LOCAL EXPRESSION OF FACTOR X IS INCREASED IN THE INJURED AND FIBROTIC LUNG

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Introduction: Extravascular pro-coagulant activity is increased in fibroproliferative lung disorders. Circulating coagulation proteinases (usually of hepatic origin) such as factor Xa (FXa) can exert both pro-inflammatory and pro-fibrotic effects via activation of proteinase-activated receptors (PARs). Mice deficient for PAR1 are significantly protected from bleomycin-induced pulmonary fibrosis, indicative of a causative role for coagulation proteinases in this disease model.
Hypothesis: FX is expressed locally in the lung, and thus increases extravascular pro-coagulant activity and contributes to a pro-fibrotic microenvironment.
Results: Microarray analysis of mouse lung following bleomycin instillation revealed 481 genes with increased expression at 7 days, and 346 genes at 14 days compared with saline-treated controls. FX mRNA was detectable and increased twofold and fivefold at 7 and 14 days respectively ($p < 0.05$). Immunohistochemistry for FX showed a marked increase in FX immunoreactivity post-bleomycin, localised to type II alveolar and bronchial epithelial cells and macrophages. Human tissue arrays containing 18 UIP lung specimens had a similar pattern of FX immunoreactivity. Real-time RT-PCR analysis of microdissected epithelial septae from 5 normal and 5 IPF human lung sections showed a sevenfold increase in FX gene expression in IPF ($p = 0.055$). In vitro analysis confirmed that human bronchial (BEAS-2B) and type II alveolar (A549) epithelial cells express FX mRNA and protein.
Conclusions: Local upregulation of FX following lung injury is consistent with the existence of an inducible extravascular lung coagulation system. FX blockade may represent an attractive target for therapeutic intervention in a number of respiratory conditions associated with local FXa signaling and excessive matrix deposition.

S105 T-BET EXPRESSION IN BRONCHOALVEOLAR LAVAGE CELLS FROM PATIENTS WITH SARCOIDOSIS

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Introduction: T-bet is a recently discovered member of the T-box transcription factor family and plays a central role in Th1 development by activating Th1 genetic programs and repressing Th2 cytokine synthesis. GATA-3 in contrast is a Th2 transcription factor promoting the Th2 cytokine secretion and inhibiting IFN-γ production through repression of IL-12 signalling. There is considerable interest in the role of Th1 and Th2 cells in the aetiology of sarcoidosis. We postulate that T-bet expression is increased in sarcoidosis leading to an exaggerated Th1 response which is responsible for granuloma formation.

Methods: In order to test this hypothesis 31 patients with sarcoidosis, 20 patients with IPF and 15 normal controls underwent bronchoscopy and bronchoalveolar lavage and real time PCR for T-bet, GATA-3, IFN-γ, and IL-4 performed on recovered cells using specific primer pairs. The same analysis was also performed on peripheral blood to determine whether any associated effects were systemic or confined to the lung environment.
Results: Results showed a significant increase in T-bet and interferon-γ mRNA in sarcoid lavage when compared to control subjects ($p<0.01$). The IPF patients also showed significantly increased levels of T-bet and interferon-γ mRNA when compared to control subjects. Interferon-γ was however significantly lower in the IPF patients when compared to the sarcoid group ($p<0.05$). There was no difference between any of the parameters measured in the peripheral blood samples.
Conclusions: These results provide evidence for a Th1 driven inflammatory process in both sarcoidosis and to some extent IPF. The higher levels of interferon-γ mRNA in the lavage fluid from sarcoid patients also provides evidence for a Th1 response. The lack of any significant differences between gene expression in peripheral blood suggests that these cells are localised within the lung.

S106 TUMOUR NECROSIS FACTOR-ALPHA ACCENTUATES TRANSFORMING GROWTH FACTOR-BETA DRIVEN EPITHELIAL TO MESENCHYMAL TRANSITION IN LUNG EPITHELIAL CELLS

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Introduction: Excessive focal fibrogenic responses in the lung parenchyma are believed to be an important mechanism in the development of pulmonary fibrosis (PF) in humans. Many previous studies have shown in both animal models and in humans that PF is associated with increased levels of TGF-β in the lungs. Furthermore, a recent study in alveolar epithelial cells from rats suggested that epithelial to mesenchymal transition (EMT), driven by TGF-β, may have a role in the pathogenesis (Willis *et al, Am J Pathol* 2005). During EMT cells loose their epithelial properties, such as ability to form tight junctions and gain features of a mesenchymal cell such as invasiveness and collagen production. The action of TGF-β in vivo is dependent on the microenvironment in which it acts. We hypothesised that TGF-βs ability to induce EMT in vivo may be exaggerated if it acts in a pro-inflammatory environment. TNFα is a potent pro-inflammatory cytokine which has also been implicated in fibrotic lung conditions.
Aims: This study aimed to investigate the effect of a pro-inflammatory microenvironment on TGFβ driven EMT in alveolar epithelial cells.
Methods: A549 cells were cultured to ~50% confluence and then stimulated with TGFβ1 (10 ng/ml) in the presence or absence of TNFα (20 ng/ml). The morphology of the cells was monitored using phase contrast microscopy. After 72 hours cells were either fixed for confocal microscopy or harvested for western blotting. The expression of the epithelial marker, E-cadherin and the mesenchymal marker, Vimentin were then assessed in the treated and untreated cells.
Results: In the absence of exogenous stimulus, the cells showed a uniform epithelial morphology with a high level of E-cadherin expression. Stimulation with TGFβ induced the cells by 72 hours to adopt a biopolar phenotype characteristic of fibroblasts as well as inducing the down-regulation of E-cadherin by 100% and significantly increasing expression of Vimentin by 15-fold consistent with EMT. However, the addition of TNFα to the growth media dramatically exaggerated both the phenotypic change and the associated upregulation of Vimentin expression, a 2.5-fold increase compared to TGFβ alone. TNFα alone had no effect on either phenotypic change, E-cadherin expression or upregulation of Vimentin.
Conclusion: The data suggest that a pro-inflammatory microenvironment containing TNFα can dramatically accentuate TGFβ driven EMT in alveolar epithelial cells. This mechanism may be important in driving excessive and rapid episodes of fibrogenesis in the pathophysiology of pulmonary fibrosis.

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S107 DETERMINANTS OF BRONCHOALVEOLAR ALVAGE FLUID CHEMOTACTIC ACTICTIVTY IN WEGENER'S GRANULOMATOSIS: THE INTERDEPENDENCE OF IL-1 AND IL-8

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Introduction: Neutrophil counts are persistently elevated in the bronchoalveolar lavage fluid (BALF) of patients with Wegener's granulomatosis (WG), even when patients are in disease remission. Ongoing neutrophil recruitment and the release of neutrophil products may damage local lung tissue. The molecular determinants of neutrophilic inflammation within the lung in WG are unknown.
Methods: Under agarose chemotaxis was performed using neutrophils from a normal control and incubated with BALF from 31 WG and 6 normal controls. BALF chemokine levels were measured by Luminex array and myeloperoxidase by colorimetric assay. WG activity was determined using the BVAS system.
Results: WG BALF had significantly elevated neutrophil %, MPO, IL-1β, IL-8 and G-CSF compared to controls (see table). The neutrophil % correlated with IL-1β ($r=0.591$, $p=0.001$) and IL-8 ($r=0.468$, $p=0.012$) but not with other chemokine levels.

BALF chemotactic effect was increased in WG patients compared with normal controls ($p<0.001$). WG lavage during relapse had the greatest increase in chemotactic response (mean = 4.44 mm) compared to acute (3.53 mm) and remission (2.81 mm) groups and controls (1.734 mm). BALF chemotactic activity strongly correlated with IL-1β ($r=0.761$, $p=0.001$) and IL-8 ($r=0.64$, $p=0.012$) but not with other measured chemokine levels. To ascertain the relative importance of IL-1β and IL-8 in determining the chemotactic response, experiments were repeated using neutralising antibodies and a CXCR2 antagonist. Both anti-IL-1β and anti-IL-8 antibody inhibited BALF chemotaxis by 80% ($p=0.001$). The combination of anti-IL-1β and anti-IL-8 or CXCR2 antagonist virtually abrogated (95%, $p=0.001$) the chemotactic potential of BALF. To determine any interrelationship between IL-1β and IL-8 in our system, their effects were blocked with anti- IL-1β and anti-IL-8. The chemotactic effect of IL-1β was significantly blocked by anti-IL-8 (91%, $p=0.004$) suggesting that IL-1β chemotactant actions are IL-8 dependent.
Conclusions: Our data show that even during remission WG BALF is a stronger neutrophil chemotactant than normal BALF with a resulting increase in the neutrophil product MPO. Neutrophilic chemokines are elevated in the BALF of WG patients compared with normal controls. IL-1β and IL-8 are the predominant determinants of neutrophil chemotactic activity in WG BALF. IL-1β appears to have its affects via IL-8 and the CXCR-2 receptor. Anti-CXCR2 therapy may have potential to limit neutrophilic inflammation in patients with WG.

S108 THE FREQUENCY OF OCCURRENCE OF CT FEATURES OF DIFFUSE PARENCHYMAL LUNG DISEASE IN SECONDARY CARE

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Introduction: Over the last decade there has been an increasing use of thoracic CT to help diagnose diffuse parenchymal lung disease (DPLD). To our knowledge no published studies have examined the frequency of occurrence of CT features of DPLD in an unselected population.
Methods: A retrospective search was made of thoracic CT reports at the Norfolk & Norwich University Hospital (NNUH) over a 2 ½ year period from June 2001 to December 2003 looking for diagnostic labels and radiological features of DPLD. The NNUH is a secondary hospital with a

Abstract S107

pg/ml	Neut%	MPO	IL-8	IL-1β	GCSF	GMCSF
WG BALF	26.54	0.351	1795	161.6	119.6	10.9
Normal BALF	1.14	0.015	158	12.9	19.2	9.2
p value *t* test	0.05	0.038	0.015	0.029	0.015	0.493

Abstract S108 Incident cases

	No	Mean age	Median age	M:F	Number with emphysema	Number biopsied
CTD	16	67.4†	72	7:9	6 (38%) *	2 (13%)
Asbestosis	14	75.8	79	9:5	3 (21%)	0
HP/RBILD	27	61.7†	60	5:22*	1 (4%) *	5 (19%)
IPF	45	75.9	78	33:12*	10 (22%)	5 (11%)
IIP	70	74.0	74	42:28	11 (16%)	10 (14%)

* $p<0.05$ †$p<0.05$ *v* IPF, IIP, Asbestosis.

catchment area of 750 000 people in the East of England. On the basis of referral source (rheumatologist *v* chest physician), report diagnosis or radiological features (pleural disease or mosaic attenuation) disease likely to be secondary was classified as ''Connective Tissue Disease'' (CTD), ''Asbestosis'' or ''HP/RBILD''. All other cases were thought to be primary, either ''IPF'' if this or UIP was thought the likely diagnosis with no differential or otherwise ''IIP'' (Idiopathic Interstitial Pneumonia). The frequency of emphysema was recorded as was the age, spirometry and gas transfer and frequency of biopsy. Incident cases were those first diagnosed during the study period. Prevalent cases were those identified still living on the final day of the study

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

Conclusions: Radiological features of DPLD are common in secondary care, especially with increasing age. Average age is higher than in the BTS CFA study Mean age of CTD and HP/RBILD was lower than other groups. Emphysema was more common in CTD but infrequent in HP/RBILD. Men were overrepresented with IPF but underrepresnted with HP/RBILD. Biopsy was uncommon.

Therapeutic approaches to COPD management

S109 THE TORCH (TOWARDS A REVOLUTION IN COPD HEALTH) STUDY: SALMETEROL/FLUTICASONE PROPIONATE IMPROVES QUALITY ADJUSTED SURVIVAL OVER THREE YEARS

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

Abstract S109

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

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

Results: The propensity method indicated that withdrawal was associated with lower health status. The table shows the estimated quality adjusted survival time (95% CI) following imputation for each of the treatment arms of the trial, for the subsample that provided EQ-5D data.

Conclusions: Results show a significant benefit of treatment in terms of quality adjusted survival, with the greatest increases in the SFC group. It is important to account for the informative nature of withdrawal and results are sensitive to this. SGRQ results provide an interesting comparison in terms of the difference between treatments based on a disease-specific HRQoL instrument; however, the EQ-5D results have the advantage of representing Quality Adjusted Life Years, the preferred measure for economic appraisal.

S110 HIGH FLOW OXYGEN, HYPEROXIA, HYPERCAPNIA, ACIDOSIS, AND DEATH IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE. DO THE DATA SUPPORT A CAUSAL LINK?

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Background: It has been proposed that the administration of high concentrations of oxygen (HFO) can lead to relative hyperoxia, hypercapnia, acidosis, and death in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The epidemiological evidence for this assertion is weak (Plant, Owen *et al.* 2000; Denniston, O'Brien *et al.* 2002; Durrington, Flubacher *et al.* 2005). We evaluated whether the sequence of events described above were supported by data from 1016 admissions to Kings College Hospital for AECOPD.

Methods: Consecutive patients admitted to hospital with AECOPD between 1 October 2004 and 17 July 2006 were identified by specialist COPD nurses. The first blood gas taken in hospital was recorded. HFO was defined as FiO_2 >28% or >2 l/min O_2 via nasal speculae. Hypercapnia was defined as $PaCO_2$>6 kPa and acidosis pH<7.35. Death was recorded in our COPD database and cross checked with the hospital computerised administrative system.

Results: There were 1182 admissions of which 1016 had a complete record of blood gases. Five hundred and sixty seven (55.8%) were male median age 70 years (5th centile 50 95th centile 86 years). One hundred and seventy six (18.4%) of 957 patients received HFO. The administration of HFO was associated with higher PaO_2 (mean PaO_2 15.2 kPa *v* 9.1 kPa $p<0.001$). PaO_2 correlated positively with $PaCO_2$ (Pearson correlation co-efficient (PCC) 0.15, $p<0.001$), and negatively with pH (PCC −0.19, $p<0.001$). pH was strongly negatively correlated with pCO_2 (PCC −0.81. $p<0.001$). Three hundred and seven patients (30.2%) were acidotic and 499 hypercapnic (49.1%). The vast majority (296 of 307 (96.4%)) of acidotic patients were also hypercapnic. Fifty (65.8%) of 76 patients who died were acidotic on admission compared with 257 (27.3%) of 940 patients who did not die (χ^2 $p<0.001$).

Conclusions: These data support the following conclusions for patients with AECOPD; HFO increases arterial oxygen tensions, high oxygen

tensions lead to CO_2 retention, CO_2 retention is associated with acidosis, and acidosis is associated with death.

S111 FUNCTIONAL STATUS MEASUREMENT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE VALUE OF THE FUNCTIONAL STATUS DOMAIN OF THE CLINICAL COPD QUESTIONNAIRE

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Introduction: Improvement of HRQoL is an important treatment goal in COPD; the assessment of health status is therefore relevant for caregivers and for this reason, both in daily clinical practice as well as in research setting, short and validated outcome measures are needed. The Clinical COPD Questionnaire (CCQ) is a recently introduced short 10-item validated health status questionnaire which contains three domains: symptoms, functional status, and mental status. The functional status of a patient is one of the main determinants of health status and improving functional physical capacity by itself is a major treatment goal.
Purpose: To assess the value of the functional status domain of the CCQ in measuring functional status of COPD patients.
Methods: Datasets of two studies were re-analysed. Dataset 1: 88 COPD patients completed the CCQ before lung function assessments and after 2 weeks this was repeated and a global rating of change was assessed. Dataset 2: 210 COPD patients, hospitalised because of an acute exacerbation, completed the CCQ at days 1–7 and at day 42. Day 42 data were used for the current analysis. A validation process similar to the validation of the total CCQ was performed. We measured floor and ceiling effects, internal consistency using Cronbach's α and test-retest using the Intra Class Coefficient (Study 1). We hypothesised that the CCQ functional domain score correlated stronger with SGRQ activities and impact subdomain scores than with SGRQ symptoms or with FEV1 and furthermore that the BORG dyspnoea scores would correlate only modestly with the individual (functional status related) CCQ items (Study 2).
Results: Minimal (floor) and maximal (ceiling) scores occurred in 8% and 0% of the 88 patients respectively. Crohnbach's α was 0.89. The ICC was 0.82. The a priori hypotheses were confirmed (see table).
Conclusion: CCQ functional status domain shows good measurement properties and can be used to measure functional status in COPD patients.

Abstract S111

Pearson correlation coefficient,* p<0.01	CCQ function score
SGRQ symptom	0.34*
SGRQ activities	0.77*
SGRQ impact	0.74*
SGRQ total	0.79*
FEV1 (%predicted)	−0.34*
CCQ question number and subject	**BORG score**
7. Strenuous physical activities	0.42*
8. Moderate physical activities	0.50*
9. Daily activities at home	0.54*
10. Social activities	0.45*
CCQ functional status score	0.56*

S112 A RANDOMISED STUDY OF TIOTROPIUM RESPIMAT SOFT MIST INHALER VERSUS IPRATROPIUM PMDI IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: Tiotropium provides prolonged muscarinic M_3 receptor blockade and sustained bronchodilation with once-daily dosing. The aim of this study was to compare the efficacy and safety of tiotropium, delivered via Respimat Soft Mist Inhaler (SMI), an innovative propellant-free device, with ipratropium pMDI and placebo in patients with chronic obstructive pulmonary disease (COPD).

Abstract S112

Diff. -mL	Tiotropium 5 μg - PLA	Tiotropium 10 μg - PLA	Tiotropium 5 μg - IPR	Tiotropium 10 μg - IPR
Mean (SE)	118** (23)	149** (23)	64* (23)	95** (23)
95% CI	0.072–0.164	0.103–0.195	0.018–0.110	0.050–0.141

*p<0.01; **p<0.0001; IPR, ipratropium; PLA, placebo; Tiotropium doses were o.d. and IPR doses were q.i.d.

Methods: Two identical, 12-week, randomised, double dummy, placebo controlled studies were performed in 64 centres worldwide. COPD patients were randomised to inhaled tiotropium 5 μg or 10 μg Respimat SMI, ipratropium 36 μg pMDI or placebo. The primary endpoint was the change in morning pre-dose FEV1 after 12 weeks of treatment. Secondary endpoints included FVC, PEFR, rescue medication use, COPD symptom scores, and the Physician's Global Evaluation (PGE). Safety was monitored from adverse events.
Results: The majority of patients (n = 719) were male, with a mean age of 64 years, and mean FEV1 (% predicted) of 40.7%. At week 12, tiotropium (both doses) significantly improved the primary endpoint compared with ipratropium or placebo (table).

The increases in peak FEV1, FEV1 $AUC_{(0\text{-}6h)}$, and FVC for both tiotropium doses were superior to placebo and ipratropium. PEFR was significantly improved after tiotropium (largest: p<0.001 *v* placebo and ipratropium). Rescue medication use was significantly reduced for all active treatments (largest: p = 0.03 *v* placebo). Both doses of tiotropium significantly improved the 'tightness of chest score' compared with ipratropium and the PGE score compared with placebo. Adverse events were comparable across groups. Dry mouth was more common with tiotropium (8.3% (5 μg) and 10% (10 μg)) than ipratropium (3.9%) or placebo (2.2%).
Conclusions: Tiotropium (5 μg and 10 μg), delivered via Respimat SMI, significantly improved lung function compared with ipratropium pMDI and placebo. Tiotropium Respimat SMI also provided a number of symptomatic improvements over ipratropium pMDI.

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

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Introduction: Predicting survival time for patients with severe chronic obstructive pulmonary disease (COPD) is difficult, despite there being a number of well validated prognostic factors. FEV1 is reported to be the best single correlate of mortality (Celli *et al*, 1995). Although dyspnoea has been shown to be even more discriminating than FEV1 in terms of mortality (Nishimura *et al*, 2002), MRC score is not usually included as a prognostic indicator. We characterised a group of patients who died whilst under a Chronic Respiratory Support (CRS) team. Patients under CRS have, by entry criteria, had >2 admissions for exacerbations of COPD in 1 year, and the annual mortality of this group is high (16%). We assessed whether known prognostic indicators were predictive of death, and therefore useful in guiding the most appropriate time to introduce end of life planning.
Method: Case notes of 29 CRS patients with COPD who had died over a 24 month period (December 2003–December 2005), were retrospectively analysed and compared with 29 living COPD patients under CRS over the same period. Factors analysed included: age, FEV1, body mass index (BMI), number of exacerbations in the year prior to death, Medical Research Council (MRC) Dyspnoea score, smoking status, use of long term oxygen therapy (LTOT) and optimised resting oximetry, comorbidities, and social factors, including living alone and alcohol excess. The rapidity and place of death was assessed for deceased patients, as was the use of advance directives. A further case-note analysis of COPD patients, not under CRS, (n = 16) who had died during the same period, was also undertaken.
Results: There were no significant differences in age, FEV1, BMI, number of exacerbations, use of LTOT or optimised oximetry, smoking status, co-morbidities or social factors between patients who had died and patients alive under CRS. However, deceased CRS patients had an MRC score of 4.3 (0.17) (mean (SEM), n = 29), which was significantly (p = 0.05) higher than the MRC score of living CRS patients which was 3.8 (0.13) (n = 29). In the group that died, there was no documentation of a living will despite the fact that only 8 deaths (24%) were sudden (that is, the

patient had been stable for hours/days prior to admission), and only 4 patients (14%) died at home rather than in hospital. Comparison of the group of deceased CRS patients with deceased COPD patients who had not been under CRS, revealed that whilst the latter group had significantly ($p<0.01$) better lung function (FEV1 1.1 (0.15) l, n=7)) compared to the group under CRS (0.65 (0.04) l, n=21), there was no significant difference in age at death or in MRC score between the groups. The patients not under CRS, however, had significantly ($p=0.03$) more cardiac comorbidity (11/16 patients; 69%) compared to the group under CRS where only 24% (7/29) had cardiac comorbidity.
Conclusion: An MRC score of ⩾4 in patients with COPD should be used as a marker of a higher risk of death, prompting appropriate end of life planning. It should also prompt careful assessment to diagnose and treat coexisting cardiac disease.

S114 DOES A NURSE-LED PALLIATIVE CARE SERVICE FOR CHRONIC LUNG DISEASE HAVE A POSITIVE IMPACT ON QUALITY OF LIFE AND PATIENT SATISFACTION?

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Background: Patients with non-malignant severe chronic lung disease (CLD) suffer significant levels of morbidity and mortality. There is recognition that they are poorly supported within primary and secondary care resulting in recurrent hospital admissions. The NICE guideline recommends that all COPD patients should have access to multidisciplinary palliative care teams. A nurse-led palliative care service for CLD was introduced in August 2004 to promote and maintain the best possible quality of life and end-of-life care for patients with severe disease through symptom control and improvement in functional capacity. The aim of this audit was to assess the impact of this service after 15 months.
Methods: Service intervention consists of home visits by the CLD palliative care nurse on a needs-led basis varying from monthly to three monthly. At baseline, the following assessments and measurements were carried out: patients' needs, spirometry, pulse oximetry (SpO2), St Georges Respiratory Questionnaire (SGRQ) and Hospital Anxiety and Depression Scale (HADS). Subsequent visits consist of symptom control, follow up SGRQ and HADS questionnaires, psychosocial support, end of life decision making and home pulmonary rehabilitation where appropriate. The service was evaluated after 15 months by auditing patient admissions, patient outcome measures and patient/carer satisfaction survey. SGRQ and HADS were analysed comparing baseline and follow-up scores using Mann-Whitney U test. Analysis of hospital admissions used admissions in the previous 15 months as historical control.
Results: 166 patients with severe chronic lung disease (125 had COPD, 8 had bronchiectasis, 33 had interstitial fibrosis) have been assessed. Mean age 69 years, SpO2 97% and FEV1 0.99 l (42% predicted). Median MRC dyspnoea score was 5. At baseline, 39% patients had >11 HADS anxiety score and 11% had >11 HADS depression score. For those with complete HADS assessments (n=42), there was significant improvement in HADS anxiety score (median 8 vs 6.5; for difference 95% CI 1.0 to 4.0; $p<0.05$) but not for depression. For those with complete SGRQ assessments (n=39), there were no significant differences in Symptom and Activity domains or Total scores. There was a trend towards a reduction in Impact domain scores (median 55.65 *v* 42.01; $p=0.05$). There was a significant reduction in hospital admissions (115 *v* 62; $p<0.05$). Patient and carer satisfaction survey scored 100% for helpfulness of nurse visits, with 93% of patients and 94% of carers benefiting in coping with the disease.
Conclusion: The chronic lung disease service has shown a positive impact on patients' and carers' quality of life and a reduction in hospital admissions.

Training tomorrow's chest physicians

S115 SPECIALIST TRAINING IN RESPIRATORY MEDICINE, HOW DO WE LEARN?

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Specialist training in the UK has changed over the 10 years. Since the introduction of Calman training programme there has been numerous changes to the structure of training programmes. We cannot ignore the facts that our training is based on service provision. Supervision and training by experienced consultants is vital to how and what we learn. All respiratory Specialist Registrars (SpRs) in Yorkshire region were asked to fill in a questionnaire as a part of their preparation for the annual assessment (RITA) in June 2005. The question from the Programme Director was phrased as follows: ''I am keen to find out in which part of your SpR experience you are learning the most. Please estimate the percentage of your SpR learning in each of the following areas …''.The trainees were given five potential categories for learning.
Results: See table.
Conclusion: Respiratory trainees in Yorkshire report that nearly two thirds of their training is based on hands-on experience, especially working closely with the consultants. Those involved in organising SpR training should take note of this important finding. Each year there are more requests for SpRs to take time out for structured training days and for self-directed learning. It is important that training through experience is given a higher profile and not further compromised.

S116 BTS QUESTIONNAIRE SURVEY OF FLEXIBLE TRAINING AND ATTITUDES SURROUNDING FLEXIBLE TRAINING AND WORKING IN SPECIALIST REGISTRARS IN UK

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A questionnaire survey of training and working patterns and associated attitudes was carried out in all respiratory specialist registrars in UK in March 2006. This was a second survey following a survey in 2003. In total 286/507 (56%) responded, median age 32 years (26–45), 120/286 (42%) female, 166/286 (58%) male. There were 23/286 (8%) part time trainees, 22F:1M, (8% in 2003, all female). The median number of sessions worked was 6 (5–8) and 3/23 (13%) were in a slot share, 15/23 (65%) supernumerary, 4/23 (17%) in a whole time post and 1/23 (4%) in research. For these part time trainees 13% intended to return to full time training at some point and 87% (55% in 2003) had no such intention whereas 52% (89% in 2003) intended not to work full time as a consultant but 22% intended to return to full time work in <5 years and 26% in 5–10 years. There were 263 full time trainees and 190/263 (73%) had no intention of training flexibly of which 21% were female, 20 (7.6%) definitely planned to train flexibly in the future of which 90% female, and 51 (19.5%) probably planned to train flexibly of which 76% were female. As a consultant 138/263 (53%) did not plan to work flexibly (12% female), and 60/263 (23%) did plan possibly to work flexibly (58% female), 45/263 did plan probably to work flexibly (74% female), and 19/263 (7.3%) did plan definitely to work flexibly (74% female) as a consultant. Five trainees had been flexible and returned to full time work. All the trainees were asked if they would feel welcome, neutral, worried or resist if a trainee colleague was to be supernumerary, slot share or whole time. There was a substantial swing from welcome 193/286 (67%), worried 16/286 (5.6%) when the trainee colleague

Abstract S115

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

Thirty of the 31 SpRs answered the question. Seven trainees were females. Questionnaires were coded for sex and year of training.

was to be in a supernumerary post, to welcome 128/286 (45%), worried 54/286 (19%) when in a slot share post, to welcome 72/286 (25%), worried 118/286 (41%) when in a whole time post. In total 32/286 (11%) reported coming across bad attitudes to flexible training while 65/286 (23%) reported good attitudes. In total 18 trainees reported having considered giving up respiratory medicine due to their experiences and 99/286 (35%) indicated that they would leave if they could not start flexible training when they wished.
Conclusions: Flexible training remains at 8% with 42% of trainees female. A high proportion of full time trainees, predominantly female, expected to train flexibly at some time and to work flexibly as a consultant but not necessarily for their entire career. The trainees reported some support but also overt criticism and the type of post and organisation of the posts seems likely to be important. A failure to allow for flexible training/working will lead to many trainees leaving respiratory medicine.

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

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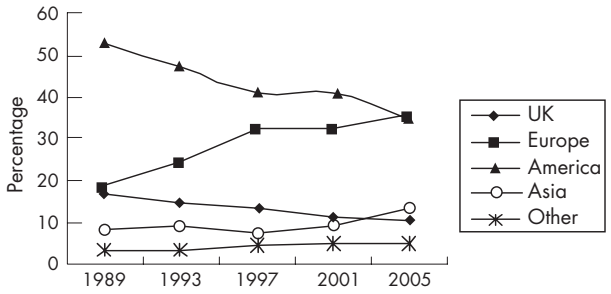
There is genuine concern among UK based respiratory clinicians that research opportunities in UK based institutions have been on the decline over the past two decades. Reasons for this are probably multifactorial but direct supportive evidence at best anecdotal; further, whether the same is true of research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



Abstract S117.

S118 THE IMPACT OF EUROPEAN WORKING TIME DIRECTIVE UPON RESPIRATORY SPECIALIST REGISTAR TRAINING

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Background: There is concern that new shift structures, to ensure European Working Time Directive (EWTD) compliance, have reduced the opportunities for specialist registrar (SpR) specialist training, little evidence exists to demonstrate this.

Abstract S118 Table 1

	Days missed 2002–03	Days missed 2004–05
Teaching hospital	58	75
DGH	60	127

Abstract S118 Table 2

	% Reduction in outpatient attendance by SpR	% Reduction in bronchoscopy list attendance by SpR	% Reduction in SpR performed bronchoscopies
Teaching hospital	10	9	16
DGH	41	45	55

Methods: Attendance at outpatient clinics, and bronchoscopy lists and the number of bronchoscopies undertaken by SpRs were used as markers of training. Work days missed due to annual leave, study leave and on-call commitments were calculated. A comparison was made between the periods October 2002–03 and October 2004–05. The change over, to EWTD compliant rotas occurred in the intervening year. Data were collected from a teaching hospital, and a district general hospital (DGH) within Yorkshire, from hospital files and SpR training records. The teaching hospital rota changed from a 3 month general medicine partial shift to full shift. The teaching hospital SpR continued to spend 9 months each year on a non-resident specialty on-call rota. The DGH changed from 1 in 6 on-call rota to 1in 8 full shift, throughout the year. Full day educational events have replaced evening sessions.
Results: Missed working days, due to annual and study leave, on-call commitments including night shifts and compulsory rest days increased in both hospitals, the greater impact being in the DGH. Both hospitals demonstrated a reduction in SpR outpatient clinic attendance, bronchoscopy list attendance and bronchoscopies performed by SpRs. These reductions being greater in the DGH.
Conclusions: Specialty training opportunities have been reduced by the change to EWTD compliant working patterns. This is likely to be compounded by further time constraints to be imposed in 2009. Action must be taken to enhance quality of training as quantity is reduced.

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

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

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

In order to evaluate the current state of training in CCM for Respiratory SpRs the group sent out a survey to all SpRs registered with the BTS in May 2005. One of the aims of this questionnaire was to establish the level of interest in respiratory critical care amongst the trainees. There was an overall response rate of 54% (208/389).

69% of responders expressed an interest in developing a special interest in at least one area of respiratory critical care (intensive care, medical high dependency, non-invasive ventilation, weaning). 36% were interested in one area, 20% in two areas, 7% in three areas and 6% in all four areas. Looking at these areas individually: intensive care was considered an area of special interest by 19% of responders, medical high dependency by 33%, non-invasive ventilation by 57% and weaning by 13%.

Our survey data may be biased since those interested in respiratory critical care might be more likely to respond. However if it is assumed that all non-responders have no interest in respiratory critical care, 37%

of all Respiratory SpRs still have a special interest in at least one of these areas.

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

Basic mechanisms of lung disease

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

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

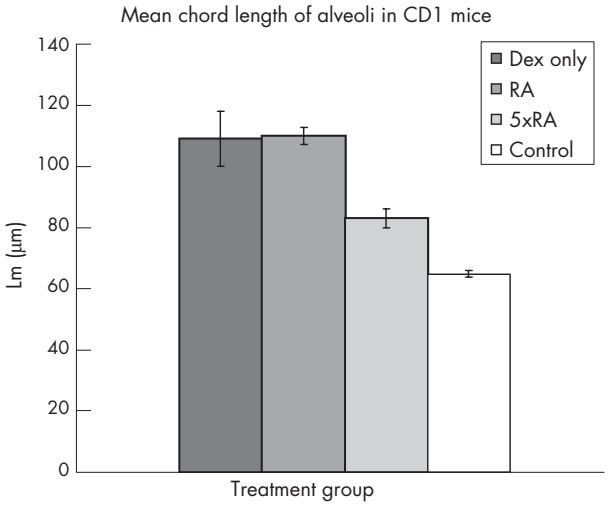
Method: Male CD1 mice were all Dex-treated (0.4 mg/kg Dex in PBS, daily subcutaneous injection) from postnatal day 4–15 (P4–P15). From P46–57 animals received either RA (2 mg/kg in DMSO/oil) or 5xRA (10 mg/kg in DMSO/oil) or vehicle (DMSO/oil) by intraperitoneal injection. Control group received vehicle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

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

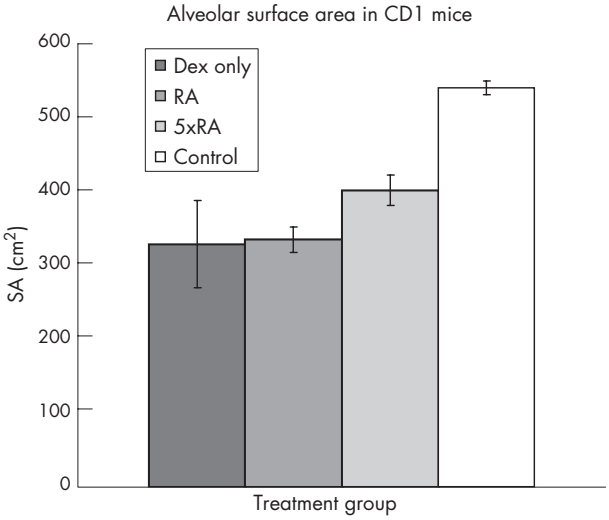
Conclusion: The Dex-treated mouse model of emphysema is robust and repeatable in different strains. RA dose threshold for inducing alveolar regeneration is higher in CD1 mice, suggesting a difference in retinoid pharmacokinetics and/or metabolism between strains. However, RA-induced regeneration of mouse lung architecture in our model is not strain specific. This supports the theory that RA plays a central role in mammalian alveolar maintenance, repair and regeneration, and may provide a novel therapy for emphysema in the future.

Abstract S120

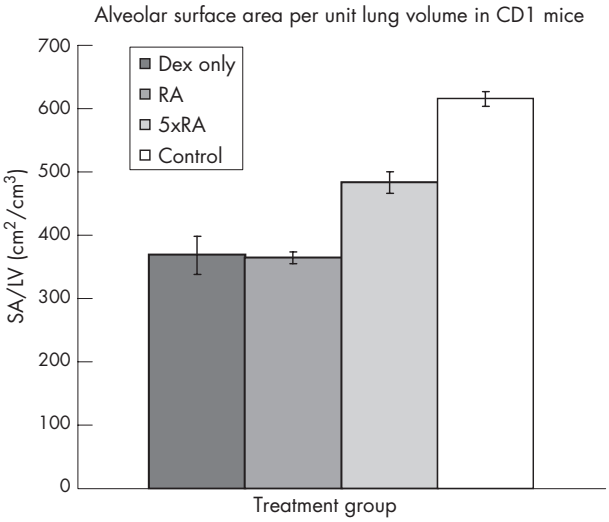
Treatment group	Lm (mm)	SA (cm^2)	SA/LV (cm^2/cm^3)
Dex only	109.06	328.29	369.61
RA	109.89	334.45	365.20
5xRA	83.05	401.44	484.76
Control	64.87	540.11	617.49



Abstract S120 Figure 1 Mean chord length of alveoi in CD1 mice.



Abstract S120 Figure 2 alveolar surface area in CD1 mice.



Abstract S120 Figure 3 Alveolar surface area per unit lung volumn in CD1 mice.

S121 SPUTUM METAL IONS ARE BIOMARKERS FOR SUPPURATIVE AND INFLAMMATORY LUNG DISEASE

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Background: The cellular and fluid components of induced sputum provide information about the degree of inflammation in respiratory diseases. Previous studies have demonstrated the utility of sputum

cytology in the assessment of asthma and chronic obstructive pulmonary disease (COPD), and the fluid component of sputum contains important mediators and biomarkers of inflammation such as cytokines, but these proteins may be liable to the action of proteases such as neutrophil elastase. The presence of increased levels of sputum iron in inflammatory lung disease is well documented. We therefore hypothesised that other metal ions present in sputum may be affected by airway inflammation and sought to assess their value as biomarkers for the investigation and monitoring of respiratory diseases.
Methods: Induced sputum was obtained from 20 healthy control subjects and a range of patients with inflammatory pulmonary diseases: 23 patients with cystic fibrosis (CF), 16 with (non-CF) bronchiectasis, 17 with asthma, and 23 with COPD. The fluid phase of processed sputum was subjected to inductively coupled plasma optical emission spectrometry to detect levels of iron, zinc, manganese and copper. 14 patients with CF were also followed through an exacerbation cycle, with sputum being collected and analysed at the beginning and end of antibiotic therapy.
Findings: Sputum zinc differentiated CF and bronchiectasis from controls with $p<0.001$ at the following levels in ug/l (SEM): control 17.6 (3.0), bronchiectasis 112.1 (20.6), CF 150.0 (23.4), COPD 34.6 (7.1), asthma 36.2 (13.6). Sputum iron also differentiated CF and bronchiectasis from controls at $p<0.001$. Levels of manganese and copper were numerically lower, but were elevated for CF ($p<0.05$), bronchiectasis and asthma ($p<0.01$) versus controls for manganese, and were elevated for all diseases ($p<0.05$) compared with controls for copper. Sputum zinc level decreased significantly following antimicrobial therapy for an exacerbation in CF subjects from 236 μg/l (47.1) to 140 (30.1) ($p<0.0086$).
Interpretation: Sputum zinc and iron represent markers of airway inflammation in CF and bronchiectasis, but zinc has better potential to monitor disease activity. While there is a wealth of information about the significance of iron in lung inflammation, the role of fluctuating zinc levels revealed by this study merit further investigation.

S122 MURINE MESENCHYMAL STEM CELLS GENERATE OSTEOSARCOMA-LIKE LESIONS IN THE LUNG: IMPLICATIONS FOR STEM CELL THERAPY

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Rationale: Recent studies have demonstrated the ability of donor bone marrow stem cells (BMSC, both haematopoietic stem cells (HSC) and mesenchymal stem cells (MSC)) to engraft as alveolar epithelium after bone marrow transplantation (BMT). These observations raise the possibilities that circulating BMSC contribute to repair of the alveolar epithelium and that this process may be supplemented and manipulated with therapeutic benefit. Importantly however, several early studies have been difficult to reproduce and indeed recent studies have shown that subpopulations of BMSC may exacerbate lung damage. In addition MSC populations that were previously thought to be ''pure'' have now been shown to be contaminated with HSC. Our objective was to determine the engraftment potential of a highly purified population of MSC.
Methods: Murine MSC were selected based on CD45-/CD11b- adherent cells. They were infected with lentivirus expressing eGFP with 96% transduction efficiency. These cells were injected into mice following whole body gamma irradiation of 375cGy to ablate their bone marrow. Lungs were harvested and fixed at 1, 2, 7, 14, and 28 days. The lungs were subsequently stained with antibodies against epithelial markers TTF1, AE1/3, T1-alpha, SPC and SPB; endothelial marker CD31; and bone markers.
Results: Transplanted mice were sacrificed at 28 days owing to breathlessness. Donor derived bronchiolar epithelium and rare pneumocytes were identified by co-expression of GFP and tissue specific markers. However, a large percentage of the lung parenchyma at 28 days after MSC transplant showed bone tumor formation explaining the breathlessness. Posterior karyotype analysis showed chromosomal instability in MSC at the time of injection (passage 4 or 5) but not at early passages.
Conclusions: MSC engraft into the lung after transplant but remain multipotent with uncontrolled differentiation into inappropriate lineages causing fatality. This malignant transformation can be explained, at least partially, due to chromosomal abnormalities.

S123 STEPWISE INCREMENTAL CHANGES IN ADAM33 EXPRESSION DURING MOUSE LUNG DEVELOPMENT

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Rationale: Polymorphisms of *ADAM33* are strongly associated with asthma and bronchial hyperresponsiveness (BHR) (Van Eerdewegh P, *et al. Nature* 2002;**418**:426–30). The homolog for *ADAM33* in the mouse has also been associated with BHR (De Sanctis GT, *et al. Nat Genet* 1995;**11**:150–4). As SNPs in ADAM33 predict impaired lung function in asthma and in young children (Simpson A. *et al. AJRCCM* 2005;**172**:55–60), we hypothesised that ADAM33 is expressed during lung development where it may contribute to airway ''modelling''. Therefore we studied the temporal expression of ADAM33 in developing and mature mouse lungs.
Methods: MF-1 mice were time mated and lungs were harvested by microdissection at embryonic day (ED) 11–19, postpartum day (PD) 1 and day 8 and adult mice (AM) ($n=5$–8). Samples were processed for mRNA analysis by RT-qPCR. To establish the most stable genes for normalising, control gene expression was measured in embryonic, postpartum and adult lungs. 12 normalising gene control kits were selected for analysis and the 3 most stably expressed ''house-keeping genes'' (HKGs) were determined by GeNorm analysis. These were used for normalisation of ADAM33 and α-smooth muscle actin (αSMA) expression.
Results: The best HKGs for normalisation of mRNA expression in developing lung were found to be GAPDH, cytochrome C1 and ATP synthase subunit. Using these HKGs, ADAM33 mRNA expression increased in 4 significant (all $p<0.002$) steps during normal mouse lung development. These steps corresponded to the progression from the embryonic stage (ED11) to pseudoglandular stage (ED12–15), to the canalicular stage (ED16,17), to the saccular alveolar stage (PD1&8) and to the adult stage (AM). The greatest increases in ADAM33 expression could be observed from ED11 to 12 and postpartum. The smooth muscle marker, α-SMA, showed a similar stepwise incremental pattern of expression.
Conclusion: ADAM33 is expressed at all stages of murine lung developmemnt. The marked increase in expression in the early stages of lung development and postpartum suggest that ADAM33 might be induced by tubular contraction that starts in the pseudoglandular stage around ED12/13 and mechanical stretch from breathing after birth. Polymorphisms in ADAM33 might be involved in mechanical stretch-induced abnormal bronchial smooth muscle development.

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

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

S124 IL-13 SIGNALING POLYMORPHISMS PREDICT ASTHMA AND ATOPY PHENOTYPES IN AN UNSELECTED POPULATION

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

Abstract S124 Summary of significant genetic predictors of clinical outcomes

ID	Outcome	OR (95% CI)	p Value
IL13 Arg110Gln	Asthma ever	1.38 (1.06–1.79)*	0.015
IL4RA Ile50Val	Asthma ever	1.38 (1.06–1.79)*	0.015
STAT6 rs324015	Current eczema	2.62 (1.40–4.89)†	0.003
	Current hayfever	1.99 (1.19–3.32)†	0.008

*Carriage of at least one mutant allele *v* wildtype homozygote.
†Mutant homozygote *v* other genotypes.

Methods: Twenty two polymorphisms were genotyped in IL13, IL4RA and STAT6 genes in 1614 unselected volunteers aged 18–30 years. Data included physician-diagnosed asthma, eczema and hayfever (validated questionnaire) and total IgE levels. Results were analysed by multiple logistic and linear regression, adjusting for relevant covariates.
Results: Physician diagnosed ''asthma ever'', ''eczema ever'', and hayfever were recorded by 22.6%, 23.1%, and 32.5% of our population respectively. Geometric mean total IgE was higher in males ($p<0.001$). Genetic data are presented for the Caucasian group (n=1445). Significant predictors are summarised in the table. IL13, IL4RA, and STAT6 loci were associated with physician-diagnosed ''asthma ever'', current eczema and hayfever. A novel prediction was seen between a 3'UTR variant of IL13 and total IgE ($p<0.05$). Novel predictions of IgE were also demonstrated for IL4RA 3'UTR and intron variants and previously reported associations were confirmed at a population level ($p<0.01$).
Conclusion: Although the genetics of asthma is complex, involving polygenic and heterogenous effects, we have shown that common variants of IL-13 signaling have identifiable predictive effects in an unselected population. Novel predictions demonstrated between IL13, IL4RA, and STAT6 with clinical atopy and total IgE levels offer new targets for therapeutic manipulation and improve our understanding of the underlying complex genetic associations underpinning asthma and atopy.

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

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Rationale: Cilia play a critical role in mammalian embryogenesis, especially for normal positioning of internal organs. The expression of ciliated bronchial epithelium (CBE) 1 is highly associated with bronchial ciliated epithelial cells (*AJRCMB* 2004;**31**:491–500). In order to explore the role of CBE1during differentiation in lung development, we have studied its expression in mouse embryonic and adult lungs and human embryonic lungs (HEL) in vitro and in vivo.
Methods: MF-1 mice were time mated and embryonic lungs were harvested at embryonic day (ED) 11–19 and postpartum day (PD) 1 and 8 and from adult mice (AM) (n=5–8); human embryonic lungs (HEL) (7–10 weeks) were collected following the Polkinghorne Committee guidelines after informed consent and ethical approval. HELs were dissected and explants were cultured in vitro for 3–18 days. Samples were processed for mRNA analysis using RT-qPCR and embedded in glycol methacrylate resin for immunohistochemistry (IHC).
Results: In the mouse lungs, CBE1 was strongly induced at ED11, declined between ED12–15 and then increased again from ED16, with highest levels postpartum and in the adult lung ($p<0.001$). In contrast, expression of Foxj1, a forkhead transcription factor which regulates expression of ciliated cell genes, was low at ED11 but increased from ED15. In HELs, CBE1 mRNA was first detectable at about 10 weeks post conception (wpc), whereas that of Foxj1 was detected from 7 wpc. No expression of tektin-1 was observed up to 10 wpc. IHC showed that CBE1 was hardly visible at 10 wpc, but was strong at 12.3 wpc, with concomitant appearance of visible cilia. When HELs at 9 wpc were cultured in vitro, CBE1 mRNA was temporally increased with more than a one hundred-fold increase in mRNA expression at day 12 ($p=0.03$) and day 18 ($p=0.01$) compared to day 0 (start of the culture). IHC showed no expression at day 0 and 6 but could be strongly detected in the developing epithelium at day 18.
Conclusions: The timing of induction of CBE1 was similar to that of Foxj1, consistent with a role for CBE1 in ciliogenesis. However, the high expression of CBE1 in murine lung primordia (ED11) suggests that it may play an additional early role in asymmetric lung development, possibly as a regulator of monociliary function.

Funded by Asthma Allergy & Inflammation Research (AAIR) Charity (UK) and the Roger Brooke Charitable Trust (UK).

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

Diagnosis and management of pleural disease

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

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Background: Great controversy still exists regarding the role of radical versus less invasive surgery for the management of malignant pleural mesothelioma (MPM). While there is initial evidence that radical surgery may benefit younger patients there is no information available regarding the procedure of choice for the older age group. Standard of care in the elderly is symptom control. Radical excision has been offered to this age group but remains controversial. VATS debulking offers a probably less morbid therapeutic alternative. We aimed to evaluate the results of these alternative techniques.
Methods: We retrospectively analysed the data for 63 concecutive patients with MPM undergoing therapeutic surgery, Stage I-III pleuropneumonectomies n=13 and radical decortications n=8) and non-radical (VATS decortications n=42) surgery in our unit over a period of 9 years. Survival data were analysed with the Kaplan Meier method and perioperative variables were compared.
Results: In the pleuropneumonectomy (EPP) group 30 day mortality was 3/13 (23%) and the median survival was 247 days (8.2 months). In the Radical Decortication Group 30 day mortality was 1/8 (12.5%) and the median survival was 373 days (12.4 months). In the VATS Decortication Group 30 day mortality was 3/42 (7.1%) and median survival was 433 days (14.4 months).
Conclusion: In the over the age of 65 patients with malignant pleural mesothelioma minimally invasive debulking surgery is the preferred therapeutic option.

S127 EPIDEMIOLOGY OF SPONTANEOUS PNEUMOTHORAX: A HOSPITAL BASED STUDY

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Background: Pneumothorax is the presence of air in the pleural cavity. Spontaneous pneumothorax (SP) occurs without a preceding cause and can be subdivided into primary spontaneous pneumothorax (PSP), occurring in otherwise healthy individuals and secondary spontaneous pneumothorax (SSP) which occurs in patients with an underlying lung disease. There is a paucity of data on the epidemiology of pneumothorax, especially from the Indian Subcontinent.
Aim: This study describes the aetiology and clinical profile of patients admitted with a diagnosis of SP to a large hospital in India.
Methods: This was a descriptive prospective hospital based study. All the patients admitted at a tertiary care hospital with a diagnosis of SP over a two year period were included in the study. Relevant clinical and epidemiological details were recorded on a proforma for analysis. Patients were considered as having a PSP if an underlying aetiology could not be found and a SSP when the cause could be established. Risk factor analysis for PSP was done for variables like age, sex, smoking, body mass index, height, upper to lower segment ratio and presence of

Abstract S126

	n	Age (mean)	M/F	30 day mort	Post op stay days	Median surv months
EPP	13	68	13/0	3/13, 23%	36	8.2
Radical Decort	8	67	8/0	1/8, 12.5%	14	12.4
VATS Decort	42	71	38/4	3/42, 7.1%	14	14.4

exertion at the onset using patients with SSP as controls. Comparison was made between the PSP and SSP groups. $p<0.05$ was taken as being significant.
Results: The most common cause of SSP was found to be pulmonary tuberculosis (41.66%). Age distribution showed a biphasic pattern, the first peak occurring between 20 to 30 years of age and second between 40 to 50 years. Male to female ratio was 5:1. Incidence of SP was found to be 99.94/year/100 000 hospital admissions. Incidence figures for PSP and SSP were 19.98 and 79.96/year/100 000 hospital admissions respectively.
Conclusions: The epidemiology of SP in India is slightly different from that seen in the West. The relative incidence of SSP was comparatively higher as compared to reports from the West. Pulmonary tuberculosis was the most common cause of SSP as compared to chronic obstructive pulmonary disease in the West.

S128 BEDSIDE TRANSTHORACIC ULTRASONOGRAPY BY RESPIRATORY PHYSICIANS

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Background: Transthoracic ultrasonography (TUS), has acquired a wider use by Respiratory Physicians. Historically these procedures were performed in the Radiology department by skilled Ultrasonographers or Radiologists. Newer ultrasound devices are lightweight and user friendly. Respiratory Physicians can learn bedside TUS to asses the pleural space which can help in patient management.
Aim: We report our experience with bedside TUS, indications, outcomes and safety of bedside TUS. We also wanted to determine how many scans need to be performed under supervision to train a Respiratory Physician in TUS.
Methods: Bedside TUS is being done by Respiratory Physicians in our hospital for the past one year. We maintained a record of the patient details and indications for TUS as well as procedures done subsequent to scanning and their complications. We prospectively assessed the training requirements needed by the trainees in Respiratory Medicine to become competent with bedside TUS. Record was kept whether a scan was performed independently or under supervision. Data was analysed as to number of scans needed to be done under supervision before becoming competent to perform independent bedside TUS.
Results: A total number of 260 bedside thoracic ultra sound scans were performed. The indications included small pleural effusion (n = 154), large pleural effusion (n = 49), empyema (n = 13), pleural thickening (n = 19), pneumothorax (n = 2), and scans for suspected pleural disease in which no abnormality of the pleura was found (n = 23). A total number of 110 procedures, which included pleural aspiration, drainage and biopsy, were successfully performed. Other than one patient who developed a pneumothorax post aspiration of a small pleural effusion necessitating an emergency pleural intubation, no complications were noted. During this period we assessed nine respiratory physicians in training. It was found that a median of 10 (range 8–17) thoracic ultrasonography procedures was required prior to trainees becoming competent in the technique of TUS.
Conclusions: Transthoracic ultrasonography can easily be learned as a bedside procedure. It improves diagnostic yield and safety of pleural procedures. Our data support the Royal College of Radiologists' guidelines recommending 15 procedures to be performed under supervision before Respiratory Physicians can become competent.

Abstract S129

Complication	Patient number (%)
Skin/intrapleural/suture site infection	0
Haemorrhage	1*
Pneumothorax complicating effusion†	4
Misplacement	1
Displacement ''drain fell out''	21
Drain blockage	9

*73 year old man with coexisting myelodysplasia and thrombocytopaenia developed a chest drain site haematoma.
†Excluding trapped lung.

S129 AN AUDIT OF SELDINGER INTERCOSTAL CHEST DRAIN COMPLICATIONS

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Introduction: The British Thoracic Society Pleural Disease guidelines were introduced when most hospitals were using blunt dissection for chest drain insertion (BTS Pleural Disease Group. *Thorax* 2003;**58**(Suppl II)). It is now routine practice in most UK centres to use small (10–14F) bore chest drains inserted by the Seldinger technique and in our hospital 12F Seldinger tubes are used initially in all medical patients requiring pleural drainage. A complication rate of 18% has been quoted for chest drain insertion for all indications (Chan L, *et al. Am J Emerg Med* 1997;**15**:368–70) but comparable data for Seldinger systems are lacking.
Aim: To quantify the frequency of complications from 12F Seldinger chest drains.
Method: A retrospective case note audit of 100 randomly selected patients (59M, 41F/mean age 61 years (range 19–92 years)) requiring pleural drainage between March 2005 and 2006 was performed.
Results: 74% were emergency admissions. Symptomatic malignant effusions were the most frequent indication (46%) for chest tube insertion, followed by pneumothorax (23%) and empyema (14%). Ultrasound guidance was utilised in 24% (20% insertion, 4% skin site marked). The mean time to drain removal was 1.5 days. 13% required chest drain replacement (9% had ''fallen out'' and in 4% the initial chest drain was blocked), 4% were re-sited with radiological assistance. There were two cases of trapped lung and 8% of the audit population were referred for cardiothoracic input (2% as outpatients). Pleurodesis was delayed in 10% of cases as a result of chest drain complications.
Conclusion: Serious complications from Seldinger small bore chest drains are few with aberrant tube placement rates comparing favourably to those previously quoted (1% *v* 6%). There were no empyemas on initial tube insertion (other series report up to 6%). However, there is a substantial rate of chest tube displacement necessitating further pleural procedures which add to patient morbidity and prolong hospital stay.

S130 THE EFFECT OF BLIND PERCUTANEOUS PLEURAL BIOPSY ON SUBSEQUENT VIDEO ASSISTED THORACOSCOPY

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

Abstract S130

	BPPB group, n = 12	Control group, n = 22
Cancer?	6 (50%)	18 (82%)
Diagnostic yield of VATS	5/6 (83%)	15/18 (83%)
Pleurectomy *v* VATS Biopsy	6 (50%) *v* 6 (50%)	12 (55%) *v* 10 (45%)
Lung biopsy	2 (17%)	6 (27%)
Intraoperative complications	0	1
Postoperative complications	2	12
Mean length of operation	47 minutes	53 minutes
Mean time under surgeons care	4.8 days	7.8 days
Turbid effusion reported	1 (8%)	5 (42%)
Blood stained effusion reported	4 (33%)	6 (27%)
Adhesions reported	1 (8%)	5 (42%)

75% for tuberculosis and 57% for carcinoma. Concerns were raised at the 2004 British Thoracic Society Winter Meeting that performing a BPPB may increase complication rates and decrease diagnostic yield of subsequent video assisted thoracoscopy (VATS). Our aim was to explore these concerns further.
Methods: Patients undergoing a diagnostic VATS for pleural effusion between December 2004 and January 2006 were identified from our hospitals thoracic surgery database and case notes. Patients were excluded if they underwent decortication or if any lung surgery besides lung biopsy was carried out.
Results: A total of 34 patients were identified, of which 12 had had non-diagnostic BPPB prior to VATS, the remaining 22 patients forming the control group. Age and Body Mass Index did not differ significantly between the two groups. Median and mode performance score (PS) in both groups was 1, although the control group had a higher percentage of patients with PS 3–4 (18%) than the BPPB group (8%). Age adjusted Charlson Comorbidity Index Scores (CCIS) also tended to be higher in the control group (45% above 6 compared to 17% in the BPPB group) although the mode and median CCIS for both groups were similar. The results are summarised in the table.
Conclusion: The tendency towards higher PS and CCIS in the control group may explain the longer operation times and lengths of stay in this group. However, it is reassuring that this survey suggests that having a BPPB does not interfere with the diagnostic yield or the complication rate of subsequent VATS, supporting the rationale for including BPPB in the diagnostic pathway for the investigation of unilateral pleural effusions.

Therapeutics for tuberculosis

S131 TUBERCULOSIS DRUG RELATED HEPATITIS IN PATIENTS TREATED WITH STANDARD RIFAMPICIN/ ISONIAZID/PYRAZINAMIDE THERAPY OVER A 25 YEAR PERIOD

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Introduction: Drug-induced hepatitis is known to occur in a proportion of patients on treatment for active tuberculosis (TB). Some colleagues feel that this is increasing in incidence and have reported rates of grade 3 or 4 hepatitis (transaminases either >5× normal; or >20× normal) requiring interruption to treatment in over 10% of patients independent of HIV status.
Methods: Drug reactions, together with presumptive drug, have been recorded prospectively since 1981, when short course chemotherapy using rifampicin (R) and isoniazid (H) for 6 months, supplemented by 2 months initial pyrazinamide (Z) was introduced. We examined prospective data on 1710 patients treated between January 1981 and December 2005. Variables examined included age, sex, ethnic origin, and causative drug.
Results: 845 (49.4%) were males and 865 (50.6%) were females. 411 (24.03%) were white, and 1278 (74.74%) were of South Asian origin. Only 21 (1.23%) were of Black-African or other ethnic origin. 48 (2.81%) of all patients had drug related hepatitis. This equated to 22 (5.35%) whites and 26 (2.03%) south asian and 0 other. Since there were only 21 of other ethnic group with no hepatitis cases this group were not analysed further. Statistical analysis showed that the hepatitis rate was significantly higher for all white cases (χ^2 13.24; $p<0.001$), with the significance maintained for females (χ^2 11.83; $p<0.01$), but not for males (χ^2 3.23; $p>0.05$). There was no significant sex difference within ethnic groups (χ^2 2.23 for white; χ^2 0.13 South Asian; both $P>0.05$). There was also no significant difference with age in either ethnic group using under/over 20, 30, 40, 50, 60, or 70 years as the variable tested. The drug reaction rate over time showed 15/497 (3.02%) for 1981–85; 4/320 (1.25%) for 1986–90; 7/266 (2.63%) for 1991–95; 12/299 (4.01%) for 1996–2000; and 10/328 (3.05%) for 2001–05. There was no statistical trend over time (χ^2 4.62: 4 degrees of freedom: $p>0.05$). Of the 48 cases of hepatitis 27 (56.3%) were attributed to pyrazinamide, 15 (31.3%) to rifampicin, 5 (yy%) to isoniazid (10.4%), and the 1 (2%) fatal case occurred on all 3 drugs.
Conclusion: This study of a 25 year prospective cohort shows just over 3% of significant hepatitis overall, which is not rising in incidence. The incidence of hepatitis was higher in the white group overall, but only significantly higher in females. Surprisingly there was no age related effect in either major ethnic group.

S132 COMPARISON OF TWO, TRIPLE-DRUG REGIMENS CONTAINING CLARITHROMYCIN OR CIPROFLOXACIN AND ASSESSMENT OF IMMUNOTHERAPY WITH M VACCAE IN THE TREATMENT OF LUNG DISEASES CAUSED BY M AVIUM-INTRACELLULARE-SCOFULACEUM (MAIS OR MAC), M MALMOENSE AND M XENOPI

Dr I. A. Campbell, on behalf of Research Committee of British Thoracic Society (BTS). *Llandough Hospital, Penarth, Wales*

The previous BTS trial in patients with lung diseases caused by these mycobacteria showed that two years of rifampicin (R) and ethambutol (E) +/− isoniazid achieved results as good as or better, and were better tolerated, than previous 5 or 6-drug regimens containing second or third line antimycobacterial drugs. Clarithromycin (Clari) and ciprofloxacin (Cipro) are active in vitro against MAIS, M malmoense and M xenopi. In this further trial patients were treated with 2 years of RE Clari or RE Cipro, with an optional further randomisation to immunotherapy with M vaccae or not. Dosages were: rifampicin 450 or 600 mg om, ethambutol 15 mg/kg om, clarithromycin 500 mg bd, ciprofloxacin 750 mg bd, orally. Four doses of M vaccae were given intradermally over the first 6 months. Patients aged 16 years and over, with clinical and/or radiological evidence of active mycobacterial lung disease and with sputum positive on culture on at least two occasions were eligible for entry. Pregnancy or co-infection with M tuberculosis or M bovis or HIV excluded the patient. Clinical and bacteriological outcomes were monitored annually up to 5 years. Patients with positive culture at 12 months were given Clari or Cipro as a fourth drug for the rest of treatment.

From 1995 to 2000, 191 physicians entered 386 patients (177 MAIS, 174 M malmoense and 35 M xenopi), 194 randomised to RE Clari and 192 to RE Cipro). At entry the treatment groups were broadly comparable in terms of age, gender, cavitation and extent of disease. In the RE Clari group 81 (42%) died, 6 (3%) from the mycobacterial disease, cf. 78 deaths (41%) in the RE Cipro group, 5 (3%) attributed to mycobacterial disease. 19 (10%) of those allocated to RE Clari either failed to become culture negative by end of treatment or relapsed thereafter, cf 25 (13%) in the RE Cipro group. Cipro was stopped in 16% because of unwanted effects, cf 8% with Clari. The failure of treatment, relapse and death rates differ little, if at all, from those of the previous BTS study. Those who had received M vaccae fared much the same as those who had not received it.

S133 OUTCOME OF TUBERCULOSIS TREATMENT: BLACKBURN 1986–2005

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Introduction: The outcome our tuberculosis (TB) programme for 1988–2000 was described in 2002 (Ormerod LP *et al. Int J Tuberc Lung Dis* 2002;**6**:862–5) using the European definitions of outcome (Veen *et al. Eur Resp J* 1998;**12**:505–10).
Methods: We have added 2 more years' retrospective data (1986–87) and 5 more years' data (2001–05) collected prospectively and reported under HPA enhanced surveillance.
Results: A total of 1189 cases were notified, with 342 definite (culture positive) pulmonary cases. Of the 328 treated in life; 304 received self-administered treatment (SAT) and 24 directly observed therapy (DOT), with an 89% cure/completion rate and 10.8% deaths. The WHO target is 85% cure/completion rate for confirmed respiratory cases. The relapse rate with SAT was 2/281 (0.6%) and for DOT was 1/24 (4.2%). 150 cases of non-culture confirmed pulmonary tuberculosis (TB), 207 cases of other respiratory TB (pleural effusion and isolated mediastinal lymphadenopathy), and 478 non-respiratory TB cases were treated, largely by SAT (all but 5 cases). 12 cases with prior treatment history were treated by DOT. For all cases in the programme, there was a cure/completion rate of 93.7%, a 5.2% death rate, no treatment failures, 0.25% treatment interruption and 0.85% transferred out. The relapse rates for non-culture confirmed pulmonary TB treated by SAT was 1/147 (0.6%), for other respiratory TB 0/207 (0%), and for non-respiratory TB 3/477 (0.6%).
Conclusion: Very high cure/completion rates were achieved by regular (at least monthly) but randomly monitored SAT, with only 41 patients (including 12 with prior treatment histories) or 3.5% of cases having selective DOT. Universal DOT could only at best have improved outcome by under 1% but at greatly increased cost, as the 0.25% with treatment interruptions completed treatment, and most of the 0.85% transferred out to other areas are likely to have done so. Our 20 year cohort data support a policy of selective rather than universal DOT for TB treatment,

but we are fortunate to have a fairly stable and cooperative local population, with only a small number of ''difficult to reach'' patients, plus those with a prior treatment history requiring, or those demonstrating non-compliance during treatment, requiring DOT.

S134 MANAGING MULTI-DRUG RESISTANT TUBERCULOSIS IN THE UK

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Background: Past (BTS) and current (NICE) guidelines for the management of multidrug resistant tuberculosis (MDR-TB) recommend that treatment should be carried out by, or in consultation with, physicians who have specific experience with such cases. This study investigates the degree to which this advice is followed.
Methods: A postal questionnaire was sent to 259 hospital trusts across the UK, addressed to the individual thought likely to be the principal physician for tuberculosis (TB). Recipients were requested to re-direct the questionnaire if appropriate. A second copy was sent to non-responding hospitals after 3 months.
Results: Responses were received from 186 consultants who considered themselves the most experienced TB physician in their hospital (response rate 186/259 hospitals; 72%). Only 15 physicians reported seeing more than one case per year over the previous 5 years, of whom 7 worked in London. 100/186 respondents (54%) would refer all MDR-TB to another physician. 38/186 (20%) stated they would manage MDR-TB with advice from another physician. 48/186 (28%) of respondents felt they had the expertise to manage MDR-TB without advice from others. 33 of these 48 (69%) had seen 1 case or fewer per year over the previous 5 years and 8 of them (17%) had seen none in that period. 16 of the consultants seeing 1 or fewer cases/year would also accept MDR-TB referrals from other physicians.
Discussion: Even among consultants taking the clinical lead for TB in their hospital, very few encounter more than one case per year of MDR-TB. Some with little or no experience of MDR-TB were willing to manage patients without advice from others, and some who would manage it with advice were uncertain about sources of help. A balance must be struck between the desirability of treatment in an experienced setting, and the patient's need to be close to home, but our study suggests that this balance is in many cases not the correct one. Developing a more formalised advice network for MDR-TB management may be a step forward.

S135 FACTORS CONTRIBUTING TO DELAY IN DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

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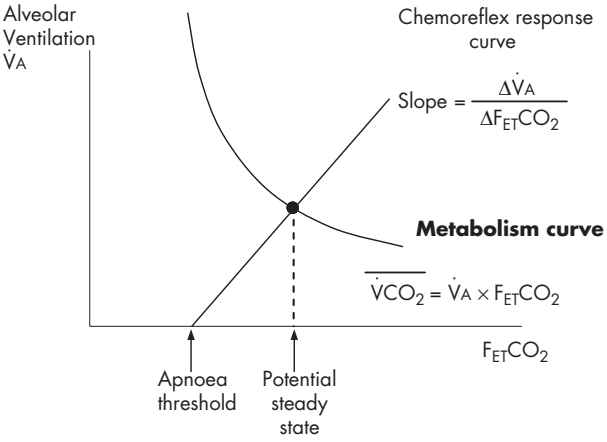
Aims: To study the factors, which contribute to delay in diagnosis and treatment of tuberculosis (TB) in the Borough of Greenwich. The incidence of TB has risen in this catchment area, with infection rates having risen from 36/100 000 to 47/100 000 since 1997.
Methods: We reviewed 292 cases of TB treated between 2003–05. We examined the time taken from the first suggestive chest *x* ray (CXR) to commencement of treatment. The radiological data were collected and reviewed using the HISS and PACS system. We reviewed all the notes in which there was delay of over 28 days from the initial suggestive CXR to treatment.
Results: A total of 56 out of 292 cases had a delay of over 28 days from the initial suggestive CXR to commencement of treatment. The median time of delay was 56 days. The reasons for delay were; patients not keeping their clinic appointments in 9 cases (range of 68–851 days), delays in investigation in 19 cases (range of 32–649 days), CXRs not being acted upon or delays in referrals in 15 cases (range of 41–483 days), diagnosis not suspected due to concomitant lung disease in 6 cases (range of 92–1020 days) and delays in diagnosing pleural effusions in 7 cases (range of 44–793 days). The patients who failed to attend their clinic appointments were all immigrants. Concomitant lung disease was a confounding factor in indigenous white patients in 5 out of 6 cases.
Conclusion: There needs to be an increased awareness of the rising incidence of TB, particularly among the immigrant population. The mobility of this group, with some not having fixed addresses and some not having an appointed general practitioner seemed to contribute to poor clinic attendance. In all cases the diagnostic process needs to be speeded up. A high index of suspicion is needed in patients with other chronic lung diseases.

Respiratory physiology and clinical science

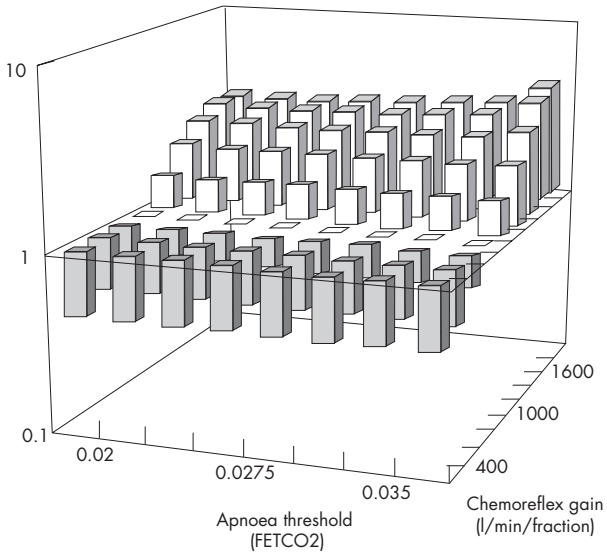
S136 APNOEIC THRESHOLD: A TRUE DETERMINANT OF CARDIORESPIRATORY CONTROL STABILITY OR A MARKER OF CHEMOREFLEX GAIN?

C. H. Manisty, K. Willson, R. Wensel, Z. I. Whinnett, J. E. Davies, W. L. G. Oldfield, J. Mayet, D. P. Francis. *International Centre for Circulatory Health, Imperial College & St Mary's Hospital, London, UK*

Background: Clinical observational studies suggest that periodic breathing is more common in subjects with low end-tidal CO_2, high apnoeic thresholds or high chemoreflex sensitivity. It is, however, difficult to determine the individual effect of each because they are intrinsically related (fig 1). Modelling studies, in contrast, can be designed to distinguish the effect of isolated changes in a single parameter. Our model distinguishes the effect on cardiorespiratory stability of independent changes in chemoreflex sensitivity, end-tidal CO_2 or apnoeic threshold.
Method and Results: To distinguish the effect of isolated changes in chemoreflex sensitivity, mean $FETCO_2$ and apnoeic threshold, we employed a modelling approach to break their obligatory in vivo interrelationship. We found that a change in mean CO_2 fraction from 0.035 to 0.045 increased loop gain by 70 (0.083)% ($p<0.0001$), irrespective of chemoreflex gain or apnoea threshold. A 100% increase



Abstract S136 Figure 1.



Abstract S136 Figure 2.

in the chemoreflex gain (from 800 l/min/fraction CO_2) resulted in an increase in loop gain of 275 (6)% ($p<0.0001$) across a wide range of values of steady state CO_2 and apnoea thresholds (fig 2). Increasing the apnoea threshold $FETCO_2$ from 0.02 to 0.03 had no effect on system stability. Therefore of the three variables, the only two destabilising factors were high gain and high mean CO_2; the apnoea threshold did not independently influence system stability.

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

S137 CAN CARDIAC PACEMAKERS DIRECTLY CONTROL VENTILATION?

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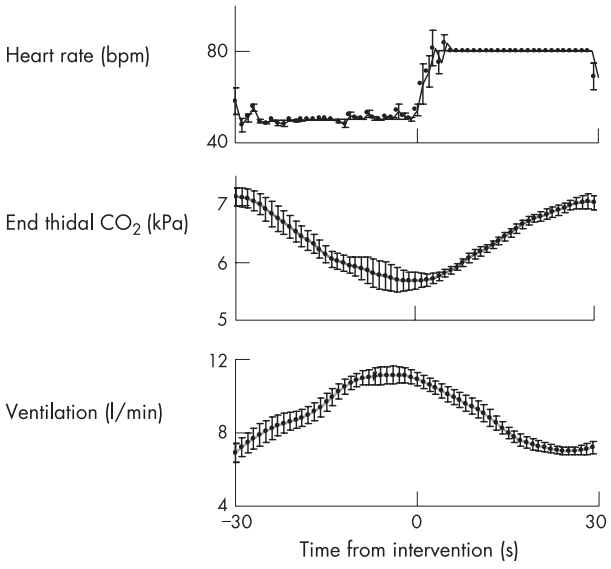
Background: In periodic breathing in chronic heart failure and central sleep apnoea, there are repeated oscillations in ventilation and CO_2, with unstable cardiorespiratory control.

Using patients with pre-existing pacemakers, we tested the hypothesis that dynamic changes in cardiac output acutely affect the delivery of CO_2 into the lung, and thereby influence ventilation.

Method and Results: We studied the effect of repeated alternations in heart rate by 30 bpm and period 60s, on cardiorespiratory parameters in 22 subjects with implanted cardiac pacemakers and stable breathing patterns (14 with systolic heart failure and 8 subjects with normal systolic function). This pattern of heart rate alternation elicited consistent oscillations in both $ETCO_2$ and ventilation exhibited consistent sinusoidal oscillations with period 60 seconds (fig). The mean amplitude of oscillations in $ETCO_2$ was 4.2 (2.5)%, with a mean amplitude of oscillations in ventilation of 12.2 (9.4)%. The magnitude of the oscillations generated in ETCO2 correlated with the cardiac output changes produced by the heart rate alternation ($r=0.59$, $p=0.001$). Subjects with impaired systolic function had a greater ventilatory response to changes in $ETCO_2$ (716 (412) l/min/atm *v* 387 (122) l/min/atm, $p=0.04$).

Conclusions: Cardiac output modulation using pacemakers can elicit consistent oscillations in CO_2 and ventilation in patients with stable cardiorespiratory control. The size of effect depends on the magnitude of the cardiac output response. This mechanism could be potentially therapeutic, if appropriately harnessed and timed to counteract the fluctuations in CO_2 and ventilation seen in periodic breathing and central sleep apnoea, thus avoiding the need for ventilatory support.



Abstract S137 The effect of acute heart rate alternations on end tidal CO2 and ventilation in one subject (averaged over 6 cycles).

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

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

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

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

S139 EXERCISE VENTILATION IN DIFFUSE PLEURAL DISEASE

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This study investigates the causes for an increased exercise ventilation during moderate exercise in men with diffuse pleural disease, but no significant angina, who were referred by Pneumoconiosis Medical Panel during 1980–90. Lung function was measured by standard methods[1] and progressive treadmill exercise was performed up to an O_2 uptake of 45 mmol/min (1.0 l/min). Ventilation at this work rate ($V'E_{st}$) was considered abnormal if it exceeded the normal range of 17–30 l/min.[2] Pattern of breathing was assessed in terms of tidal volume and respiratory frequency at a ventilation of 30 l/min (designated *Vt*30 and *fR*30 respectively) for which the reference values were with respect to forced vital capacity. The study aimed to investigate by relatively simple methods the contributions to an increased $V'E_{st}$ of (a) uneven lung function, (b) increased alveolar ventilation sufficient to raise the respiratory exchange ratio (RER $\geq$0.9)) and (c) a shallow breathing pattern that materially increased the ventilation of the tidal deadspace.[3] A clinical grade of breathlessness of 4 or 5[4] was taken as evidence for impaired capacity for daily living, whilst a normal transfer factor was assumed to exclude asbestosis.

There were 41 men with a normal transfer factor, who were able to exercise at the designated work level and had radiographic evidence for diffuse pleural thickening, extensive calcified plaques or filling of at least one costophrenic angle. One man was not considered further on account of functional hyperventilation and another had incomplete data. Amongst the remainder $V'E_{st}$ was linearly related to *fR*30. In 4 men the capacity for daily living was impaired; in one the incapacity was due to obesity and in the other three the cause was respiratory. In these men and in 7 others the $V'E_{st}$ was increased. The mechanisms were found to be one or more of those given above, including in two of them dynamic shallow breathing. In two of the three men with incapacity the respiratory impairment would have been apparent from simple spirometry. In the third the principal contributory factor was shallow breathing on exercise without hyperventilation or other evidence for functional overload. The lung compliance was within normal limits.

Conclusion: In diffuse pleural disease dynamic shallow breathing contributes to disability and respiratory exercise testing may be diagnostic.

1. **Cotes JE**, *et al. Lung function: physiology, measurement and application in medicine*, Sixth edition. Blackwell Publications, 2006.
2. **Weller JJ**, *et al. Br J Ind Med* 1988;**45**:532–7.
3. **Cotes JE**, Reed JW. *Proc Physiol Soc* 2006;**3**:C39.
4. MRC Questionnaire on respiratory symptoms. London: Medical Research Council 1976.

S140 FLIGHT ASSESSMENT IN PATIENTS WITH RESPIRATORY DISEASE: AGREEMENT BETWEEN HYPOXIC CHALLENGE TESTING AND PREDICTIVE EQUATIONS

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Background: Predictive equations have been proposed as a simpler and cheaper alternative to hypoxic challenge testing (HCT) for determining the risk of in-flight hypoxia. The aim of this study was to assess agreement between the individual hypoxic response measured during HCT and predictive equations.
Methods: Patients with chronic obstructive pulmonary disease (COPD) n = 15, mean (SD): age (years), 62 (8) FEV1 % predicted, 38 (13); interstitial lung disease (ILD) n = 15: age (years), 69 (13) FEV1 % predicted, 83 (28); cystic fibrosis (CF) n = 15: age (years), 27 (6) FEV1 % predicted, 44 (19) were studied. Spirometry was recorded pre testing and oxygen saturations (SpO_2) were recorded pre, post and during HCT. Capillary ear lobe samples were collected and analysed for pH, PCO_2 and PO_2, pre and post testing and when $SpO_2 = 85\%$. A HCT was performed using the Ventimask method. The PaO_2 at altitude was estimated for each group using four published predictive equations which use values of PaO_2 at sea level (breathing room air) and lung function measurements to predict altitude PaO_2. The results were interpreted using the BTS recommendations for prescription of in-flight oxygen post HCT; $PaO_{2Alt} > 7.4$ kPa in-flight oxygen not required; $PaO_{2Alt} < 6.6$ kPa in-flight oxygen required; PaO_{2Alt} 6.6–7.4 kPa borderline for in-flight oxygen which may require further investigation.
Analysis: The Stuart Maxwell test of overall homogeneity was used to assess agreement between hypoxic challenge test results and each of the predictive equations.
Results: During HCT the $PaO_{2\ (ground)}$ kPa mean (SD) in each disease group decreased; COPD from 8.37 (0.85) to 6.9 (0.65); ILD from 8.9 (0.53) to 7.3 (0.64); CF 9.6 (0.86) to 7.5 (0.91). In each group the results show that fewer patients would require in-flight O_2 if prescription was based on HCT compared to the four predictive equations; COPD, HCT n = 6, equations n = 13–15; ILD, HCT n = 1, equations n = 1–15; CF, HCT n = 2, equations n = 7–12. With the exception of equation 3, these differences reached statistical significance ($p < 0.05$).
Conclusions: Predictive equations tend to overestimate the need for in-flight supplemental oxygen. The cost of in-flight oxygen can be substantial and as some airlines do not permit its use, HCTs should be performed to ensure accurate in-flight oxygen prescription for patients with respiratory disease.

Basic mechanisms in acute lung injury

S141 DIFFERENTIAL EFFECTS OF VASCULAR ENDOTHELIAL GROWTH FACTOR ISOFORMS ON PRIMARY HUMAN LUNG MICROVASCULAR ENDOTHELIAL CELL PROLIFERATION

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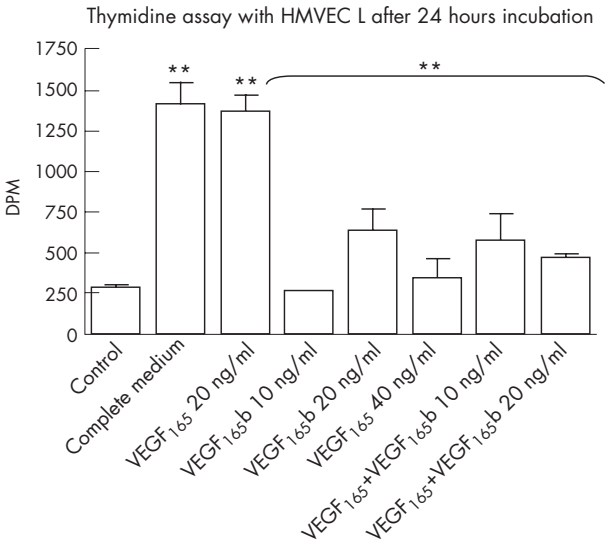
Vascular endothelial growth factor (VEGF) is a potent permogenic and mitogenic factor. It has been detected in high concentrations within the normal lung, compartmentalised to the alveolar space. In patients with acute respiratory distress syndrome we have shown that intrapulmonary levels of VEGF fall and plasma levels increase with a return to normal levels in survivors. Human VEGF commonly occurs as at least three different isoforms formed by pre mRNA splicing- $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$, characterised by their exon number and named according to their base pair number. $VEGF_{165}$, the dominant form,



Abstract S141.

and $VEGF_{121}$ are soluble products, whereas $VEGF_{189}$ remains primarily cell-associated. Another family of VEGF splice variants, $VEGF_{xxx}b$ has been identified, formed by splicing from exon 7 into the previously assumed 3′ untranslated region (UTR) of the VEGF mRNA. $VEGF_{165}b$ has been shown to have significantly differing biological effects to that of $VEGF_{165}$. We hypothesised that the balance between these two families of VEGF may play a critical role in the development of ARDS. As an initial step we have investigated their effect on primary human pulmonary microvascular endothelial cells (HMVEC- L, Cambrex). In order to explore this hypothesis we cultured HMVEC- L in the presence of serial concentrations of $VEGF_{165}$ and $VEGF_{165}b$. Proliferation was assessed by ^{3}H-thymidine incorporation. $VEGF_{165}$ significantly increased proliferation but no effect was detected with $VEGF_{165}b$ compared to control. However in the presence of $VEGF_{165}b$ the proliferative effect of $VEGF_{165}$ was inhibited. These data suggest that VEGF isoforms may have a differential effect on HMVEC-L with significant consequences for functional outcome in the human lung.

S142 HEME OXYGENASE-1 IS INDUCED IN HUMAN NEUTROPHILS FOLLOWING SURGERY REQUIRING CARDIOPULMONARY BYPASS

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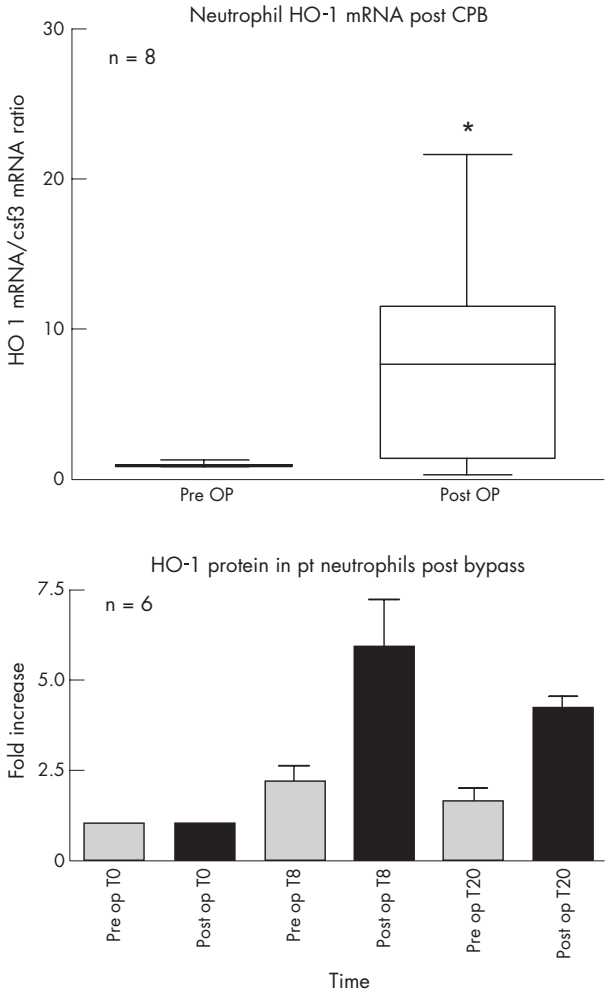
Introduction: The systemic inflammatory response syndrome (SIRS) is a common consequence of cardiac surgery necessitating cardiopulmonary bypass (CPB). SIRS if severe is associated in some patients with the development of organ dysfunction including the acute respiratory distress syndrome (ARDS). Neutrophil clearance through apoptosis and subsequent ingestion by macrophages is an essential step in the resolution of such inflammation, whilst delayed neutrophil apoptosis is observed following CPB. We have previously shown that haemoglobin, which is released from erythrocytes during haemolysis, induces the anti-apoptotic protein haem oxygenase-1 (HO-1) and delays spontaneous apoptosis in neutrophils from healthy volunteers. We now speculate that HO-1 is induced in neutrophils from patients undergoing surgery requiring CPB.
Methods: Blood was taken from 8 patients undergoing cardiac surgery, before and two hours after the cessation of CPB. Neutrophils were separated by discontinuous gradient centrifugation. mRNA was obtained using TRI reagent. Alternatively, isolated neutrophils were incubated in DME medium for a further 8 hours before collection in cell lysis buffer. mRNA concentrations were estimated by real time PCR and HO-1 protein levels were measured using a commercially available ELISA.
Results: HO-1 mRNA and protein were raised in peripheral blood neutrophils obtained from patients following CPB in comparison with neutrophils obtained prior to bypass.
Conclusion: HO-1 is induced in neutrophils following CPB. This induction may be due to haemolysis and may also contribute to delayed neutrophil apoptosis, and the development of SIRS and its more serious sequelae including ARDS, following CPB.



Abstract S142.

S143 PULMONARY FIBROSIS IS AN EARLY FEATURE OF ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME

D. C. J. Howell[1], M. Falzon[2], N. Bilbe[2], S. E. Bottoms[1], G. J. Laurent[1], R. C. Chambers[1], G. J. Bellingan[1]. *[1]Centre for Respiratory Research, University College London, UK; [2]Department of Histopathology, University College Hospital, London, UK*

Rationale: Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a serious and often fatal condition for which there are currently no pharmacological interventions. We and others have previously provided indirect evidence that fibroproliferation is an early event in the lungs of patients with ALI/ARDS and may contribute to the demise of these patients. In this study we sought to further evaluate when pulmonary fibrosis occurs in patients with ALI/ARDS by histochemical characterisation of lung biopsy tissue.
Methods: We re-evaluated the clinical progress of patients who had undergone postmortem analysis, after time spent on our intensive care unit. We identified 14 patients whose clinical history raised a suspicion of ALI/ARDS. Lung biopsy material was retrieved, stained with Haematoxylin and Eosin and the degree of histological lung injury assessed by an independent pathological expert, in a blinded fashion. The same specimens were then stained with Martius Scarlet Blue for assessment of matrix deposition and Ashcroft fibrosis scoring performed. This analysis ranks degree of fibrosis from 0 (normal) to 8 (complete obliteration of the field), using light microscopy and was undertaken by two blinded observers.
Results: In all patients with clinical suspicion of ALI/ARDS, review of biopsy material confirmed histological evidence of lung injury (14/14). Of note, only 21% (3/14) had histological evidence of lung injury recorded on the postmortem certificate as a contributory factor to the cause of death. For analysis of matrix deposition, patients were divided into two groups, those receiving assisted ventilation for <96 hours (early) and >22 days (late). In the early group, mean Ashcroft fibrosis scores were highly abnormal (4.54 (0.69); n=8)). Mean Ashcroft fibrosis scores were also elevated in the late group (6.38 (0.27); n=4) and were significantly higher compared with the early group ($p<0.05$). Two patients with elevated fibrosis scores were withdrawn from the analysis as in addition to ARDS, they also had evidence of chronic fibrosing lung disease.
Conclusion: In this study we found that histological evidence of ALI/ARDS correlated with clinical suspicion and was frequently under-reported following postmortem analysis. Clinically relevant ALI/ARDS may be more common than published studies report. Importantly, we also show that significant matrix deposition occurs extremely early in the progression of ALI/ARDS and confirm that pulmonary fibrosis is not a late manifestation of this condition. Pharmacological therapies evaluated for the treatment of this syndrome have predominantly concentrated on modulating the inflammatory response. Novel treatments targeting the early fibrotic response in this condition warrant further evaluation.

S144 EXHALED BREATH CONDENSATE GLUCOSE LEVELS PREDICT ADVERSE OUTCOME IN ACUTE RESPIRATORY DISTRESS SYNDROME

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Introduction: Exhaled breath condensate (EBC) collection may enable non-invasive real time sampling of respiratory fluid to quantify markers of inflammation and guide intervention. It has been shown previously that bronchial aspirate glucose in ventilator associated pneumonia is elevated during infection with pathogenic bacteria. This study aimed to look at the relationship between EBC glucose and infection/outcome in patients with acute respiratory distress syndrome (ARDS).
Method: Fifty seven EBC samples were collected for 20 minutes from patients within 48 hours of developing ARDS. EBC was immediately analysed in the ABG analyser (Rapidlab) for glucose. BAL was performed the same day and cultured quantitatively. Patients were divided into 3 groups: group A with glucose<3 mmol/l, group B glucose 3–6 mmol/l and group C with glucose >6 mmol/l.
Results: EBC glucose was significantly higher in non-survivors compared to survivors ($p=0.026$). There was no statistical difference in serum glucose in these groups ($p=0.4863$). %mortality of the groups increased proportionately from group A to C (see table). EBC glucose from infected patients was also significantly higher than non-infected ones ($p=0.009$) although here was no statistical difference between serum glucose in these groups ($p=0.3774$).
Conclusions: EBC glucose is a potential marker of both infection/outcome in ARDS. Since blood glucose did not differ between the groups we suggest that elevated EBC glucose may reflect the severity of epithelial injury. EBC collection may prove to be a useful tool in guiding treatment and intervention in ARDS.

Abstract S144 EBC glucose and outcome

	Patient group			Mean glucose
EBC glucose	**A<3**	**B 3–6**	**C>6**	**1.987**
Survivors	13 (44%)	2 (18%)	0 (0%)	1.125
Non survivors	16	9	5	2.493
Infection - BAL	14	8	4	2.254
No infection - BAL	9	2	1	1.168

S145 ALVEOLAR INFECTION SIGNIFICANTLY DRIVES CHEMOTAXIS BUT NOT THE INFLAMMATORY CELL INFILTRATE IN ACUTE RESPIRATORY DISTRESS SYNDROME

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Introduction: Chemotaxis is the primary mechanism for directed cell movements and is thought to play a vital role in the migration of inflammatory cells in acute respiratory distress syndrome (ARDS). We were interested in looking at the role of significant alveolar infection and

its influence on the underlying chemotactic activity and inflammatory cell infiltrate in ARDS.
Method: Thirty eight bronchoalveolar lavage fluid samples (BALF) were collected within 48 hours of developing ARDS along with 8 normals. BALF were processed for cell counts immediately after bronchoscopy and quantitatively cultured to detect any significant growth (1×10^4). Chemotactic activity was measured in all BALF. They were also assayed for various chemokines (IL1, IL8, IL6, ENA 78, MCP, and RANTES).
Results: We found that the mean chemotaxis induced by BALF in ARDS (8.961) was significantly higher when compared to normals (1.906) ($p<0.0001$). The mean chemotactic activity of BAL with significant growth was significantly higher (10.08) ($n=24$) compared to no growth (7.50) ($p=0.034$, $n=14$). The mean total cell counts in BAL with significant growth was significantly higher (154.87) compared to no growth (55.50) ($p=0.0337$). Although the chemotactic activity and the BAL cell counts were higher in patients with significant growth, they did not correlate with each other ($p=0.2690$, $r=0.1982$). There was no statistical correlation between individual chemokines and chemotactic activity in the BAL samples. The combined mean chemokine values revealed no difference in BAL with no growth (1431.7) compared to BAL with significant growth (1479.4) ($p=0.9228$).
Discussion: Although the cell counts and chemotactic activity is higher in infected BAL there was no direct correlation between the two variables and moreover the combined cytokine levels were not significantly higher. We combined the chemokine values recognising that the role of individual cytokines in chemotaxis and their interactions with each other and the inflammatory cells in ARDS is still unclear. We felt that although the infection in ARDS seems to drive a significant chemotactic activity, the total inflammatory cell infiltrate at the alveolar level would depend on the relative difference between neutrophil chemotaxis and apoptosis effects of ARDS BALF. The net cell count would therefore depend upon the balance between new chemotaxis and reduced cell death due to apoptosis.
Conclusion: We have shown for the first time a significantly raised BALF chemotactic activity in ARDS and that infection seems to significantly drive further chemotaxis. The cell count is not a direct outcome of chemotactic activity. Reduced apoptosis at alveolar level in ARDS may also be responsible and further work needs to done to unravel the exact mechanism involved

S146 MITOCHONDRIAL REACTIVE OXYGEN SPECIES ARE REQUIRED FOR MECHANICAL STRAIN-INDUCED INTERLEUKIN-8 PRODUCTION BY LUNG EPITHELIAL CELLS

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Background: Overdistension of the lung during mechanical ventilation contributes to the mortality of acute lung injury (ALI). Mechanical forces enhance the release of mediators that exacerbate lung damage and contribute to systemic inflammation and death. The neutrophil chemokine interleukin (IL)-8, has been implicated in the pathogenesis of ALI. We have previously demonstrated that stretching monolayers of A549 cells (a human alveolar epithelial cell line), a model of over-distension, increased IL-8 message expression and release. We aimed to elucidate the signaling pathways underlying this process with a view to mitigating ventilator associated lung injury.
Results: Cyclic mechanical strain (30% stretch at 20 Hz for 2 hours (Flexercell 4000X)) of A549 cells was associated with increased nuclear factor-kappa B (NFκB: p65) DNA binding activity and phosphorylation of IκBα. The IKK-2 inhibitor AS602868 (Serono, CH) abolished stretch-induced NFκB DNA binding and IL-8 induction, suggesting that activation of the transcription factor NFκB was required. 30% stretch caused intracellular oxidative stress, as evidenced by a decrease, from 1113 to 438 (mean, $p=0.02$, $n=8$) in the reduced:oxidised glutathione ratio. Stretch-induced oxidative stress was significantly attenuated by N-acetylcysteine (a thiol antioxidant) and rotenone (an inhibitor of mitochondrial complex 1). Finally, A549 cells lacking mitochondria that were subjected to cyclic mechanical strain did not generate reactive oxygen species, activate NFκB or express IL-8 in response to cyclic mechanical strain, whereas these responses could be induced by IL-1β.
Conclusion: These data suggest a specific role for mitochondrion-derived reactive oxygen species acting via the transcription factor NFκB in mechanotransduction in A549 cells.
Support: British Lung Foundation, The Dr Hadwen Trust.
These data have been presented in part at the European Respiratory Society meeting in 2006.

Non-invasive ventilation

S147 THE EFFECT OF SITE AND INSPIRATORY PRESSURE ON THE DELIVERY OF SUPPLEMENTAL OXYGEN THERAPY DURING NON-INVASIVE VENTILATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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Introduction: Supplemental O_2 is frequently added to bi-level non-invasive ventilation (NIV) circuits to maintain $S_a,O_2>90\%$. Oxygen can be added at several points and in the presence of different inspiratory pressures. The effect of varying entrainment sites and inspiratory pressures (IPAP) on PO_2, PCO_2, FiO_2, inspiratory triggering and expiratory triggering in chronic obstructive pulmonary disease (COPD) patients is unknown.
Method: Eighteen patients with stable COPD (mean FEV1 47%) participated in the study. Oxygen was added at 4 sites in the ventilatory circuit (site 1: between mask and exhalation port; site 2: just distal to exhalation port; site 3: at ventilator outlet; site 4: directly into the mask via an inlet). The effect of varying entrainment sites and inspiratory pressures on arterial PO_2, PCO_2, FIO_2, was recorded at 3 minutes. The same full face mask (Respironics, Image 3) and ventilator (Respironics, BIPAP ST 30) was used throughout.
Results: Results for PO_2 are shown at IPAP 10/EPAP 4 (table). Anova was used (Statview version 8.0) to analyse the data. Site 4 (via mask) was associated with a significantly higher PO_2 at all flow rates compared with sites 1, 2 and 3 ($p<0.001$). Site 3 (at ventilator outlet) was associated with the lowest PO_2 at all flow rates, particularly at 15 l/min ($p<0.001$).
Conclusion: During NIV, adding oxygen to the mask at lower IPAPs results in higher oxygen delivery.

S148 AUDIT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH ACUTE TYPE II RESPIRATORY FAILURE: ARE WE GIVING THEM A CHANCE?

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Introduction: The British Thoracic Society recommends the use of non-invasive ventilation (NIV) in COPD patients with an acute exacerbation and persistent respiratory acidosis, despite maximum medical treatment on controlled oxygen therapy.[1] Patients who are unsuitable for NIV or in whom NIV has failed should receive early ITU input. Acute Physiological and Chronic Health Evaluation Scores (APACHE) can be used as a predictor of in-hospital mortality for groups of patients.[2] The aim of this audit was to assess whether on-call physicians used NIV and requested ITU input appropriately.
Setting: A district general hospital with unselected medical takes. NIV facilities are available on the respiratory ward. ITU/HDU facilities are available on site.
Methods: A retrospective audit of 160 case notes from patients with a coded diagnosis of COPD, emphysema, or chronic bronchitis, admitted

Abstract S147 IPAP 10/EPAP 4

Oxygen flow rate in l/min	PO_2 at Site 1 mean (SD)	PO_2 at Site 2 mean (SD)	PO_2 at Site 3 mean (SD)	PO_2 at Site 4 mean (SD)
1	1.66 (0.57)	1.82 (0.51)	1.41(0.41)	3.03 (0.41)
5	5.92 (2.02)	6.76 (1.94)	5.02 (1.61)	10.3 (1.93)
15	18.31 (5.80)	17.46 (5.65)	10.81 (2.62)	26.03 (5.69)

between 1 January and 30 June 2005 was performed. Eight patients were excluded due to incorrect coding. In the remaining patients with persistent type II respiratory failure, an analysis of NIV use, ITU input and APACHE II score was performed.
Results: 29/152 patients (19.1%) had acute type II respiratory failure and fitted the BTS criteria for NIV. In only 11/29 patients (37.9%) was NIV considered and only 5 of those went on to receive NIV. Reasons for failure to progress to NIV were unclear in 4 patients, and no respiratory bed was available for 2 patients. 4/29 (13.8%) patients received ITU review, 3 of whom had received NIV. One patient went on to receive mechanical ventilation due to NIV failure. All of the 29 patients had APACHE II scores of 27 or less, indicating a predicted mortality of less than 51.4% in this group. 23/29 (79%) scored 20 or less, indicating a predicted mortality of less than 28%. There was no correlation between APACHE II score and consideration of NIV or ITU input.
Conclusion: Although NIV is known to reduce in-hospital mortality and the need for invasive ventilation, NIV is still not being utilized appropriately. Only a minority of acutely ill COPD patients are receiving ITU review. As a group, the predicted mortality figures using APACHE II were low. Acute physicians should be giving more consideration to NIV and invasive ventilation in patients with COPD and acute type II respiratory failure.

1. Non-invasive ventilation in acute respiratory failure. British Thoracic Society Standards of Care Committee. *Thorax* 2002;**57**:192–211.
2. **Knaus W**, *et al.* APACHE II: A severity of disease classification system. *Critical Care Medicine* 1985;**13**:818–30.

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

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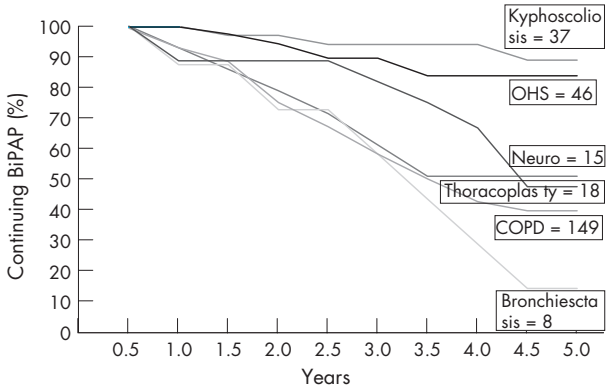
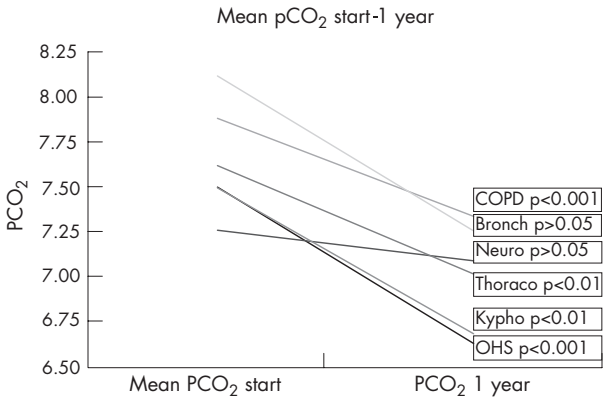
Background: Previous retrospective studies show that long term non-invasive positive pressure ventilation (NIPPV) is effective in patients with extrapulmonary restrictive disorders but less effective in patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis. (Simonds AK, Elliot, MW. *Thorax* 1995;**50**:604–9. Leger P. Bedicam JM, *et al. Chest* 1994;**105**:100–5). There is no evidence to suggest that NIPPV has a mortality benefit in the management of chronic respiratory failure in COPD. However, it is used in patients with hypercapnic ventilatory failure who have received assisted ventilation during an exacerbation or are hypercapnic or acidotic on LTOT in accordance with NICE recommendations. We conducted a retrospective study on patients receiving domiciliary NIPPV at the London Chest Hospital (LCH) to compare current outcome with previously published data and to review the outcome in patients with obesity hypoventilation syndrome (OHS).
Method: For patients commenced on NIPPV at the LCH between 1 July 1993 and 1 June 2005 information was collected on diagnosis, start date, date of death or of stopping NIPPV, and $PaCO_2$ at start, 1 year and 5 years. The 5-year probability of remaining on NIPPV was used as a surrogate for survival. Kaplan-Meir curves were plotted to show the probability of continuing on NIPPV within the different diagnostic groups. Paired student *t* tests were used to show any significant difference between $PaCO_2$ at the start, 1 year and 5 years for patients within the different diagnostic groups.



Abstract S149 Figure 1.



Abstract S149 Figure 2.

Results: Data were available for analysis on 275 patients commenced on NIPPV in the 77 month period. 149 had COPD, 57 thoracic cage abnormalities, of which 18 were post thoracoplasy and 37 had kyphoscoliosis, 46 OHS, 15 progressive neuromuscular disorders and 8 bronchiectasis. Death was the principle cause for withdrawal. The mean (95% confidence interval) 5-year actuarial probability of continuing NIPPV with OHS was 83.3% (100–60), post thoracoplasty 47.7% (92–4), kyphoscoliosis 89% (100–75), COPD 39.8% (58–21), progressive neuromuscular disorders 51% (100–20.8) and bronchiectasis 14.5% (83-0) (fig 1). $PaCO_2$ improved in all patient groups at 1 year including statistically significant falls in OHS (0.87 kPa, $p<0.001$), COPD (0.52 kPa, $p<0.001$) kyphoscoliosis (0.81 kPa, $p<0.01$) and post thoracoplasty (0.6 kPa, $p<0.01$) (fig 2).
Conclusions: This is one of a small number of studies to show that patients with OHS have a very good long term outcome with NIPPV and the first involving direct comparison against different pathologies. Patients with kyphoscoliosis also have a good outcome, but those post thoracoplasty have much a lower probability of continuation. NIPPV resulted in $PaCO_2$ falls in all groups at 1 year. The outcome in COPD is comparable to previous studies and remains encouraging but more research is awaited.

S150 RESPIRATORY FUNCTION AND SURVIVAL IN MOTOR NEURONE DISEASE

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

Abstract S150

	Sensitivity	Specificity
VC <90%	1.00	0.44
VC<72%	0.87	0.88
Pimax <86%	1.00	0.48
Pimax <47%	0.80	0.88
Pemax <74%	1.00	0.36
Pemax <45%	0.73	0.80
SNIP <51%	1.00	0.52
SNIP <40%	0.80	0.92

as % predicted, were chosen to (1) maximise sensitivity and (2) optimise both sensitivity and specificity.
Results: Fifteen subjects died within six months. One subject was unable to perform Pimax. The sensitivity and specificity of different cut-off values for each index are shown in the table.
Conclusions: All indices of respiratory muscle strength, but particularly VC and SNIP, proved useful in identifying subjects at risk of death within six months. In patients with MND, surveillance of respiratory muscle function should be performed routinely.

S151 COMPARATIVE PULMONARY MECHANICS IN CHILDREN AND ADULTS WITH NEUROMUSCULAR DISEASE

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

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

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Physiology of obstructive sleep apnoea

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

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Background: Obstructive sleep apnoea (OSA) has been found to be associated with glucose intolerance and insulin resistance, independent of obesity. The severity of the insulin resistance is proportional to the severity of the OSA. It is hypothesised that the disordered glucose metabolism and insulin resistance are due to increased sympathetic nervous system activation caused by the frequent arousals and fragmented sleep; also the sleep deprivation itself and the hypoxia associated with OSA may cause insulin resistance. The effects of continuous positive airway pressure (CPAP) treatment for obstructive sleep apnoea (OSA) on insulin resistance are not clear; trials have found conflicting results and none have used control groups.
Methods: Forty two men with known type 2 diabetes and newly diagnosed OSA (>10, >4% SaO2 dips/hour) were randomised to receive therapeutic (n = 20) or placebo CPAP (n = 22) for 3 months. Baseline tests, including euglycaemic clamp, glycosylated haemoglobin, homeostatic model assessment, adiponectin, anthropometric measurements, bioimpedance and actigraphy were performed and repeated after 3 months. The study was double blind.
Results: Results are expressed as mean (SD). CPAP improved the ESS significantly more in the therapeutic group than the placebo group (−6.6 (4.5) *v* −2.6 (4.9), p = 0.01). The maintenance of wakefulness test improved significantly in the therapeutic group, but not in the placebo group (+10.6 (13.9) *v* −4.7 (11.8), p = 0.001). Glycaemic control and insulin resistance did not significantly change in either the therapeutic or placebo groups: HbA1c (−0.02 (1.5) *v* +0.1 (0.7), p = 0.7, 95% CI −0.6% to +0.9%), euglycaemic clamp (M/I: +1.7 (14.1) *v* −5.7 (14.8), p = 0.2, 95% CI −1.8 to +0.3 l/kg/min1000), HOMA-%S (−1.5 (2.3) *v* −1.1 (1.7), p = 0.4, 95% CI −0.3 to +0.08%) and adiponectin (−1.1 (1.2) *v* −1.1 (1.3), p = 0.2, 95% CI −0.7 to +0.6 ug/ml). Body mass index, bioimpedance and anthropometric measurements did not significantly change in either group. Activity measured by actigraphy increased overall in the group receiving therapeutic CPAP, but the results were variable and did not reach statistical significance. Hours of CPAP use per night were: therapeutic 3.6 (2.8) *v* placebo 3.3 (3.0), p = 0.8. There was no correlation of CPAP use with any of the measures of glycaemic control or insulin resistance.
Conclusion: Therapeutic CPAP does not improve measures of glycaemic control or insulin resistance in men with type 2 diabetes and OSA.

This study was presented at the ATS in 2006.

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

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Introduction: The recommended treatment for patients with obstructive sleep apnoea (OSA) is continuous positive airway pressure (CPAP), which can improve hypersomnolence, cognitive function, vigilance and quality of life. Current guidelines (SIGN, 2003), however, do not provide recommendations on the necessary duration of a trial of CPAP. The aim of this study was to compare the changes in health status following either a 2 or a 4 week trial of CPAP using the Epworth Sleepiness Scale (ESS) and the Quebec Sleep Questionnaire (QSQ) (Lacasse *et al. Thorax* 2004;**59**:494–9).
Methods: Thirty patients with OSA (27 male; median age 46 years, IQR 39–53, median body mass index 37.5 kg/m^2, IQR 32–44) underwent a trial of CPAP therapy for either 2 weeks (Group 1: n = 22) or 4 weeks (Group 2: n = 8). All patients completed an overnight oximetry study (Pulsox 3i, Minolta), ESS (18/30 patients) and a QSQ at the start and the end of the trial. The QSQ consisted of 5 domains: daytime sleepiness (DS), diurnal symptoms (DSY), nocturnal symptoms (NS), emotions (EMOT) and social interactions (SI), the minimum clinically important

Abstract S151

	Adult	Child	p Value
BMI (kg/m2)	24 (5)	17 (6)	0.0001
VC (l)	1.6 (0.9)	1.0 (0.5)	0.03
VC (%)	43 (23)	45 (21)	0.7
V_T/Wt (ml/kg)	6.5 (3.5)	8.6 (3.3)	0.05
F_R/V_T/Wt (bpm/ml/kg)	0.9 (0.5)	7 (7)	0.001
V_T/Ti/Wt (ml/s/kg)	0.005 (0.003)	0.009 (0.004)	0.002
CL_{dyn} (ml/cmH20)	81 (45)	47 (30)	0.006
R_L (cmH2O/s/l)	4.7 (3.6)	9.7 (8.4)	0.01
WOB_{tot} (J/l/kg)	9 (4)	26 (18)	<0.0001
WOB_{res} (J/l/kg)	3 (2)	9 (9)	0.001
WOB_{el} (J/l/kg)	7 (3)	17 (13)	0.0002

Abstract S153 Change in scores from start to end of CPAP trial

Group	DS	DSY	NS	EMOT	SI
1 (n=22)	12.5 (4.8–19.0)	22.0 (9.3–35.8)	17.0 (7.0–24.5)	9.0 (2.8–13.5)	11.0 (4.0–14.5)
2 (n=8)	18.0 (3.3–22.5)	4.5 (3.3–17.0)	9.0 (1.5–18.0)	15.5 (2.0–26.3)	18.5 (3.3–37.8)

difference (MCID) for each being 1.8, 2.0, 1.5, 1.1, and 2.5 points respectively. All data are presented as median (IQR).
Results: At baseline there were no significant differences between the groups for age, BMI or number of oxygen desaturations per hour (Group 1 median 50.5 dips/h, IQR 19.8–69.0; Group 2 46.5 dips/h, IQR 14.9–72.9). Similarly, there was no difference in the reduction in dips/hr at the end of the trial between groups 1 and 2 (−20.1 and −36.5 dips/hour respectively; p=0.482). In both groups there were statistically significant improvements in all QSQ domains (table) which were similar between the groups and above the MCID. There was also a reduction in ESS (median 13, IQR 10–17 and 6, IQR 2.5–7.5 pre and post trial, p=0.004; n=18) which was correlated with the changes in each domain of the QSQ (DS $r=-0.747$, $p<0.001$; DSY $r=-0.519$, p=0.03; NS $r=-0.586$, p=0.01; EMOT $r=-0.417$, p=0.04; SI $r=-0.653$, p=0.003). No significant correlations were observed between changes in health status and either baseline BMI or severity of OSA (dips/h at baseline).
Conclusion: Changes in health status were similar between patients undergoing a 2 or 4 week CPAP trial and could not be predicted by baseline severity of OSA. Changes in QSQ scores after the trial were correlated with changes in the ESS.

S154 CARDIOVASCULAR RISK ASSESSMENT IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA: CLINICAL UTILITY OF THE JOINT BRITISH SOCIETIES CARDIAC RISK ASSESSOR PROGRAM

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Background: Epidemiological evidence suggests a strong link between obstructive sleep apnoea (OSA) and cardiovascular diseases (CVD). Statins are highly effective in reducing cardiovascular events in a wide range of patients. The recent Joint British Societies (JBS)-2 guideline recommends that statins should be initiated for primary CV prevention in non-diabetic patients whose 10 year CVD risk is estimated to be >20%.[1] Because the accuracy of risk prediction using a framingham based risk tool is less clear in high risk patient groups, we sought to determine its clinical utility when applied to OSA patients.
Methods: A total of 79 patients (41 OSA, 38 non-OSA) referred with clinical suspicion of OSA, who are not taking lipid or glucose lowering drugs and with no previous history of CVD were included. Fasting lipids, insulin, glucose and blood pressure (BP) were measured after an overnight fast. 10 year CVD risk was calculated using the JBS Cardiac Risk Assessor Program.
Results: Subjects with OSA were more obese, more insulin resistant, more hyperglycaemic and higher systolic blood pressure levels. Based on the JBS risk calculator, mean 10 year CVD risk was significantly higher in the OSA group compared with the non-OSA group (11.74% *v* 6.97, p=0.003). Using stepwise multiple regression model, after adjusting for age, BMI and smoking history, increased 10 year CVD risk score did not significantly predict OSA status (p=0.054). To determine a 10 year CVD risk levels that would distinguish between the OSA and non-OSA groups, we used 20%, 15%, and 10%, 10 year CVD risk cut offs to arbitrarily defined patients that require statin treatment. No significant difference was found in the proportion of patients who qualifies for statins between OSA and non-OSA patients when 15% or 20% 10 year CVD risk were used as cut off levels (p=0.07 and p=0.15 respectively). However, by lowering the cut off level to 10%, the proportion of patients that qualifies for statins was significantly higher in the OSA compared with the non-OSA groups (55.2% *v* 29.2%; Pearson's χ^2 5.484, p=0.02).
Conclusion: This finding suggests that whilst patients with OSA have a higher mean 10-year CVD risk compared with similar patients without OSA, currently used risk calculator may underestimate the need for statins in patients with OSA. Using a lower 10 year CVD risk value of 10% may be more appropriate when risk calculator is required to determine the need for statins in this high risk patient group.

1. JBS-2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;**91**(Suppl 5):v1–52.

S155 HIGH PREVALENCE OF SLEEP APNOEA AND NOCTURNAL HYPOVENTILATION IN PATIENTS ASSESSED FOR BARIATRIC SURGERY

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Introduction: Obesity is increasing in the UK. Bariatric surgery is offered in our hospital to reduce excess weight and cardiovascular morbidity at body mass index (BMI) >40 or BMI >35 with another risk factor. Obese patients undergoing assessment for bariatric surgery often complain of tiredness and are at high risk of obstructive sleep apnoea (OSA). At present there are no clear guidelines on appropriate assessment or peri-operative ventilatory support. We aimed to define the prevalence of daytime sleepiness, OSA and nocturnal hypoventilation in patients considered for bariatric surgery.
Methods: Between November 2005 and June 2006 patients considered for surgery were referred for assessment. Daytime sleepiness was recorded using the Epworth Sleepiness Score (ESS). Due to bed weight restrictions, patients <150 kg were offered inpatient multi-channel sleep study (Win Visi 3, Stowood Scientific Instruments, Oxon, UK). Heavier patients were offered overnight oximetry at home.
Results: Of the 35 patients (25 females) referred, three were above 150 kg and were offered overnight oximetry only. Of these one had hypoventilation (mean overnight oxygen saturation <92%) one had less than 10 >4% dips in oxygen saturation per hour and one did not attend. Three patients did not attend the sleep study, leaving 29 patients (21 females) with full sleep study data. Patients anthropometric data at baseline was mean (SD) age 46.8 (10.7), BMI 45.0 (14.2). Mean Epworth score was modest 11.3 (5.0) but 17 patients (58%) rated themselves as sleepy scoring >10. All patients had more than 6 hours of data on sleep study. Mean overnight saturation was 93.1 (4.0). Six patients (21%) had nocturnal hypoventilation (mean saturation <92%). Mean saturation was weakly negatively correlated with BMI $R^2=-0.25$. The mean number of >4% dips in oxygen saturation per hour (dip rate) was high 24.9 (36.4) due to a non-normal distribution (median dip rate 7.45 range 0.13–117). 11 patients had a dip rate more than 10 per hour of sleep, 8 patients more than 20/h and 6 patients more than 30/h. Daytime sleepiness poorly predicted either sleep apnoea or hypoventilation with a very weak correlation between either ESS and dip rate $r^2=-0.13$, or between ESS and mean saturation $r^2=-0.1$. Four patients (14%) had a normal <10 ESS and dip rate <10/h. Twelve patients (41%) reported sleepiness but had dip rate <10/h. Six patients (28%) reported little sleepiness but had a dip rate >10/h, and in some cases severe OSA. Seven patients (24%) reported sleepiness and dip rate >10/h.
Conclusion: Sleep apnoea and nocturnal hypoventilation are very common in the obese and super obese considering bariatric surgery and should be considered prior to surgery. The Epworth sleepiness score poorly predicts OSA in these patients.

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

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

Method: A sleep questionnaire, including the Epworth Sleepiness Score (ESS) and modified subscales of the Developmental Behaviour Checklist-P and A were sent to 699 people with DS and their families/carers in Scotland.
Results: Of 329 responses (47%), 290 were valid for analysis (subjects aged >4 years). 158 children had a mean age of 11.4 (SD 4) years and 75 (47%) were snorers. Snoring children were more obese BMI kg/m^2: 22 (SD 5) *v* 20 (SD 4) p = 0.02) and more depressed (p = 0.012) than non-snorers. Higher BMI was significantly associated with snoring in children (p = 0.034). Male children scored higher than females on the anxiety and antisocial behaviour scales (p <0.05). Of 132 adults, median age was 28 (IQR 22–34) years and median ESS 4 (IQR 2–7.25); 53 (40%) snored. Snoring was associated with younger age (p = 0.006), higher BMI (p = 0.05) and trended to an association with hayfever (p = 0.055). The ESS correlated with snoring (p = 0.001). Snorers were more depressed (p = 0.003) and more sleepy (p = 0.016) than non-snorers. The ESS correlated significantly with all three behavioural subscales (p<0.006).
Conclusion: This is the first population survey of SDB in both children and adults with DS. Only BMI predicted snoring status in children. Both children and adult snorers were significantly more depressed than non-snorers. ESS is useful in the adult DS population and correlated with behavioural disturbances and snoring.

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