MULTIDISCIPLINARY TEAMS: MYTH OR REALITY?

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Background: With increasing technology and specialisation patient management in asthma cannot be provided by one clinician or discipline alone. Yet physicians and nurses have a long history of examining patient issues separately. The view is taken that multidisciplinary health care teams that recognise the complementary role of each person in the team have the potential not only to improve patient outcomes and decrease direct institutional health care costs over time but also to increase the quality of patient care. The purpose of this study was to identify the similarities and differences in the work practices especially those related to patient education between the clinical nurse consultant (CNC) and the respiratory physician. Method: An ethnographic approach was employed for this study. Data were collected over a 30 month period. Data collection techniques involved field observation and in-depth interviews with 35 participants (CNC's, patients and physicians). Data collection, analysis and interpretation was cyclical and utilised a funnel structure, that is, it had a broad exploratory beginning and became more directed and focused over time. Results and discussion: This study found that although many similarities were identified in the work patterns of the CNC and physicians, distinct differences were also identified particularly in the approach taken to the patient. These differences complemented rather than reinforced or reiterated the approach taken by the physician. Conclusion: From this study it appeared that the question is not one relating to multidisciplinary teams: myth or reality? Rather it is one that focuses on how to acknowledge the contributions of each discipline in the asthma management team.

HEALTH INFORMATION SYSTEM FOR ASTHMA

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Aims: To establish a Health Information System capturing key asthma data focusing on ACHS Clinical Indicators for asthma, clinical information and demographics. Methods: The Asthma Hospital Episode System [AHES] Tool (Filemaker Pro V3.0), was developed in consultation with key personnel and trialed in the clinical setting. To ensure co-operation & ownership, all medical officers offered suggestions. A single form data sheet for E.R. episodes replaced chart entry. Results: In April/May 1999 32 patients were admitted with DRG codes of asthma, 28 were captured using the AHES tool, meeting 100% of Indicators 8.1 (severity assessment) & 8.2 (ongoing assessment), Of 4 charts not using this tool 50% met 8.1 and 75% met 8.2.

| KEY DATA | April/May 1999 |
|----------|---------------|
| Total Number [AHES] | Female | Male |
| Mean age | 37 | 48 |
| Mean FEV1/FVC presentation | 0.96 / 1.4 | 1.12/1.9 |
| AV LOS = 5.4 days |

It is estimated that >200 data entries will have been collected by March 2000. Conclusion: Successful use of this system clearly shows it is possible to meet 100% of indicators 8.1 & 8.2. As yet computerised discharge planning is not included and Indicator 8.3 is not addressed, however we are addressing this. Ongoing liaison with medical officers will ensure adherence with the tool and improve health informatics usage. The utilisation will be enhanced in the near future by converting the form to a scannable format.

Nil Funding Support

Key words: Informatics, Asthma Hospital Episode System, Clinical Indicators.

Nominated for prizes: Respiratory Nurses Prize

BACK TO THE FUTURE

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In 1998 the South Eastern Sydney Area Health Service (SESAHS) developed a Respiratory Clinical Accreditation Programme (CAP), a joint venture with the University of Technology Sydney (UTS) to augment their Graduate Diploma in Acute Care Nursing. Due to declining enrolments in both programmes, a 6 month trial Respiratory CAP was conducted during 1999 at the Prince of Wales Hospital as an independent clinical programme. The aims of the programme were to provide registered nurses the opportunity and environment to promote their clinical expertise in mutually agreed upon areas of respiratory nursing competencies. This was achieved through a coordinated and supported workplace programme. Participants engaged in critical reflection of experiences utilising theory and patient centred activities. Consequently the respiratory CAP has now evolved into a 1year-workplace programme, in which the participants gain 2 subject credits with the University of Technology Sydney. The planned date of commencement of the programme is June 2000. It is the aim of this paper to outline the following issues: Evolution, structure, benefits and future directions of the programme, as well as the experiences of facilitating the programme at the Prince of Wales Hospital.

AMBULATORY INTRAVENOUS THERAPY IN CYSTIC FIBROSIS
A UNIQUE APPROACH

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Ambulatory care of patients with cystic fibrosis has become an increasingly important mode of treatment delivery in recent years. Achieving a safe, efficient, personalized service with a high level of patient satisfaction is a challenge being faced by healthcare providers across Australia. Our ambulatory intravenous antibiotic service has had 50 cystic fibrosis admissions representing 862 patient days since 1996. The average length of stay is 17.2 days, range 4-44 days, average age 22years, range 9-40 years. Most patients have drugs delivered via peripherally inserted central catheter (54%) and port-a-cath (38%). Many patients are treated with dual antibiotic therapy. The most frequently used drugs being Cefazidime (50%), Tobramycin (44%). Most patients receive 24hour continuous infusions; other treatment modes include bolus injection and intermittent infusions. Clinical response is measured by weight change and lung function. Outcomes and complications are carefully evaluated. An advantage of our approach is that intravenous therapy continues until the desired clinical response is achieved. Although initially reluctant to participate the cystic fibrosis population in the Hunter region has since embraced the service enthusiastically.

* Refer to page A62 for
VIRAL INFECTION INDUCES IL-8 MEDIATED EOSINOPHIL ACTIVATION AND NEUTROPHIL INFLUX IN ACUTE ASTHMA.

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Acute exacerbations of asthma are often caused by viral infections and remain an increasing cause of hospital admission. The inflammatory mechanisms in viral-induced asthma are poorly understood. Aims: To characterise the pattern of airway inflammation associated with viral induced asthma. Methods: Adults (n=59) presenting to John Hunter emergency room with acute asthma were examined for infection by: (a) serology for influenza (Flu) A and B, mycoplasma pneumoniae, legionella pneumoniae; sputum DFA detection for respiratory syncytial virus (RSV); and sputum RTPCR for Flu, RSV, rhinovirus, coronavirus, adenovirus and parainfluenza virus 1 and 3. Subjects testing positive to one of these were classed as having an infection and acute asthma. Subjects had spirometry and sputum induction on presentation, and were compared to a group with stable moderate-severe asthma (n=31) and healthy controls (n=8). Results: Forty five subjects had infection and acute asthma while 14 had acute asthma and no infection. Sputum induction demonstrated those with infection had a higher sputum total cell count (p<0.001), increased neutrophils (65.5%, p<0.001) and increased IL-6 (39ng/ml, p<0.001), in comparison to the other groups. Levels of IL-8 correlated with neutrophils (r=0.7). Those with non-infective exacerbations had more eosinophils compared to all groups (p<0.001) and more cells staining positive for IL-5 which correlated with sputum numbers (n=0.4). Both groups with exacerbations had elevated sputum eosinophil cationic protein which correlated with total cell count (r=0.5), sputum IL-8 (r=0.7) and eosinophils (r=0.5). Subjects with acute asthma and infection had a longer length of hospital stay (median 2 days), compared to those with non-infective acute asthma (0, p<0.001). Conclusion: Acute severe exacerbations of asthma associated with infection are characterised by sputum inflammation, IL-8 release and eosinophil degranulation. Exacerbations of asthma not associated with infection are characterised by eosinophilic airway inflammation mediated by IL-5. In both cases there is marked eosinophilic degranulation and there appears to be an interaction between IL-8 mediated inflammation and eosinophilic degranulation.

Funded by Asthma Foundation of New South Wales, Australia.

PERIPHERAL & CENTRAL CHEMOSENSITIVITY TO CARBON DIOXIDE IS RAISED IN CENTRAL SLEEP APNEA WITH HEART FAILURE.

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Non-hypocapnic central sleep apnea (CSA) in congestive heart failure (CHF) is due to hyperventilation and hypocapnia, which has been attributed to excessive sensitivity of slowly responding central CO2 receptors situated in the medulla. However, in a typical 60-second cycle of CSA, three changes of ventilation occur, namely crescendo, decrescendo and apnea. This suggests that there are rapidly responding peripheral chemoreceptors, situated in the carotid body, which are involved. Hypothesis: Peripheral chemoreceptor sensitivity is raised in CHF CSA, and correlates with CSA severity. Methods: Peripheral and central chemosensitivities were measured using McClean's single breath hypercapnic ventilatory response (SB), and Read's rebreath hypercapnic ventilation (HCVR) under hyperoxic conditions, respectively. Three groups of males were studied: healthy volunteers (Normal), 'idiopathic' CSA patients with LVEF<55% (N-CSA), & stable, severe CHF (LVEF<45%). CHF patients were divided into 3 groups based on the absence (CHF-N) or presence of sleep apnea (AHS>5, obstructive =CHF-CSA, central =CHF-CSA). Results: are mean ±SD. 10 patients had AHS>5, 20 with CSA, and 20 with no CSA. The SB and HCVR did not differ between groups. SBR and HCVR were significantly reduced in CHF-CSA compared to CHF-N (p<0.001). The SBR and HCVR were not significantly different between CHF-AHS and CHF-N. Conclusion: Peripheral chemosensitivity (SB) correlated with AHI (r = 0.58, p < 0.003) and the percentage of central to total apneas (r = 0.64, p = 0.001), whereas central chemosensitivity (HCVR) correlated inversely with awake PaCO2 (r = -0.67, p < 0.001), and less so with AHI (r = 0.435, p = 0.030). Conclusions: In CHF peripheral chemosensitivity is directly related to CSA severity, whereas central chemosensitivity is more related to background carbon dioxide. It is therefore likely that elevated central chemosensitivity predisposes to CSA, yet the periodicity is determined by elevated, rapidly responsive peripheral chemosensitivity.

Supported: NHMRC, Viertal Foundation, ALF.

Key words: central apnea, heart failure, chemosensitivity, ventilatory response

Nomination for Awards: John Read Prize

2-METHOXYESTRADIOL INHIBITS EOSINOPHIL ACTIVITY AND AIRWAY HYPERRESPONSIVENESS IN A MURINE MODEL OF ALLERGIC BRONCHOOCONSTRICTION.

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Airway wall remodelling (AWR) contributes to both airway hyperresponsiveness (AHR) and the progressive development of fixed airway obstruction. We have previously reported that the anti-angiogenic estradiol metabolite, 2-methoxyestradiol (2-MEO) inhibits mitogen-stimulated DNA synthesis and proliferation of human cultured airway smooth muscle (AHRCCM 155, AS1, 1999) raising the possibility that this compound may inhibit smooth muscle hyperplasia, a key component of AWR. Aim: To examine the effects of 2-MEO on the development of bronchovascular laveage fluid (BALF) eosinophilia and AHR in a murine model of allergic bronchoconstriction. Methods: Male C57BL/6 mice were sensitised by intraperitoneal (i.p.) injection of ovalbumin (OVA) on days 0 and 12, followed by 8 aerosol challenges (30 min) with a combination of OVA (5% w/v) and fetal calf serum (FCS, 5% v/v) on days 20-27. 2-MEO (0.5-50 mg/kg) was administered daily by i.p injection at least 1 h before OVA/FCS challenge. Control mice were challenged with saline and received vehicle (3 ml/kg, 4% DMSO + 96% peanut oil) by i.p injection. On days 18 and 27, airway responsiveness to acetylcholine methacholine (MCh, 3-12 mg/ml) was measured using non-invasive, whole body plethysmography (Pent). On day 28, the mice underwent BAL with sterile saline and cytospot preparations were stained with DiffQuick for eosinophils. Results: There was no difference in MCh reactivity between groups prior to 2-MEO treatment and OVA/FCS challenge. 2-MEO dose-dependently reduced OVA/FCS-induced AHR to MCh. Moreover, 2-MEO reduced OVA/FCS-induced BALF eosinophilia. Conclusion: These results indicate that 2-MEO reduces AHR and BALF eosinophilia induced by repeated allergen inhalation. 2-MEO displays several properties desirable in an agent that targets airway wall remodelling.

Supported by Armap Operations Pty Ltd.

Key words: Airways hyperresponsiveness, 2-methoxyestradiol, eosinophilia

IMPROVING THE DIAGNOSIS OF OBSTRUCTIVE SLEEP DISORDERED BREATHING IN INFANTS BY INCORPORATING ESOPHAGEAL MANOMETRY INTO CONVENTIONAL POLYSOMNOGRAPHY.

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Obstructive sleep disordered breathing (OSDB) is currently diagnosed in infants using overnight polysomnography (PSG). Due to 'central - like' obstructive events and normal paradoxical breathing in this population, the accuracy of overnight PSG is unknown. Methods: Nine infants (1-18 months) underwent an overnight PSG with the addition of a manometric pressure-sensing catheter. Respiratory events were identified using both the conventional and the manometric techniques. The proportion of agreement and disagreement between the two methods was calculated for the total events scored and for the individual event types. The composition of missed events was investigated and the respiratory effort present with obstructive apneas, hypopneas and episodes of increased upper airway resistance (UAR) deduced. Results: Conventional PSG agreed with the more accurate manometric PSG scoring for only 47% of events. Hypopneas had the highest disagreement rate (56%) when compared to other respiratory events (p<0.01) and central apneas the lowest (16%, p<0.0001). Of events missed by conventional analysis, 90% were periods of increased UAR. The respiratory effort associated with hypopneas, obstructive apneas and increased UAR was the same for all events (p<0.1). Conclusions: Conventional PSG is routinely used to diagnose OSDB in infants. This study supports that esophageal manometry is a more sensitive indicator of respiratory effort in infants. The data suggest that the incorporation of esophageal manometry into current PSG scoring procedures would substantially improve our ability to diagnose OSDB in the infant population.

Key words: Infants, Esophageal Manometry, Sleep Disorders, Diagnosis.
TUMOUR NECROSIS FACTOR IS DOWNREGULATED IN ASTHMA AND UPREGULATED BY INHALED CORTICOSTEROID: COMPARATIVE ANALYSIS BY IN SITU HYBRIDISATION, IMMUNOHISTOCHEMISTRY AND COMPETITIVE RT-PCR IN AIRWAY SAMPLES.

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'Tumour necrosis factor (TNF) is thought to be a mediator of inflammation and fibrosis. Evidence suggests that TNF upregulation occurs in asthmatic subjects, especially those with acute, severe symptoms. Hypothesis: TNF mRNA and/or protein production is upregulated in stable asthmatics compared with normal controls and that inhaled corticosteroids (ICS) downregulate this response.

Methods: In situ hybridisation (ISH) and immunohistochemistry (IHC) were performed on airway endobronchial biopsies (EBBx) and bronchoalveolar lavage (BAL) cells from 24 normal controls and 35 stable asthmatics, 22 on ICS. Signal per area in EBBx was measured in the lamina propria and epithelium, with the area of holes subtracted. Competitive (c)RT-PCR was also performed on EBBx from 23 normal controls and 75 stable asthmatics, 62 on ICS and on BAL cells from 30 normal controls and 87 stable asthmatics, 70 on ICS. Results: In EBBx, epithelial TNF was decreased in asthmatics compared with normal with both ISH (p=0.0001) and IHC (p<0.002). TNF protein was increased in ICS-treated asthmatics, compared with asthmatics not on ICS (IHC, p<0.01) and there was a trend towards increasing mRNA expression with ICS treatment (ISH, p=0.058). There were no differences in the lamina propria, cRT-PCR also demonstrated increased TNF mRNA in asthmatics compared with normal (p=0.05). In BAL, total TNF positive cells and TNF positive macrophages by IHC were again lower in asthmatics compared with normal (p=0.015 and 0.01 respectively), but there were no differences by IHC or cRT-PCR. Conclusion: Paradoxically, TNF expression was lower in asthmatic airways compared with normal and normalised in the epithelium with ICS. Stable asthmatics may demonstrate impaired TNF expression, whilst 'normal' TNF levels may have a physiologically protective effect.

Supported by Glaxo Wellcome Australia and NHMRC

Key words: tumour necrosis factor, asthma, in situ hybridisation, immunohistochemistry, competitive RT-PCR, inhaled corticosteroid

IMPLEMENTATION OF EVIDENCE BASED MANAGEMENT OF ACUTE VIRAL BRONCHIOLITIS

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Background: Acute viral bronchiolitis (AVB) is the most common lower respiratory tract infection in the first year of life. Systematic reviews of the literature would suggest that pharmaceutical agents do not influence the course of the disease. Implementation of clinical guidelines is frequently delayed well beyond their dissemination and the publication of clinical evidence. The recently published Australian guidelines for the management of AVB have been evaluated by assessing the current practice of all paediatricians in Australia.

Methods: Questionnaire survey and literature review

Results: From a total of 691 questionnaires 555 (82%) were returned, 373 (57%) responders treated children who had over 200 (53%) treated 10-50 children per year. A wide variation in the management practice of AVB was noted. Up to 70% of paediatricians, who treat AVB, indicated the use of pharmaceutical agents in their outpatient management (88% in inpatient management), most only using these agents sometimes or in high-risk children. Paediatric respiratory physicians tend to use bronchodilators and corticosteroids less frequently than the general paediatricians. Compared with many countries in Europe, few Australian paediatricians always use supplementary drugs in the inpatient management of AVB. In particular, bronchodilators (61% vs. 8%) and corticosteroids (11% vs. 1%) are used far less often.

Conclusions: Despite the evidence and the recommendation of the Australian guidelines pharmaceutical agents are used frequently in the management of AVB by paediatricians in Australia. Guidelines alone are not sufficient to implement change and there is a need for more specific strategies to ensure that children receive appropriate management for this common condition.

Key words: acute bronchiolitis, bronchodilators, evidence-based medicine

INHALED FLUTICASONE PROPIONATE (FP) DOES NOT ALTER INFLAMMATION IN THE ALVEOLAR SAC OF LUNG ALLOGRAFTS: A DOUBLE BLIND PLACEBO CONTROLLED TRIAL.

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Progressive airflow obstruction i.e. Bronchiolitis Obliterans Syndrome (BOS) remains a major factor limiting long term survival after lung transplantation (LTX). It is likely that inflammation precedes the scarring and remodeling of airways that occurs in this process. Inhaled steroids are widely used in asthma to treat airway inflammation, and have been used post LTXs in the setting of early BOS.

Methods: 23 stable LTX recipients (LTR) with early BOS recruited 3 to 9 months post LTX, and randomised to receive either 750µg FP or an identical appearing placebo. Baseline endobronchial biopsies were taken at routine bronchoscopy at the time of randomisation, and repeated 3 months later. Immunohistochemical staining of the biopsies was performed for CD2 (pan Tcell), CD8 (T suppressor/cytotoxic), CD4 (T helper/inducer), LCA (leukocyte common antigen) and Neutrophil Elastase. Positive cells were counted per mm2 of subepithelium. Biopsies taken from 10 healthy, non-smoking volunteers were compared to those of the stable LTR.

Results: Medians and ranges. 20 paired biopsies suitable for analysis.

**p<0.05.

CD8 positive cells were increased in the LTR compared to controls, no other significant differences were detected. No significant differences in any of the cell markers were found after 3 months treatment with FP compared to baseline and placebo.

Conclusions: In stable LTR on triple immunosuppression the addition of inhaled FP does not affect the degree of airway inflammation. CD8 positive cells are increased in stable LTR, but neutrophil numbers in the subepithelium are stable. This contrasts with the effects of neutrophils in established BOS. This group of patients is being followed over a longer period to assess whether emergent changes reflect the long-term risk of BOS.

Supported by the NHMRC & Glaxo Wellcome Australia.

Key words: Lung transplantation, airway inflammation, inhaled steroids

IN-UTERO CIGARETTE SMOKE EXPOSURE AND ALVEOLAR INFLAMMATION IN THE SUIDDEN INFANT DEATH SYNDROME

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The harmful effects of passive cigarette smoke exposure to infants include increased frequency of asthma exacerbations, increased incidence of lower respiratory viral infections, reduced lung function in the neonatal period, and an increased risk of Sudden Infant Death Syndrome (SIDS). We have previously shown an increase in the thickness of the inner airway wall in infants who have died of SIDS and were exposed to maternal cigarette smoke. To determine the effects of in-utero cigarette smoke exposure on the structure of the lung in infancy, we examined airway dimensions and airway alveolar attachments in 319 infants from 32 infants who died from SIDS. Cases were divided into four groups based on the maternal history of cigarette smoking: no smoke exposure (n=6); post natal smoke exposure only (n=4); in-utero smoke exposure only (n=4); and both in-utero and post natal exposure (n=18). We found no significant differences between the groups with regard to airway size (internal perimeter) or outer airway perimeter. The mean ± (SE) distance, in millimetres, between alveolar attachments was similar in infants who had no smoke exposure (0.06 ± 0.02) and those that had post natal exposure only (0.08 ± 0.004). This distance was greater in infants exposed to cigarette smoke in-utero (0.1 ± 0.04, p<0.05) and in those exposed both in-utero and post natal exposure (0.09 ± 0.02, p<0.05). These findings suggest that in-utero cigarette smoke exposure may have significant effects on infant lung structure and may help explain the observed abnormalities of lung function in infants of smoking mothers. Support: the National SIDS Council of Australia and NHMRC.

Key words: In-utero cigarette smoke, Alveolar attachments, SIDS.

Awards: nil.
MEASUREMENTS OF EXHALED NITRIC OXIDE WITH THE SINGLE-BREATH TECHNIQUE IN INFANTS.

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Exhaled nitric oxide levels in adults are flow dependent. We have reported that exhaled nitric oxide (eNO) can be measured in infants using a modified single-breath technique with positive expiratory pressure (1). The aim of this study was to investigate whether this modified technique could detect a flow dependence for eNO in infants. Further we compared the single-breath technique with other methods of collecting eNO from infants – bag collections (mixed expired NO) and tidal breathing (peak tidal NO).

Methods: Exhaled NO were measured in 6 infants using three different collection methods: (i) single-breath technique using two different expiratory flows (10 and 40 ml/s), (ii) tidal breathing into a gas sampling bag and (iii) tidal breathing directly into a nitric oxide analyser. All collections were made on the same day while the infant was asleep following a dose of choral hydrate (80-100 mg/kg). Results: A significant flow dependence for eNO was demonstrated using the single-breath technique. Average eNO levels were 28.8 ppb with a flow of 10 ml/s and 20.1 ppb with a flow of 40 ml/s. There were significant correlations between the eNO levels measured by the single-breath technique and both bag collections (r=0.84) and peak tidal NO (r=0.93). Conclusions: A flow dependence for eNO can be demonstrated in infants using single-breath measurements. There is good agreement between eNO levels measured by the single-breath method with levels measured using other techniques.

1. Wildhaber et al. 1999. AJRCCM, 159: 74-78. Supported by the NHMRC

Key words: Exhaled nitric oxide, infants

Nominations for awards: nil

AIRWAY INFLAMMATION IN CHILDREN WITH INFREQUENT EPISODIC WHEEZE.

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In Australia 1 in 4 children will have at least one episode of wheeze per year. In adults the role of airway inflammation in asthma is well characterised with increased T lymphocytes activation and a bias towards TH2 cells, however, few studies have been performed in children. In this study, a non-bronchoscopic bronchoalveolar lavage (BAL) technique was used to obtain T-cells from the lungs of children with a history of infrequent episodic wheeze (2-12 episodes/year) and a control group with no history of cough or wheeze. 32 children were studied (16 asthmatic, 16 controls) aged 0.5 to 12 years and all children were asymptomatic at the time of study.

There was no significant difference in the differential cell count on BAL fluid. Cell surface markers were performed on 12 asthmatics and 15 controls. In both groups the majority of T cells were CD3,CD8 positive with a CD4:CD8 ratio of 0.8. No differences were found between the groups in the level of T-cell CD25, CD38, CD69 and HLA-DR expression. Intracellular cytokine studies were performed on 9 asthmatics and 6 controls. CD4 T-cell cytokine (IFNγ, IL-2, IL-4, IL-10) production was measured by flow cytometry following stimulation. No statistically significant difference between the groups was found, with IFNγ being the highest in both groups. There was no correlation between total and specific serum IgE and markers of airway inflammation.

These results suggest that significant airway inflammation is not present in asymptomatic children with infrequent episodic wheeze. They support the current guidelines for asthma management in Australia that children with infrequent episodic asthma do not require treatment with anti-inflammatory asthma medications between exacerbations of their lung disease.

Key words: asthma, airway inflammation, paediatrics

PATIENTS WITH A WRITTEN ASTHMA PLAN HAVE A SHORTER HOSPITAL STAY.

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Aims: Asthma continues to be a major burden for its sufferers, their families and society in general. We wished to obtain a better understanding of our local population, to see how this compared with other published work and to see if there were areas in which we were deficient or could improve.

Methods: A 3 part "PAQART" (paediatric asthma quality assurance review team) questionnaire was administered to all asthma admissions (or their parents/guardians) from 01/04/98 until 30/06/98. This consisted of parental information on background and current asthma status, as well as an admission and a discharge part filled in by medical staff.

Results: There were 102 admissions with asthma over this time to 98 patients and forms were completed on 79 of them (76.9%). Firstly we compared patients without forms (by medical record review) with those who had data and found no significant differences in: age, sex, length of stay, first diagnosis, prior oral steroid use, prior antibiotic use, "PAQART" admission score, other medical problems and those who received specialist medical follow up.

37 of the 68 known asthma patients had a written asthma plan, which was followed by 14. When these groups were compared there was a significant decrease in the length of stay in those patients who had an asthma plan versus those without, which was further decreased, though not significantly, if the plan was followed. There was no difference in their age, admission score, background disease as measured by days off school and courses of steroids in the past year, and frequency of wheezing. They had a non-significant increase in pre-hospital oral steroids (25% Vs. 12.5% P=0.21), and a tendency to be girls (59.5% Vs. 38.6% P=0.09).

Discussion: Our study further advances the benefits of having an asthma plan, while raising the question of why in our population boys seem to be less likely than girls to actually possess one.

GREATER AIRWAY SMOOTH MUSCLE CONTENT IN THE LUNGS OF MALE INFANTS.

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Growth-related changes in lung structure may have a significant impact upon the normal functioning of the paediatric lung. Male children and adolescents have lower maximal airflow values and hence airway calibre than females of the same height and age. In addition to these differences in airway function, there is evidence for gender differences in the rate of growth, of large and small airways in children. Gender differences in small airways structure in infants studied at post-mortem have recently been reported. Such differences have been suggested as part of the pathophysiological basis, of the greater prevalence of lower respiratory tract illness in male children. In this study, standard methodology was used to perform computer-assisted morphometry. The inner (Wi) and outer (Wo) airway wall areas, as well as the area of airway smooth muscle (Apm) and cartilage (Acm), were measured in formalin fixed lungs from 7 male and 5 female infants (age: 2-123 days). These children had died suddenly from non-respiratory causes and their parents had donated their lungs for research purposes after coronial investigation. Random effects regression was used to calculate and compare the relationship between the airway internal perimeter (Pm) and these components in cartilaginous (n=127, Pm=1.4 - 19.8mm) and non-cartilaginous (n=135, Pm=6.0 - 59.0mm) airways from male and female infants. Relative differences, and statistically significant gender differences (*P<0.01) are shown below.

| Component | Non-cartilaginous airways | Cartilaginous airways |
|-----------|---------------------------|------------------------|
| Female    | Male                      | Female                | Male                |
| Wi/Mo     | 0.0098±0.0010             | 0.0099±0.0001          | 0.0063±0.0000       | 0.0067±0.0000 |
| Wo/Mo     | 0.192±0.044               | 0.135±0.032            | 0.168±0.017         | 0.199±0.041 |
| Apm/Mo    | 0.054±0.0003              | 0.056±0.011            | 0.032±0.004         | 0.034±0.007 |
| Acm/Mo    |                          | 0.101±0.010            | 0.109±0.010         | 0.106±0.010 |

Therefore, while airways of the same size in infant male and female lungs have similar advartential thickness, cartilaginous airways in infant males have significantly more tissue luminal to the smooth muscle. There is also significantly more smooth muscle in airways of all sizes from male infants. Airway structure therefore differs in male and female infants, and this greater amount of smooth muscle and thicker inner wall may provide part of the explanation for gender differences in airway function.

Supported by: The Financial Markets Foundation for Children and The New Children's Hospital Teddy Bears Picnic

Key words: airway smooth muscle, airway wall structure, gender, infant
AEROBIC FITNESS AND PHYSICAL ACTIVITY IN BOYS

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Aerobic fitness (AF) was estimated in two groups of boys by assessing the distance covered in a 6 minute run (6MD) and was compared with direct measurements of peak aerobic power (VO2p) in subgroups of these boys. 21 year old boys (14.1yr, 1.68m, 56.5kg, 99% pred) was not significantly correlated with 6MD (1249m, P=0.15) and treadmill run time (11.7min, P<0.01) but negatively correlated with BMI (P=0.002). The regression equation predicting VO2p from 6MD was VO2p = 0.0385 x 6MD + 2.39 (R2=0.27). In the younger group, peak HR reached 195 bpm (95%pred) and RER 1.09 and peak VO2p (36.4 ml/kg/min, 99% pred) was not significantly correlated with 6MD (107ml, P=0.075) or BMI (P=0.67) but was related to treadmill run time (10.5min, P=0.03). The 7 day recall Physical Activity (PA) Questionnaire for Children (PAQ-C) was administered to both groups of boys but no significant relationship was seen between PAQ-C scores and peak VO2p and PA at 60% and 90% respectively. These results suggest that PA and AF levels vary with age and population selection and that in confirmation of previous investigations, in the age groups examined AF may be largely independent of PA.

Key words: Boys, peak aerobic power, 6minute run, physical activity

Monday April 10 – Population Health SIG Orals (1330-1530)

DETERMINANTS OF ‘HEALTHY’ LUNG FUNCTION IN A REMOTE ABORIGINAL COMMUNITY IN NORTHERN AUSTRALIA

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Respiratory disease is a significant cause of morbidity and mortality for Indigenous Australians, especially chronic respiratory disease. It is becoming clearer that determinants of respiratory health in non-Aboriginal Australians can not be generalised to Aboriginal Australians. We have commenced a multidisciplinary study of respiratory disease with the aim of optimising prevention, intervention and standards of care for remote Aboriginal communities. Our initial work has focused on a detailed assessment of baseline lung function. Methods: Cross-sectional survey of 202 adult residents (18-80 years) of a remote northern Australian rural Aboriginal community. Spirometry, histamine challenge, respiratory symptoms and signs, and established risk factors for respiratory disease were assessed. Results: Data from 54% of participants who had no evidence of respiratory disease or significant bronchial hyperreactivity (BHR) were used for analysis. These subjects were those with no recent wheeze, chronic bronchitis, BHR (PD20FEV1 < 3.8muL histamine) or reversibility with salbutamol and unremarkable chest auscultation. Of those without respiratory disease/BHR, 61% of men and 70% of women were current or past tobacco smokers. Age, height and gender explained 59% of the variance in FEV1 and 60% in FVC. Predicted values for FEV1 were 6.3% (0.3(SEM)) lower and FVC 0.6% (0.5(SEM)) lower than those predicted by Veale et al[1]. The decline in predicted FEV1 and FVC over increasing age paralleled that of Veale. Conclusion: This ‘healthy’ spirometry findings in this northern Australian Aboriginal community support the generalisation of the findings of Veale to at least other remote rural populations, with values of FEV1 and FVC being lower than those of non-Indigenous Australians. Further studies are required to determine if these values apply to Indigenous Australians in southern and urban centres. We are now planning prevention and intervention programs for chronic respiratory disease in remote communities.

Supported by: AMA/APMA Aboriginal Health Initiative, Flinders University Northern Territory & Tiwi Island Community, Commonwealth and Anti-Tuberculosis Association, CRC for Aboriginal and Tropical Health.

Key words: Indigenous health, respiratory physiology

Nomination for Awards: nil

DECLINE IN LUNG FUNCTION IN ADULT AUSTRALIANS OF ABORIGINAL DESCENT (AAAD)

Musk AW, James AL, Ryan GF, Mukherjee S, Waring JA, LeSouef PN, McCarthy J, Wood MM, Johnson G, Palmer LJ, de Klerk NH. Perth Respiratory Epidemiology Group, Sir Charles Gardner Hospital, WA.

Background: AAAD are known to have lower levels of lung function than adult Australians of European descent. Our previous studies of cross-sectional design have been unable to determine if this results from reduced lung growth during childhood, earlier cessation of lung growth or a greater decline with age paralleled that of Veale with those of other remote rural populations.

Methods: Surveys of respiratory function were carried out in a community of AAAD in the north-west of Western Australia in 1989, 1995 and 1999 to provide data for longitudinal analysis. Subjects answered a modified BMRC cough questionnaire on cough, sputum, dyspnoea and smoking. FEV1 was measured with a dry bellows spirometer. Generalised estimating equations were used to estimate the effect of calendar year on the rate of decline in FEV1, where people were assumed to be random effects with repeated measures. Fixed effects for age, height and smoking were included using the STATA v5.0 software. Results: In the 1999 survey, the prevalence of cigarette smoking was 54.4% in males and 29.6% in females. Levels of lung function measured cross-sectionally were similar to those in our previous studies and comparable with those of other studies of AAAD. After adjustment for height and smoking, the average rate of decline in FEV1, in adults was estimated to be 31 ml/yr (SE=3 ml/yr) in males and 23 ml/yr (SE=2 ml/yr) in females. The prevalence of doctor diagnosed asthma was associated with an increased decline of 9 ml/yr (SE=3 ml/yr) (P=0.008), self-reported wheeze with an increased decline of 5 ml/yr (SE=2 ml/yr) (P=0.06) and current cigarette smoking with an increased decline of 9 ml/yr (SE=3 ml/yr) (P=0.002). The prevalence of cough, sputum, or dyspnoea was not associated with a significant increase in the rate of decline of FEV1.

Conclusions: Cigarette smoking, a history of asthma and the presence of wheeze are associated with greater rates of decline of lung function. This provides further evidence that environmental factors may be important in determining the level of impairment of lung function in AAAD. Supported by HDWA & MEDWA.

ADRENOCORTICAL SUPPRESSION AND BONE MINERAL DENSITY IN ASTHMATIC CHILDREN TREATED WITH HIGH DOSE FLUTICASONE PROPIONATE

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ADRENOCORTICAL SUPPRESSION AND BONE MINERAL DENSITY IN ASTHMATIC CHILDREN TREATED WITH HIGH DOSE FLUTICASONE PROPIONATE

It is recognised that inhaled corticosteroids have systemic effects on the hypothalamic-pituitary-adrenal (HPA) axis and bone metabolism. Fluticasone propionate (FP) is a high potency corticosteroid with moderate accumulation after multiple dose therapy. The prevalence of HPA axis suppression and low bone mineral density in children treated with high dose fluticasone propionate was investigated in this cross sectional study. Methods: 45 children and adolescents aged 4 – 20 years attending asthma clinics at Monash Medical Centre were enrolled. Criteria for inclusion into the study were subjects treated with FP at a dose > 500 mcg for at least 6 months using a powder and spacer or Accuhaler® with mouth rinsing. Subjects were excluded if they had received oral or systemic steroids in the previous two weeks or had another chronic illness. Early morning serum cortisol levels were obtained and those subjects with a cortisol level less than 400 nmol/L underwent a modified Synacthen test (tetraacosactrin 250 mcg IM) to confirm adrenocortical suppression. Results: The subjects of mean age 12.9 years (range 4 – 20 years) had been treated with mean daily dose FP 97.6 mcg/m2/day (range 33 – 2985 mcg/m2/day) for a mean duration of 2.3 years (range 6 – 48 months). 69% of subjects had serum cortisol levels less than 400 mmol/L. Of these subjects, 25% demonstrated an inadequate cortisol response to tetracosactrin stimulation, defined as a less than twofold increase in serum cortisol from baseline and a peak cortisol level < 550 nmol/L at ≤ 60 min post tetracosactrin administration. None of the subjects in the study demonstrated low bone mineral density for bone age < -1.5 SD from mean when compared to healthy sex and age matched controls. There was a significant negative correlation (correlation coefficient -0.31, p < 0.05) between the dose of FP / body surface area and morning serum cortisol levels. Conclusion: These results indicate that use of high dose inhaled fluticasone propionate may be associated with significant adrenocortical suppression in a dose dependent manner. There was no associated reduction in bone mineral density in this study group.

Key words: adrenocortical suppression, bone mineral density, fluticasone propionate, asthma, paediatrics.
IMPROVEMENTS IN RESPIRATORY HEALTH STATUS & PREDICTING UTILISATION IN THE SA HEALTHPLUS SOUTHERN RESPIRATORY COORDINATED CARE TRIAL

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The Council of Australian Governments (COAG) approved the development of a national Co-ordinated Care trials with the primary aim to show that co-ordinating patient care will improve health outcomes and reduce demand. AIMS: 1) to test the hypothesis that a significant proportion of health service utilisation variance can be predicted from baseline health-outcome measures, demographics and historical utilisation. 2) to test the hypothesis that coordinated care will yield significant improvements in respiratory health status and quality of life over time. Method: A sample of 225 patients with a diagnosis of COPD from the Southern region of Adelaide were randomly allocated to either the co-ordinated care intervention (1) (n=145) or the control (C) group (standard medical care, n=80). All patients were administered an SF-36 health status questionnaire, a respiratory disease questionnaire and had their Medical Benefits, Pharmaceutical Benefits Scheme (MBS & PBS) and hospital in-patient data tracked for 2 years prior and up to 1 year after enrolment. RESULTS: Using multiple regression (stepwise) analysis 40% of the variance associated with hospital utilisation (as measured by inpatient days), 14% of MBS utilisation and 41% PBS utilisation could be predicted from a combination of historical utilisation, SF-36 scores and the Dyspnoea of a national Co-ordinated Care trials with the primary aim to show that health status and quality of life over time.

LONGITUDINAL VALIDATION OF AN EPIDEMIOLOGICAL DEFINITION OF ASTHMA

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Current asthma, defined as the presence of both wheeze in the last 12 months and airway hyperresponsiveness (AHR), differentiates children with more severe abnormality from children with either measure alone. However, the prognostic value of this epidemiological definition has not been well described. In 1982 we enrolled a random sample of 718 schoolchildren aged 8-10 years. We re-studied a representative sample of 573 (70%) during 1997-1999, when the subjects were aged 22-27 years. AHR was defined as 20% fall in FEV1 at < 3.9μmol of histamine. Wheeze, sleep disturbance and activity limitation due to asthma during the last 12 months were measured by questionnaire. The outcomes in 1997-1999 were compared between groups classified by their status in 1982.

| 1982 classification | Normal n=463 | Wheeze only n=34 | Wheeze & AHR only n=30 | Current asthma n=26 |
|----------------------|--------------|-----------------|----------------------|---------------------|
| recent wheeze (%)    |              |                 |                      |                     |
| 95% CI               | (23.8, 31.8) | (33.2, 66.8)    | (39.0, 74.4)         | (65.7, 95.9)        |
| 27.6                 |              |                 | 56.7                 | 80.6                |
| Sleep disturbance (%)|              |                 |                      |                     |
| 95% CI               | (6.9, 12.1)  | (7.0, 34.2)     | (11.1, 25.5)         | (27.0, 65.4)        |
| 9.5                  |              |                 |                      |                     |
| Activity limitation (%)|            |                 |                      |                     |
| 95% CI               | (2.1, 6.7)   | (0.1, 3.3)      | (5.7, 34.3)          | (16.3, 52.9)        |
| 4.8                  |              |                 |                      |                     |
| mean %pred FEV1/FVC  |              |                 |                      |                     |
| 95% CI               | (99.5, 101.0)| (94.7, 102.5)   | (90.5, 97.5)         | (88.5, 97.9)        |
| 100.3                |              |                 | 94.0                 | 93.2                |

There were statistically significant trends in all four outcomes measured (p<0.001).

We conclude that this classification differentiates groups of children who have different prognoses. Furthermore, seventeen years after original classification, adults who were classified as having current asthma during childhood are much more likely to have 'asthma that matters'.

Support: CHATA, Allen + Hanbury, NHMRC, Asthma NSW, AstraZeneca

AT-HOME TREATMENT OF DEEP VENOUS THROMBOSIS (DVT) USING ENOXAPARIN IS MORE COST-EFFECTIVE THAN STANDARD CARE

Josephine Weekley1, Brian Smith2, Tim Howe2, Mark Hoppes1, Bob Benoit2, Dawn Brown4, Grace Leonellos
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Introduction of low molecular weight heparins (LMWH) permit safe and effective treatment of DVT at home, for patients with minimal complications, compared to standard care involving hospital admission with continuous heparin infusion for 5 to 7 days1,2. Substantial health-care costs savings have also been demonstrated. The aim of this study was to conduct a cost analysis of DVT treatment at home with the LMWH enoxaparin, compared to standard inpatient care at 'The Queen Elizabeth Hospital (TQE)'. Methods. Subjects participating in the Emergency Department with principle diagnosis of DVT, or inpatients in whom DVT developed, were recruited over 1997-1999. Patients were eligible for inclusion according to criteria previously described and associated costs were tracked prospectively. Subjects were matched (2:1 where possible) to historical controls (1988/86) for age, gender and level of comorbidity (same or lower), checked with binding by a physician uninolved in the study. Control costs were obtained using the clinical costing system Trendata3. Results: The mean total cost associated with at-home treatment was $649 ± 15 (SEM) ($n=28) per patient, compared to $2,353 ± 120 (SEM) ($n=19) per patient receiving standard care, constituting a mean saving of 72.4% per patient. Minimal cost shifts of <1% to patients and 7% to Medicare were demonstrated (n=22). Recruitment was estimated as 29% of those eligible (62% of total DVT coded patients) based on patient numbers for the financial year 1998/99. The gap between actual and potential recruitment was likely due to clinical practice preferences. Extrapolating from this recruitment data, estimated potential savings to the South Australian hospital systems range from $194,233 to $415,257 per year (29% to 62% of eligible patients), based on the mean total number of DVT admissions to metropolitan hospitals for the financial years 1995 to 1999. Conclusion: At-home treatment of uncomplicated DVT using enoxaparin is more cost-effective than standard care, without involving substantial cost-shifts.

1. Levine M, et al 1998 2. Koopman MMW et al, N Engl J Med 1996;334:682-87 3. Spyropoulos AC et al, Arch Int Med 1999;159:1139-40.

Key words: DVT, LMWH, cost-effectiveness

THE EFFECT OF COMBINED NICOTINE GUM AND NICOTINE PATCHES IN SMOKING CESSION

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Smoking cessation is difficult to achieve and best outcomes are seen using nicotine replacement therapy. We have previously presented outcome data from the smoking Cessation trial. In 1995-99, 107 participants were enrolled in the combination group. Their mean age was 45.0 (12.2 (SD) years) and 69.2% were female, similar to the control group of 116 whose mean age was 42.4 (11.8(SD)) years and 62.3% were female. Smoking uptake occurred at a similar age in the combination group and controls (15.5 (4.6(SD)) vs 16.0 (5.8(SD)) (p=0.48). However, there was a significant difference in the average number of cigarettes smoked per day (41.7 (12.6(SD)) vs 39.2 (11.1(SD)) (p=0.005)) and the Fagerstrom score (8.3 (4.1(SD)) vs 7.5 (1.9(SD)) (p=0.0025)). At 3 months after entry into the program only 18.9% of the combination group were abstinent compared to 31% of historical controls. Breath carbon monoxide confirmed abstinence in the non-smokers, with a mean concentration of 2.5 (2.9(SD)) ppm. Conclusion: The addition of nicotine gum to topical replacement did not improve 3 month abstinence rates in heavy smokers. This may reflect greater nicotine addiction in the group.

1. The prevalence of cigarette smoking and smoking cessation rates in a hospital population. Richard Wood-Baker. TSANZ Annual Scientific Meeting, Adelaide, 1998
SURVEILLANCE OF AUSTRALIAN WORKPLACE BASED RESPIRATORY EVENTS (THE SABRE PROJECT).
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Introduction: The Surveillance of Work related Occupational Respiratory Disease (SWORD) program has recently published its ten year results providing incidence rates and causative agents for occupational lung diseases in the UK. In Australia the only comparable scheme to report on a similar range of conditions is the SABRE scheme.

Methods: A notification form is mailed regularly to 46 full members of the TSANZ and 26 fellows of the Australasian Faculty of Occupational Medicine resident in Victoria and Tasmania.

Results: A total of 1382 forms including nil returns were returned over the first two years of the scheme. The mean (SD) age of the 337 patients notified was 53.5 (15.9) years. There were 287 (85%) males and 45 females. There were 5 cases of allergic alveolitis, 120 asthma, 30 bronchitis, 26 inhalation injuries, 30 pneumoconiosis, 33 mesothelioma, 65 malignant pleural disease (71 predominantly plaques and 14 diffuse thickening), 5 occupational lung cancers, 4 infectious diseases and 21 with another diagnosis. The most common agent reported was asbestos in 123 cases. The most common agent reported in asthma was wood dust in 21 cases.

Conclusions: Occupational asthma and malignant pleural disease are the most commonly reported conditions in a voluntary reporting scheme involving respiratory and occupational physicians. The pattern of occupational lung diseases in Australia is similar to that of overseas schemes. Further studies are being undertaken to validate these diagnoses.

Supported by the Australian Lung Foundation/Dust Diseases Board

Key words: Occupational lung disease, epidemiology

Nominations for Awards: Nil

CLINICAL MEASUREMENT OF HUMAN TRACHEAL MUCUS VELOCITY (TMV)
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Introduction: Mucociliary clearance (MCC) removes inhaled particulate matter, microorganisms, excess secretions and cellular debris from the respiratory tract. MCC is impaired in many respiratory conditions including chronic airflow limitation (CAL) and may vary over time, during acute exacerbations and with pharmacological intervention. Current methods of measuring MCC are limited by their technical requirements and are not suitable for widespread use.

Methods: A 0.1 ml droplet of macroaggregated albumin labelled with ⁹⁹mTc (2-5 MBq) was injected, after cutaneous application of local anaesthetic, through the cricotracheal membrane into the trachea of a seated subject. For data acquisition the subject lay supine for 15 min under a GE 400 gamma camera interfaced to an Icon workstation (Siemens). All data were stored in Icon interfile format and analysed by CiliaCAD, a program written in IDL specifically for the project. TMV was measured in 14 normal subjects and 17 patients with CAL. Results: The test was well tolerated and no adverse events were reported. TMV (means±SEM) in normal subjects was 8.0 ± 0.8 mm/min. TMV was significantly different in CAL patients than normal subjects (p< 0.001, Student's t-Test). Conclusions: We have developed a rapid, safe, direct, measure of TMV that gives values similar to those reported elsewhere. Using this technique we have shown that TMV is significantly slower in patients with CAL than in normal subjects.

Supported by the ALFi Boehringer Ingelheim CAL Fellowship

Key words: mucociliary clearance, scintigraphic, CAL

MORBIDITY AND 3 MONTH MORTALITY POST LUNG VOLUME REDUCTION SURGERY (LVRS): A MULTI-CENTRE ANALYSIS
FA Finlayson, S Reid, C Franklin, GI Snell, MJ Bailey, EH Vicary, JA Smith, John Finlayson, S Reid, C Franklin, GI Snell, The Alfred Hospital and Monash University, Melbourne, Victoria.

The Australia and New Zealand (ANZ) LVRS Database was established in 1997 to provide clinicians in Australia with information that leads to the best possible outcomes for people who undergo LVRS. At October 1999, the database contained individual patient data from 235 cases from 10 centres. The data have been entered and verified in Access 97 and analysed in SPSS version 9. Univariate and multivariate analysis was undertaken to examine the effect of pre-operative medical and peri-operative surgical factors on morbidity and 3 month mortality post surgery.

129 (55%) cases were male. Mean age at surgery was 62.1 (SD 7.7) years [n=230].

Pre-operatively, mean FEV₁ [% of predicted] = 0.75 L (SD 0.25) [n=228] and mean 6MWD = 323.5 m (SD 113.5) [n=202].

Multivariate Analysis:

| OUTCOME                  | Variable with greatest effect size (%) | Odds ratio [OR] | Regression co-efficient | p value |
|--------------------------|--------------------------------------|-----------------|-------------------------|---------|
| Length of stay           | No complications (19.7)              | -0.75           | 0.0001                  |         |
|                          | Pre-op 6MW (7.5)                     | -0.001          | 0.0001                  |         |
|                          | Thoracotomy (2.1)                    | -0.37           | 0.019                   |         |
| Intercostal drain time   | No complications (20.6)              | -0.74           | 0.0001                  |         |
|                          | Apical resection (5.9)               | 0.52            | 0.0002                  |         |
|                          | Pre-op 6MW (4.2)                     | -0.001          | 0.0011                  |         |
| Death within 3 months    | Thoracotomy [ 15.8 Cl 2.8-87.4]      | 2.70            | 0.02                    |         |
|                          | ICC time (log s) [ 3.86 Cl 1.65-9 ]  | 1.39            | 0.02                    |         |

Post-operative physiological (FEV₁) and functional (6 min walk) parameters improve to 12 months. Pre-operative functional status and surgical factors have the greatest effect on morbidity and 3 month mortality post-operatively.

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Cytokine Gene Polymorphisms in COPD
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Chronic obstructive pulmonary disease (COPD) is characterised by abnormal airways inflammation in response to inhaled toxins. Functionally relevant polymorphisms of key cytokines that mediate inflammation have recently been characterised. Myeloperoxidase (MPO) is a neutrophil lysosomal enzyme that produces bactericidal oxidants and bioactivates toxins in tobacco smoke. Polymorphism at position -463 of the MPO promoter removes a transcription factor binding site thereby reducing MPO expression. Variable numbers of tandem repeats in intron 2 of the interleukin-1 receptor antagonist (IL-1Ra), an anti-inflammatory cytokine, alter IL-1Ra production. A base pair substitution (TNF2 allele) at position -308 of the tumour necrosis factor-alpha (TNF-α) promoter enhances TNF-α expression in vitro. Airway TNF-α and MPO levels increased are COPD, and IL-1Ra expression is increased in asthmatic airways.

 Aim: To examine MPO, IL-1Ra and TNF-α polymorphisms as susceptibility and disease-modifying genes in COPD.

 Methods: Genotypes were determined by PCR In 133 Australian adults with COPD and 128 anonymous blood donors.

 Results: COPD patients (65% male) had mean (SD) age 69.6 (8.5) yr, FEV1 48.2 (19.7) % pred and smoking 54 (33) pack-yr. Variant allele frequencies in COPD were MPO -22%, TNF2 23%, IL1-Ra*2 29%, IL-1Ra*3 3%, which did not differ from controls. Variant alleles for IL-1Ra tended to be more frequent in COPD (32.2%) compared with controls (23.6%) (p = 0.07). IL-1Ra*2 patients had lower mean KCO (55.8%) than those without IL-1Ra*2 (64.4%) (p < 0.05). TNF-α and MPO genotypes did not predict FEV1, KCO or chronic broncos. Conclusions: IL-1Ra may influence disease severity and susceptibility in COPD. Our present data do not provide evidence for MPO or TNF-α as susceptibility genes or modifiers of lung function in COPD. Recruitment is ongoing, to achieve sufficient power to exclude effects in COPD.

 Supported by: The Prince Charles Hospital Foundation, NHMRC Postgraduate Medical Scholarship

 Key words: COPD, cytokines, polymorphisms

 Nomination for Prizes:

 EFFECT OF AN EVIDENCE-BASED GUIDELINE FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) ON PATIENT OUTCOMES.

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 Introduction: Despite the proliferation of clinical practice guidelines, there is limited evidence of their uptake in clinical settings, and even less evidence of impact on patient health outcomes. The Adelaide Collaboration on Chronic Obstructive Respiratory Disease (ACCORD) conducted a trial to evaluate the effect of a management guideline, developed from the best available evidence, on process, impact and patient outcomes. Methods: Between May 1996 and June 1999, 1250 subjects with COPD were enrolled from 4 hospitals, using a pre-post study design, with two metropolitan hospitals assigned to the control arm and two to the intervention arm. Clinical and process measures were monitored for all subjects and health status data collected from consenting subjects at baseline (in hospital), 6 weeks and 6 months (Seattle Obstructive Lung Questionnaire (SOLQ) and General Health Questionnaire, 28 item version (GHQ-28)). Impact of the intervention on length of stay, re-admission rates, and patient health status were assessed on an “intention to treat” basis initially, then adjusted for actual use of the guideline. Results: On the basis of intention to treat, no evidence was found for an effect of the intervention on patient quality of life or mental health status. After adjustment for age and sex, there were indications of a reduction in risk of re-admission associated with the intervention, but this was not statistically significant. Considerable variation in the actual use of the guideline was found, however, and further analyses will be conducted to adjust for this. Conclusions: Our findings support the view that there is a need for research on the implementation of evidence-based medicine and for outcomes to be linked to guideline use.

 Key words: Guidelines, COPD, outcomes, uptake

 Cardiovascular Responses to Incremental Shuttle Walking Test (ISWT) and Six Minute Walking Test (6MWT) in Chronic Obstructive Pulmonary Disease (COPD)

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The 6MWT and ISWT are commonly used measures of exercise capacity in patients referred for pulmonary rehabilitation. Previous research has shown lower heart rate (HR) and dyspnoea levels with the 6MWT, indicating that it may only submaximally stress the cardiorespiratory system. Aim: To compare the cardiorespiratory responses associated with the 6MWT and ISWT in patients with COPD. Methods: 15 patients (12 male), mean (SD) age 62.6 (7.7) years and FEV1, 0.91 (0.47), 31.4 (13) 4 predicted were studied. ISWT and 6MWT were conducted using standard protocols with strong encouragement to maximise performance. HR (Polar monitor) and dyspnoea ( Borg 0-10 scale) were measured at one minute intervals during both tests. Oxygen saturation (SpO2) was measured pre- and immediately post-exercise. Results: There were no significant differences in maximum HR, dyspnoea or the magnitude of desaturation with the two tests (Table). Mean(SD) distance walked in the ISWT and 6MWT was 397(136) and 507(108)m respectively.

Conclusions: With strong encouragement the 6MWT and ISWT can provide equivalent degrees of cardiorespiratory stress. However, unlike the 6MWT, the external pacing and standard increments in workload of the ISWT enables comparison between patients at equivalent workloads and the prescription of a walking program based on workload.

Supported by: Singh SJ et al (1992); Thorax 47: 1019-1024.

Key words: ISWT, 6MWT, chronic obstructive lung disease

Reduced Contribution of the Diaphragm to Postural Control in Patients with Severe Chronic Airflow Limitation

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Contraction of the human diaphragm contributes to the response of the trunk muscles that stabilises the spine during rapid limb movements. This postural function must be coordinated with the respiratory activity of the diaphragm. During repetitive limb movement there is usually phasic modulation of diaphragm electromyographic activity (EMG) with respiration, as well as tonic activity and phasic modulation with each limb movement. Aim: To determine whether this pattern of activity occurs in subjects with increased respiratory demand. Methods: Two groups were tested: (i) six subjects with severe chronic airflow limitation (CAL) who were awaiting lung volume reduction surgery; and (ii) nine subjects with no history of respiratory disease who breathed with an increased dead space for 4 minutes. EMG recordings of the right costal diaphragm were made with intra-muscular electrodes inserted into the 7th or 8th intercostal space. Movement of the left arm was recorded with a potentiometer. Patients with CAL performed rapid repetitive shoulder movements (30°) for 10-20 s while standing or sitting. The normal subjects moved their left arm for the first 10 s of each minute of closed-space breathing. The contribution of the diaphragm to respiration and postural control was assessed by evaluation of the frequencies of phasic modulation of EMG amplitude. This was quantified by analysis of the distribution of power in the power spectral densities. Results: Unlike normal subjects, the CAL subjects had no or minimal modulation of diaphragm EMG at the frequency of limb movement. In the trials in which normal subjects breathed with increased dead space the power of the EMG data at the movement frequency was significantly reduced by the second minute. Conclusions: These results indicate that in situations of increased respiratory demand the contribution of the diaphragm to postural control is reduced.

Supported by the NHMRC and the Australian Lung Foundation.
IMMUNOHISTOCHEMICAL ANALYSIS OF PROTEASE ACTIVATED RECEPTOR (PAR) EXPRESSION IN HUMAN ASTHMATIC Airways.

Darryl Knight1,2, Sam Lim3, Amelia Scaffidi1,2, Nicholas Roche2, K.Fan Chung2, Geoffrey Stewart2 & Philip Thompson1,2.

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PAR are a family of G-protein coupled receptors, auto-activated via proteolytic cleavage of the extracellular amino terminus. PAR-1,-3 and -4 are activated by thrombin, whereas PAR-2 and -4 are activated by trypsin (trypsinase). PAR-2 activation exerts a protective effect in mouse airways, suggesting an important role in the airways response to inflammation. We hypothesized that PAR-1 and PAR-2 expression would be altered in asthma.

Methods: Bronchial biopsies were obtained from 10 normal controls and 20 asthmatics, including 10 who were using inhaled steroids. Frozen sections were stained with monoclonal antibodies to either PAR-1 or PAR-2, visualized with DAB and scored semi-quantitatively for staining intensity and cellular distribution. Results: Specific PAR staining was seen in epithelium (epi), airway smooth muscle (ASM) and macrophages. In normal subjects, epl PAR-1 staining was significantly greater than for PAR-2 and was confined to the apical region of columnar cells. PAR-2 staining was homogenous throughout the epl. The intensity of PAR-1 staining in asthmatic biopsies was not different to controls, although the cellular distribution was distinctly different, appearing diffuse and widespread. In contrast, the intensity of epl PAR-2 staining was significantly increased over control. In biopsies from asthmatics taking inhaled steroids, epl staining for PAR-1 and PAR-2 was similar to controls. Expression of PAR-1 and PAR-2 in ASM was not different between the groups. Conclusion: These findings suggest that asthma per se influences the expression of both PAR-1 and PAR-2 in human bronchial epithelium. The expression of PAR-2 appears to be inducible and may initiate proteic mechanisms in response to airway inflammation.

Supported by the NHMRC and Asthma Foundation of W.A.

Key words: Protease Activated Receptor, epithelium, inflammation, asthma.

EXPRESSION OF METALLOPROTEINASES IN BRONCHOALVEOLAR LAVAGE FLUID OF LUNG TRANSPLANT RECIPIENTS

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The composition of the extracellular matrix (ECM) plays an important role in airway remodelling and increased ECM deposition is causally involved in fibrotic processes. The composition of the ECM is regulated by the balance of ECM synthesis, degradation by matrix metalloproteinases (MMP) and by the activity of their respective inhibitors. We investigated the expression of MMPs in bronchoalveolar lavage fluid (BAL) of patients following lung transplantation and compared the results to histopathological and microbiological findings. MMPs were determined by Zymography as previously described (AJRCCM 1997; 156: 1987). BAL samples of patients with acute rejection (n=15) were compared to those obtained from patients with bacterial or fungal infection (n=19) and to controls (n=17). In addition, MMPs of patients treated for rejection were analysed. MMP-2 and MMP-9 were expressed in all BAL samples. Patients with acute rejection showed a marked increased expression of MMP-2 and a moderately elevated expression of MMP-9 compared to controls. The active form of MMP-2 was typically expressed in BAL samples of patients with bronchial rejection. The amount of MMP-2 and MMP-9 decreased after successful treatment for rejection. The degree of MMP-2 and MMP-9 expression varied in BALs of patients with infection. Conclusion: The expression of MMP-2 might be a useful marker for airway remodelling and treatment success in lung rejection. Further studies will analyse the balance of MMPs and their respective inhibitors.
A KEY ROLE FOR B CELLS IN ASTHMA: BRIDGING THE GAP BETWEEN ALLERGEN RECOGNITION AND TISSUE DAMAGE. 
Alisha A Mameh
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An initial event in the development of asthma is the recognition of allergens by cells of the immune system. Allergens may be recognised by B cells and dendritic cells (DC), which process the allergens into peptides. Processed peptides are subsequently expressed on the cell surface in association with the major histocompatibility complex class II (MHC-II). DC migrate to the draining lymph nodes where they present the peptide/MHC-II complex to T cells, resulting in the activation of antigen-specific T cells. Following activation, antigen-specific T cells can provide "help" to B cells presenting an appropriate peptide/MHC-II combination. T cell "help" is provided by the expression of a new cell surface molecule, CD40L, and the secretion cytokines. It is through the provision of T cell "help" that B cells become activated and differentiate into immunoglobulin (Ig) secreting and memory cells. Igs have a number of isotypes each of which mediate different effector functions. The Ig isotype that is produced as a result of successful T / B collaboration is determined by the pattern of T cell derived cytokines.

In asthma, the formation of IgE secreting cells driven by the cytokines, interleukin (IL)-4 and IL-13, is detrimental. IgE binds to a receptor (FcRI/II) expressed on the surface of mast cells. When IgE binds to an allergen resulting in the cross-linking FcRI/II, it induces a signal that results in mast cell degranulation, releasing inflammatory mediators that cause tissue damage and ultimately lead to airway remodeling. Thus, the B cell by secreting IgE forms a bridge between the initial recognition of an allergen and ensuing tissue damage. While the recognition of allergens and subsequent production of Ig does not normally lead to disease, in asthmatics the immune response appears to be inappropriately regulated thereby allowing hyperactivation of the immune system. Asthma has the hallmarks of an inheritable trait, and one possibility is that mutations that increase the sensitivity of B cells to, or enhance the production of, IL-4 or IL-13 may lead to a predisposition to asthma.

BRONCHOALVEOLAR LAVAGE (BAL) MACROPHAGE AND LYMPHOCYTE PHENOTYPES IN LUNG TRANSPLANT RECIPIENTS. 
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There is little information regarding the role of the alveolar macrophage (AM) in lung transplantation. We hypothesised that changes in BAL AM and lymphocyte phenotypes would be apparent even in stable lung transplant recipients (SLTR) and may be important in understanding the pathophysiology of Bronchiolitis Obliterans Syndrome (BOS). We performed a cross sectional study, using a standardised 3x60ml BAL and flow cytometry in 18 SLTR, 5 subjects with BOS and 18 normals. We found significantly elevated neutrophils in the SLTR (median 4.5%, range 2.5-30.7% versus normal; median 1%, range 1-5%; P<0.05), with a frank elevation in the BOS subjects (median 12.6%, range 2.5-30.7% P<0.05 compared to normals; P<0.04 BAL versus stable). Our lymphocyte data showed increased numbers of: Natural Killer (CD56(1)/CD16(1) positive) cells, CD11b and CD11c on CD3 cells, CD8 positive lymphocytes and increased HLA DR expression on CD8 cells in SLTR and BOS versus normals. In contrast, expression of surface markers associated with a range of AM host defence functions against bacteria, fungi and viruses, were significantly lower in lung transplant recipients: AM data expressed as mean channel fluorescence.

| CD14 | HLA DR | CD11a | CD11b | CD11c |
|------|--------|-------|-------|-------|
| **P<0.05** | **P<0.05** | **P<0.05** |
| Normal | 1.9 | 29 | 10.9 | 2.7 |
| SLTR | 1.4-2.9 | 21-69 | 6-20 | 2.8-11 | 11-36 |
| **P<0.05** | **P<0.05** | **P<0.05** |

Our novel findings may be consistent with a situation in which stable allografts undergo complex lymphocyte and macrophage changes that may result from clinically silent processes of infection, partially suppressed rejection, or both.

Supported by Glaxo-SmithKline, Australia.

Key words: Transplantation, BAL, Macrophage, Infection, Rejection.

HILA-DR EXPRESSION ON TISSUE RESIDENT CELLS IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Asthma and COPD are characterised by persistent airway inflammation. We hypothesised that this results from persistent immune stimulation that activates tissue-resident cells in situ who develop COPD and in asthmatics. We measured HLA-DR expression on fibroblasts, resident macrophages (RM), lymphoid aggregates (LA), epithelium (Epi), smooth muscle (ASM) and mucous glands (G) in cases of COPD and asthma of varying severity. Transverse sections of 3 or 4 large airways from controls (CO), smokers with normal lung function (SM), mild (FEV1 <80%) and severe (FEV1 <50%) COPD and mild (nonfatal – NFA) and severe (fatal – FA) asthma; n=8 in each group, were stained with HAM56 and anti-HLA-DR monoclonal antibodies. HLA-DR+ cells counted in the submucosa were expressed as number (mean ± SE) per mm of the BM while LA, Epi, ASM and G were scored semi-quantitatively (0-100%).

Key words: Asthma, COPD, Inflammation, HILA-DR

Awards: Nil

HUMAN EOSINOPHIL-AIRWAY SMOOTH MUSCLE CELL INTERACTIONS INVOLVE VCAM-1 AND ICAM-1 
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Respiratory Research Group, Departments of Pharmacy1 and Pharmacology2, University of Sydney, NSW 2006

The airways of asthmatic subjects typically contain eosinophils, which have increased amounts of airway smooth muscle and are hyperresponsive. Eosinophils release a variety of mediators implicated in the signs and symptoms of asthma. We have previously established that in co-culture eosinophils attach rapidly to human airway smooth muscle cells (ASM), with maximal adhesion occurring after 2h and then falling gradually to 50% of maximum by 20h. The aim of this study was to determine whether the cellular adhesion molecules VCAM-1 and ICAM-1 are involved in human eosinophil-airway smooth muscle cell interactions. Methods: ASM were plated into 96 well plates, 25 x 10^3 cells/well and cultured for 48h. Purified eosinophils were obtained from the blood of healthy volunteers using immunocollagenic cell sorting and 2 x 10^5 cells/well added to the ASM for 2 or 20h in the presence or absence of antibodies to VCAM-1 and ICAM-1 at 1, 3 and 10µg/ml. Culture medium and non-adherent eosinophils were removed and the remaining attached cells washed 3 times, fixed and stained with Kymura Light. Adherent eosinophils were identified and counted across 20 fields of view using light microscopy and 200x magnification. Results: Eosinophil adhesion to airway smooth muscle cells treated with anti-VCAM-1 (1µg/ml) was significantly (p<0.05, n=4) reduced to 71±4% of control after 2h, but not after 20h, of co-culture. In contrast, adhesion in the presence of anti-ICAM-1 (3µg/ml) was not altered after 2h, but was significantly (p<0.05, n=4) reduced to 77±2.3% of control after 20h of co-culture. Conclusions: This study provides the first demonstration that VCAM-1 is involved in the initial attachment of eosinophils to airway smooth muscle cells and that ICAM-1 is involved in their prolonged adhesion. It is possible that eosinophils, attached to smooth muscle cells via these molecules, directly modulate airway smooth muscle function in asthmatic airways.

Acknowledgments: We thank the donors and acknowledge the collaborative effort of the transplant team at St Vincent's Hospital. This study was supported by NHMRC and the Ramacloti Foundation of NSW.
INTRAPLEURAL FIBRINOLYTTICS IN COMPLICATED PARAPNEUMONIC EFFUSIONS AND EMPYEMA- A SYSTEMATIC REVIEW.
R.J.Cameron, H.Davies
Background. Intrapleural fibrinolysis has been used to treat complicated parapneumonic effusions and thoracic empyema for 50 years. Randomised controlled trials (RCT) addressing efficacy, safety and equivalent dosing have emerged only in the late 1990s. Objectives To conduct a systematic review of the literature concerning the benefit of adding intrapleural fibrinolytic therapy to intercostal tube drainage in the treatment of complicated parapneumonic effusions and empyema. Selection criteria. All studies were Randomised Controlled Trials. Participants. Patients >14y with thoracic empyema or complicated parapneumonic effusions with no prior surgical intervention or traumatic thoracostomy tubes. Interventions. 1/ Intrapleural fibrinolysis v control. 2/ intrapleural streptokinase vs. intrapleural urokinase.
Data collection & analysis. All identified RCTs were reviewed independently by two reviewers. Reviews were scored according to the Cochrane assessment of methodology quality. Main results. One RCT directly comparing streptokinase and urokinase found both were equally effective in treatment outcomes, but streptokinase had a slightly higher non-fatal complication rate. Two RCTs compared streptokinase or urokinase vs normal saline control. There was significant improvement in length of hospital stay (p=0.02), time to defervescence (p=0.006), improvement in chest radiograph, treatment failure defined as death or requirement for surgery (p=0.02) when the results were pooled, although individual study results did not necessarily show this. Significant complications attributable to therapy were not seen.
Conclusions. Intrapleural fibrinolytic therapy confers significant benefit when compared with normal saline control. The numbers in the RCTs are small and results of a larger 500 patient trial are awaited. Both agents are equally efficacious but streptokinase has a slightly higher non-fatal complication rate. Life-threatening complications are rare and were not seen in the RCTs. Evidence therefore suggests that intrapleural fibrinolysis can be considered as first-line therapy in these conditions. Issues regarding optimal dosing schedules and intrapleural fibrinolysis v surgery are discussed and larger trials are awaited for this evidence.

DEVELOPMENT OF MOLECULAR DIAGNOSIS IN COMMUNITY ACQUIRED PNEUMONIA (CAP)
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Canterbury Respiratory Research Group, Waikato Respiratory Research Group, Canterbury Health Laboratories, Dept of Medicine, Christchurch School of Medicine, New Zealand.
Aim: To assess the diagnostic yield of rapid molecular diagnostic techniques, for causative pathogens in CAP.
Methods: All patients over the age of 18 years admitted to Christchurch and Waikato hospitals between 26/07/99 and 08/10/99 with a principal diagnosis of CAP were prospectively enrolled in the study. Clinical samples were taken from each participant. All samples were processed for immediate traditional and new molecular diagnostic techniques. The remaining aliquots were frozen at -80°C for subsequent molecular diagnostic testing. Participants were followed up at 6 weeks. Age and sex matched controls admitted without respiratory conditions were identified and sampled to allow comparative testing of new molecular diagnostic techniques.
Results: 183 participants were enrolled with a mean age of 64 years, 53% female. 84 (46%) had received vaccination in the proceeding 12 months, however only 6 (3.3%) received "Pneumovax". 54 (30%) had received antibiotics prior to admission. Average length of hospital stay was 6.7 days with 8 (4.4%) deaths within the 6 week follow up period. 9 (5%) were admitted to ICU and 28 (15%) had significant complications attributable to their CAP. Of the survivors, six week follow up occurred in 93%. A microbial diagnosis was achieved for 92 (50%) cases, 36 (20%) St. pneumoniae, 29 (16%), H. influenzae, 24 (13%) Influenza A, 10 (5%) Adenovirus, 5 (3%) Influenza B, 5 (3%) RSV, 5 (3%) Legionella spp, 4 (2%) S. aureus, 2 (1%) Mycoplasma pneumoniae and 5 (3%) others. In 29 (16%) cases multiple organisms were isolated. Legionella PCR has been performed for 86 cases, being positive in 9 (10%), with no positives in the controls tested.
Conclusion: These are results from an ongoing 12 month study. The diagnostic yield from traditional techniques was 50%. We have demonstrated an improved sensitivity for Legionella spp through the application of Legionella PCR in parallel to traditional culture results. Molecular tests in this population have no false positive results, neither from an ongoing 12 month study. The application of the PCR results allows for continuing work to further explore the utility of new molecular techniques for the diagnosis of Legionella spp and other common causative pathogens in CAP.

QUANTITATIVE ANALYSIS OF CMV PCR AND ANTIGENEMIA ARE COMPLEMENTARY IN PREDICTING DEVELOPMENT OF CMV DISEASE AND RESPONSE TO THERAPY POST TRANSPLANT
E. Gibbey, J. Flexman, R. Tarala, I. Kay, S. Palladino, R. Larbaletier, G. O'Driscoll, Cardiopulmonary Transplant Unit, Royal Perth Hospital, Australia.
CMV disease is a major cause of morbidity in transplant recipients. The detection of CMV DNA by PCR or antigenemia may allow early detection of CMV infection but their predictive value is uncertain. Aim: To determine whether a quantitative assessment of CMV DNA in plasma by PCR (Roche CMV Monitor assay) and CMV antigenemia (p65) could predict the development of CMV disease. Method: Serial weekly assays were performed in a blinded fashion on 16 thoracic organ recipients (9 Lung and 7 Heart) who were at risk for CMV disease (CMV Donor Positive / Recipient Negative or previous CMV disease). CMV disease was defined by tissue invasion with an appropriate clinical syndrome. Results: There were 7 episodes of CMV disease (pneumonitis 5, duodenitis 2, hepatitis 1 and colitis 2). Median (range) PCR (copies/ml) and antigenemia (positive cells/10⁴ leucocytes) in the weeks before and after disease are shown. Disease is at time-point zero. Significant differences (p < 0.05) between time points was determined by the Mann-Whitney test for paired samples.

FUNGAL INFECTIONS FOLLOWING LUNG TRANSPLANTATION
M Tamm, M Malouf, A Glanville
Heart Lung Transplant Unit, St Vincent’s Hospital, Sydney, Australia. Rejection and infection are the major contributors to morbidity and mortality after lung transplantation. Fungal infections are well recognised complications within the first few months after surgery but only few data are published in regard to the impact of late fungal infections. We analysed pulmonary fungal infections occurring later than 6 months after transplantation in 65 heart-lung (HLT), 105 single (SLT) and 108 bilateral (BLT) lung transplant recipients. Early pleural candida infection developed in 4 cases whereas late invasive candida infection was only found in two cases. Pulmonary nocardiosis was diagnosed in five patients later than 6 months after transplantation presenting as abscesses in three and empyema in another case. Three patients were successfully treated but in two the diagnosis was only made post mortem. Scedosporium apiospermum and Scedosporium prolificans was repeatedly documented in BAL fluid of 7 patients 11 to 58 months after transplantation. All 7 patients showed airflow problems. Eradication of scedosporium infection proved difficult but this opportunistic infection did not disseminate under treatment with itraconazole and fluconazole. Aspergillus could be cultured from BAL of 26.2% HLT, 28.6% SLT and 51.9% BLT recipients within the first few months after transplantation. Later than six months after surgery aspergillus was documented in 36.4% HLT, 29.6% SLT and 22.2% BLT recipients. Invasive aspergillus was most often associated with bronchitis obliterans but also developed in the native lung of 6 SLT recipients.
Summary: late pulmonary fungal infections are associated with a considerable morbidity and mortality following lung transplantation, especially in patients with bronchitis obliterans.
MYCOBACTERIUM KANSASII IN QUEENSLAND 1988-99
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Mycobacterium kansasii is the second most common pulmonary nontuberculous mycobacteria isolated in QLD. Aim: To review the clinical features, bacteriology and treatment of all pulmonary isolates of M. kansasii in PAH from 1988 to 1999. 71 isolates were obtained from 63 patients, 1 in sputum, 1 in blood and 62 in sputum. Results: Disease incidence rose from 0.073 (1988) to 0.376 (1998) per 100,000. Of the 65 pulmonary isolates, 49 (75.4%) patients were notified as having clinically significant disease, 3 had probable disease and 3 possible disease. Median age of those with disease was 56 years (range 31-86), compared with 75 years (53-86) in those without disease (p=0.007). 77% were male. Predisposing conditions were seen in less than 30% Consolidation (41.7%) and cavitation (36.7%) were the most common Xray findings, predominantly in the upper lobes (50%). Forty-five (69.2%) patients were treated; 17 had documented side effects. Most regimens involved Ethambutol, Rifampicin, and Isoniazid (American Thoracic Society recommendations). Twenty-four patients (56% of those treated) received Pyrazinamide (16 for more than 2 months). Mean duration of treatment was 12 ± 6.6 months (range 0.5-24); 86% responded. Four patients died despite treatment (2 were intolerant of the medication); 4 died before treatment was initiated. There were no documented cases of relapse. In vitro sensitivities on 28 isolates showed all were sensitive to Rifampicin, 1 resistant to Ethambutol and all resistant to Isoniazid. Conclusions: Disease incidence has increased significantly. Treatment has been successful, though side effects common. 100% resistance to Isoniazid was seen, yet this drug is still included in treatment regimens. The absence of relapse in those treated for less than 18 months is supportive of shorter course therapy. Treatment of this disease in Australia should consider local experience and sensitivities.

Supported by a Princess Alexandra Hospital Clinical Research Fellowship and the Specialised Health Services TB Control Centre

Key words: mycobacteria, kansasii, nontuberculous

A RANDOMISED TRIAL OF HOME VS HOSPITAL INTRAVENTOUS (IV) ANTIBIOTIC THERAPY IN ADULTS WITH INFECTIOUS DISEASES
Joanne Wolter, Ruth Cagney & Joseph McCormack.
University Department of Medicine, Mater Adult Hospital, Brisbane.

Delivery of hospital care in the home is a rapidly growing industry favoured by patients, their families and the medical profession. Despite widespread adoption of home care services few randomised trials have compared health outcomes in the hospital and at home. We performed a prospective randomised trial of home versus hospital therapy in adults receiving IV antibiotics and compared clinical, quality of life (QOL) and cost outcomes.

Methods: Consecutive adults with an infection requiring IV antibiotic therapy, compliance, stable disease, family support, telehome and transport were randomised to receive home care or complete their treatment in hospital. Where possible patients at home were taught to self-administer their antibiotics. QOL: Short Form 36 (SF-36) and Perceived Health Competence Scale (PHCS). Statistical analysis: unpaired t-tests, Mann-Whitney tests, ANOVA.

Results: 128 patients were referred, 81 patients were randomised (39 home). Most common reason for non-inclusion was patient preference for one form of therapy over another (23 patients). Conditions treated included cellulitis, cystic fibrosis, pneumonia, UTI, wound infection, osteomyelitis, meningitis, endocarditis. 13 patients withdrew after randomisation, 7 because of randomisation to the hospital arm where an alternative home care option was offered. There were two unexpected readmissions in the home arm (patient request and CF not responding to therapy) and three further adverse events thought to be related to the study (IV site infection, PICC-line fracture and a related DVT). Preliminary analysis indicates average mean treatment duration was 18.8 days (SD 24) in the hospital arm and 14.2 days (SD 11.8) in the home arm (p=0.38). Mean duration of home-based care was 7.0 days (SD 5.2).

Conclusion: Recruitment to randomised trials of home versus hospital therapy is hampered by patient and staff expectations. Preliminary review of results suggests home IV therapy is well tolerated and is an appropriate treatment option for selected patients. Further clinical, QOL and cost outcomes will be presented.

Key words: home therapy, intravenous, quality of life, cost, infection

Supported by: Mater Private Practice Fund, Roche Pharmaceuticals

THE TNFα-250 AND TNFα-308 GENE POLYMORPHISMS ARE IMPORTANT IN COMMUNITY ACQUIRED PNEUMONIA(CAP).
Waterlo@ GWL Quasney MW, Zhao CL, Jones CD, Wunderlich RG, Pulmonary and Critical Care Research, Methodist-Lebonheur Healthcare, Memphis. 2 Department of Pediatrics, University of Tennessee, Memphis.

Introduction: Clinically, CAP varies markedly even in similar patients with identical pathogens; genetic factors are likely to be important. The TNFα-250 and TNFα-308 gene polymorphisms influence the outcome of some infectious diseases. We hypothesized that they would have an impact on CAP. Methods: A prospective cohort study of CAP. Septic shock(SS) was defined using ACCP-SCCM criteria. Type I respiratory failure(T1RF) was defined as an O2 saturation on room air of <80% with a normal pCO2. Genotype was determined using PCR amplification and restriction enzyme digestion. Genotype proportions are given in the order AA/AG/GG.

Results: 169 patients were genotyped, 19 had SS, 45 had T1RF. The proportion of patients in each genotype developing SS were: TNFα-250 0.180/0.707/1.0 (p<0.08 AA vs non AA); TNFα-308 0.200.8/0.9/1.0 (p=NS). Carrying at least one AA genotype had an 18.6% risk of SS vs 7.3% (p=0.04). GG homozygotes at both sites had only a 3.6% risk of SS. No subject was AA at both sites. T1RF in each TNFα-250 genotype was: 0.31/0.20/0.37 (p=NS), however for T1RF in patients with no chronic respiratory disease it was 0.31/0.20/0.50 (p=0.02 for GG vs GA).

Conclusions: The TNFα-250 and TNFα-308 AA (hyper-secretor) genotypes are associated with SS and therefore these polymorphisms are important in the genetic variability of host response to CAP. The association between T1RF in patients without chronic lung disease and the TNFα-250 GG genotype (TNFα hyper-secretor) has important implications for immunotherapy in both CAP and sepsis, as well as for the definition of the systemic inflammatory response syndrome(SIRS) itself.

Wednesday April 12 – Asthma & Allergy SIG Orals (1500-1630)

DOES ENCASEMENT OF BEDDING IMPROVE ASTHMA IN ATOPIC ADULTS WITH ASTHMA?
S.C.Dharmage1, M. Bailey1, C. Wharton1, R. Raven1, D. Cao1, J. Rolland1, F. Thien4, L. Light4, N. Freezer5, E. H. Walters2, C. Wharton1, N. Freezer5, E. H. Walters2, C. Wharton1, N. Freezer5, E. H. Walters2. 1 Departments of (1) Epidemiology & Preventive Medicine, (2) Respiratory Medicine, (3) Immunology & Immunology, (4) Allergy. Asthma & Clinical Immunology, Monash Medical School & The Alfred Hospital, Prahran, 3181 and (5) Respiratory Medicine, Monash Medical Centre, Clayton 3168

The efficacy of house dust mite (HDM) avoidance in improving asthma control is controversial. Aim: To evaluate the impact of encasement of bedding with impermeable covers on asthma outcomes in HDM sensitised adults. Methods: A group of 33 young adults with current asthma and positive skin tests to HDM were recruited from Asthma Clinics. They were randomised into either an intervention group whose pillows, mattress and doonas were encased with impermeable covers, or a control group who received cotton covers. Before and 3 and 8 months after encasement, home visits were made to collect dust samples which were assayed for Der p 1. Clinical outcomes included quality of life, lung function, bronchial hyperreactivity to methacholine and symptom/medication/peak flow diaries. Differences between groups were examined using t tests and repeated measures analysis of variance. Results: Quality of life improved in both the intervention and control groups (p=0.02, 0.04), but there was no significant difference between groups. There was no significant change in FEV1, FVC or PEF. There were no significant differences between groups in daytime or nocturnal symptoms, requirements for reliever or preventive medication, morning or evening peak flows. Diurnal variability in peak flow was greater in the control group (10.4% v 8.2%, p=0.05), but the change over time did not differ between groups. Conclusions: Encasement of bedding alone is insufficient to produce worthwhile clinical improvements in asthma symptoms, medication requirements, lung function, bronchial hyperreactivity or quality of life in adults with asthma who are sensitised to HDM. Supported by the Victorian Department of Human Services.

Key words: Asthma, encasement of bedding, house dust mites, epidemiology

Nominations for awards: Nil
A METHOD FOR DETECTING AND MEASURING HDM ALLERGEN IN THE UPPER AIRWAYS
Sandros E Fonseca CMC, Rimmer J, Vanlaar C, Tovey ER, Salome C. Institute of Respiratory Medicine, University of Sydney, NSW 2050.

HDM allergen has been related to asthma pathogenesis and in susceptible individuals may be related to severity or exacerbations of asthma. Although it is possible to measure environmental HDM allergen levels, we have no non-invasive and sensitive method to measure the amount of allergen that reaches the upper airways. Aim: To develop methods to detect and measure Der p 1 in the upper airways. Methods: In 5 non-atopic subjects 0.2ml aqueous Der p 1 extract (3800ng) was sprayed into a nostril on 2 different days. A nasal wash, using a squeeze bottle containing 10ml saline, was performed before allergen inhalation. Thirty seconds after the inhalation subjects gargled with 10ml saline, then performed a second nasal wash and nasal mucus was collected. Mucus was divided into liquid (n. mucus-L)and gel (n. mucus-G). Der p 1 levels in all samples were measured by ELISA assay, and the amount of allergen was expressed as a percentage of the dose delivered. Results: The table shows % recovery in each sample on 2 test days (mean ± 95% confidence intervals).

|        | n. wash | n. mucus-L | n. mucus-G |
|--------|---------|------------|------------|
| Test 1 | 1.63 ± 2.1% | 5.18 ± 3.6% | 4.64 ± 3.8% |
| Test 2 | 0.04 ± 0.47% | 2.33 ± 2.3% | 4.3 ± 3.3% |

Conclusion: It is possible to detect Der p 1 in secretions from the upper airways following allergen administration. The allergen is primarily found in the nasal cavity, detectable in the mucus or the nasal wash, and very little passes through to the pharynx to be detected in the gargle. This method could be a useful new tool to examine amount of allergen that reaches the airways under varying conditions.

Key words: HDM, Der p 1 allergen, respiratory secretions, non invasive method

Study support: FAPESP - Brazil, Institute of Respiratory Medicine - Australia

THE ROLE OF THE SULFITE ADDITIVES IN WINE-INDUCED ASTHMA

Hasan Vally & Philip J. Thompson.

Aims and Methods:
The aims of this study were to identify asthmatics exquisitely sensitive to the sulfite additives in wine using a single dose sulfited wine challenge protocol, and to describe the dose response characteristics of these responses using a double blind placebo controlled challenge model. In addition, the efficacy of a cumulative dose sulfited wine challenge protocol to identify asthmatics sensitive to the sulfite additives was also assessed. Results: Four out of 23 self-reporting wine-sensitive asthmatics were found to respond to sulfite additives in wine using the single dose challenge protocol. In the double blind dose-response study, all of these asthmatics exhibited a significant fall in FEV1 (> 15% from baseline) following challenge with wine containing 300 ppm sulfite. Asthmatic responses were maximal at 5 min, with an average decline in FEV1 of 28.7 ± 13 %, and took between 15 and 60 min to return to baseline levels. In the cumulative dose-response study, the responsiveness of 12 asthmatics provided a history suggesting a sensitivity to the sulfite additives in wine was compared with the response of 6 asthmatics reporting no sensitivities to these drinks. No significant difference was observed in any of the lung function parameters measured (FEV1, PEF, PEF%pred) in these 2 groups. Conclusions: These results suggest that only a small number of wine-sensitive asthmatics respond to a single dose challenge with sulfited wine under laboratory conditions and that cofactors may be playing a role in the sensitivity of some asthmatics to wine. A cumulative dose challenge protocol did not increase the sensitivity of our test for reactivity to the sulfites in wine.

Acknowledgements: Wines for these studies were kindly donated by Hardy's BRL.

Key words: Asthma, wine, sulfites.

REDUCTION IN AIRBORNE HOUSE DUST MITE ALLERGEN AFTER OCCLUSIVE COVERING OF BEDDING

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Wellington Asthma Research Group. Wellington School of Medicine, Wellington, New Zealand; and National Institute of Health - Tokyo, Japan.

Mite occlusive bedding covers are recommended to reduce house dust mite (HDM) allergen exposure for HDM sensitised individuals with allergic disease. As inhaled HDM allergen is more relevant than HDM allergen levels in settled dust, we have studied whether occlusive bedding covering reduces the airborne HDM allergen, Der p 1 in 1 bedrooms. We obtained dust samples by vacuuming (1 m2/min) from pillows, duvets, and mattresses of 12 subjects. Additionally, air was sampled for 8 hnight for 7 nights with a personal sampler (Sibata, Japan) at 1 L/min. Pillows, duvets, and mattresses were then covered with occlusive covers (Alprotec, UK) for 7 days, and during this time air was sampled as described above. After the 7 days, dust samples were obtained as described above directly from the surface of the bedding covers. Der p 1 in dust samples was measured by double-monoclonal antibody ELISA, and in the air samples by an extremely sensitive fluorimetric ELISA. Der p 1 levels are expressed as geometric mean (95% confidence intervals), bedding samples as µg/m2, and airborne samples as µg/m3. Statistical analysis was by paired t-test. Der p 1 levels decreased after covering pillows (from 0.47 µg/m3, 0.20–0.10, to 0.09 µg/m3, 0.05–0.17, p = 0.0021), duvets (from 1.15 µg/m3, 0.50–4.43, to 0.07 µg/m3, 0.03–0.16, p < 0.0001), and mattresses (from 26.0 µg/m3, 5.9–114.8, to 0.34 µg/m3, 0.09–1.40, p < 0.0004). Airborne Der p 1 decreased from 102.1 µg/m3 (45.8–228.6), to 17.5 µg/m3 (7.2–42.7), p = 0.0063. This study is the first to show that, concomitant with a reduction in bedding Der p 1 levels, airborne Der p 1 levels decreased approximately six-fold after occlusive covering of bedding for 7 days.

Supported by a grant from the Health Research Council of New Zealand

SETTLING DER P 1 IS NOT AFFECTED BY ALLERGEN CONTROL IN BEDS
Vanlaar CH1, Mihrshahi SP, Peat JK2, Marks GB3, Forbes SP, Vukanis NP, Wainwright C1, Krause WP, Prater GF, Meills C2, Tovey ER11.

Institute of Respiratory Medicine, NSW 2050; Clinical Epidemiology, New Children's Hospital, NSW 2124; Dept. Respiratory Medicine, Liverpool Hospital, NSW 2170.

Rationale: Petri dishes may be used to collect settling dust to provide a simple estimate of ambient mite aeroallergen exposure over time. We measured aeroallergen near the beds of control and intervention groups involved in a study controlling mite allergens in beds and compared this to reservoir levels in those beds.

Methods: Settling dust was collected in Petri dishes placed adjacent to beds that had been fitted with occlusive mattress and pillow covers and where all bedding was laundered with an acaricidal additive. Dishes were also placed next to control beds where no intervention had been implemented. Reservoir bed dust was collected by vacuum sampling at the time dishes were opened (zero weeks) and eight weeks later. Dishes were left open for four to eight weeks. Der p 1 was extracted from reservoir and settling dust and measured by ELISA.

Results: Geometric mean (GM) and median values are presented

| Der p 1 measure | Active | Control | p value |
|----------------|--------|---------|--------|
| Median Petri dish (ng/m2/day) | 15.38 (n=79) | 15.29 (n=79) | 0.7477 |
| GM in bed (µg) | 2.56 (n=73) | 3.36 (n=71) | 0.3661 |
| Median dust (ng/m2) | 3.52 (n=79) | 7.16 (n=79) | 0.0017*** |
| Geometric mean (µg) and median (ng/m2) | 0.022 (n=77) | 0.044 (n=76) | 0.5719* |

* Mann-Whitney U test ** Independent samples t test *** Median test

Correlations (Spearman's) of Petri dish settling rate with Der p 1 concur. in beds: Week 0 rho = 0.23 (p = 0.0057); Week 8 rho = 0.27 (p = 0.0008).

Petri dish with rate of change in total allergen: rho = 0.10 (p = 0.2296).

Conclusions: The bed intervention did not result in a lower rate of Der p 1 allergen settling in Petri dishes kept adjacent to beds despite intervention beds having less total allergen and a lower concentration of allergen in dust. Petri dish Der p 1 allergen levels showed a weak but significant correlation with bed reservoir levels but not the rate of total allergen change in beds. The allergen content of settling airborne dust may be affected by sources other than the bed. (Supported by the NHMRC). Key words: allergen control, Petri dish, aeroallergen
REPORTED FOOD ALLERGY IS OVERESTIMATED
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We have previously found that young adults perceive food intolerance and allergies as common, however IgE mediated food allergy is deemed to be uncommon. Aim: To determine how much of perceived food allergy/intolerance was due to IgE mediated food allergy, as defined by skin prick tests (SPT). Methods: In 1998, 457 young adults (26-50 years) underwent SPT to five common food allergens (cow's milk, peanut milk, egg white, shrimp and wheat) and were asked whether they had ever suffered any food "illness/trouble" and if so to list such food(s). A positive SPT was defined as white formation of ≥3 mm diameter. Cohen's kappa (κ) was used to assess the agreement between SPT and self-reported reactions to food(s) which contain the allergen of interest. Results: 62 participants had a positive SPT to at least one food allergen. The table below summarises the main results. A κ value of <0.2 = poor agreement.

| Food allergen | SPT+ (n) | 'illness/trouble' (n) | SPT+ & food 'illness/trouble' (n) | κ |
|---------------|---------|----------------------|----------------------------------|---|
| Cow's milk    | 4       | 29                   | 0                                | -0.016 |
| Peanut mix    | 28      | 1                    | 4                                | 0.200 |
| Shrimp        | 13      | 20                   | 5                                | 0.77 |
| Egg white     | 9       | 2                    | 1                                | 0.053 |
| Wheat         | 13      | 9                    | 0                                | -0.024 |

Conclusions: There was little agreement between self-reported "illness/trouble" to food(s) known to contain the food allergen of interest, and positive SPT, suggesting that most reactions are not due to IgE mediated food allergy.

Supported by the NHMRC

Key words: food intolerance, food allergy, skin prick test, epidemiology
Nominations for awards: Nil

CPAP DOES NOT ABOLISH INTRINSIC POSITIVE END-EXPIRATORY PRESSURE (IPEEP) IN SEVERE STEABLE COPD.
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2)Department of Critical Care Medicine, Flinders Medical Centre, SA 5041.

Introduction: IPEEP may contribute to chronic respiratory failure in COPD, constituting an inspiratory threshold load (ITL) on muscles already at a severe mechanical disadvantage. Extrinsic PEEP has been advocated to relieve the ITL caused by IPEEP. We sought to document the effect of incrementally increasing extrinsic PEEP (as CPAP) on ITL during wakefulness. Methods: Nine patients with severe stable COPD (mean FEV1 30.7% pred) were studied. CPAP was increased in 1cmH2O increments to a maximum of 10cmH2O. At each pressure we measured: i) IPEEP as the change in esophageal pressure (ΔPoes) from the onset of inspiratory effort to the start of flow ii) ΔPeso in transdiaphragmatic pressure (ΔPdi) over the same interval iii) Pressure-time product (PTP) for the respiratory muscles. iv) End-expiratory lung volume (EELV). Results: In 8 subjects, ΔPdi closely matched ΔPoes, indicating minimal contribution of abdominal expiratory muscles to measured IPEEP. In these 8, mean (±SEM) baseline pressure was 2.86(0.61) cmH2O. CPAP significantly reduced but did not abolish measured ITL. Mean minimal ITL was 0.96(0.15) cmH2O (p<0.05). PTP per litre ventilation reduced from 5.84(1.03) to 2.10(0.42) cmH2O/L, without a change in minute ventilation, but at the expense of progressively increasing lung volume, to a maximum of 0.58(0.11) L above baseline. Conclusions: In severe stable COPD it is not possible to abolish the ITL due to IPEEP using CPAP. Intrinsic muscle pressure output is reduced but there is progressive hyperinflation. Possible reasons include i) IPEEP is not due to dynamic airway compression, but rather fixed airflow obstruction ii) marked inhomogeneity in severity of dynamic airway compression prevents complete counterbalancing of IPEEP.

Supported by the NHMRC and Dawson Park Research Foundation.

Key words: COPD, Intrinsic PEEP, CPAP
Nominated for Awards: John Read prize.

TREATMENT OF OBSTRUCTIVE SLEEP APNOEA WITH NOCTURNAL CPAP INCREASES AWAKE ALVEOLAR VENTILATION AND DECREASES VENTILATION-PERFUSION (V/Q) INEQUALITY.
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Some patients with obstructive sleep apnoea (OSA) have daytime hypoxia in the absence of significant lung disease. Treatment of OSA with continuous positive airway pressure (CPAP) can partly reverse this hypoxia: the mechanisms of improvement are unclear. We have performed detailed gas exchange studies using the multiple inert gas elimination technique (MIGET) on 4 patients with OSA, 3 with awake hypoxia and eupnea and 1 with awake hypoxia and hypercapnia (obesity hypoventilation syndrome [OHS]), at baseline and following 4 months of treatment with CPAP (3 patients) or bi-level positive pressure (1 patient). The patients were obese, BMI 48(10 kg/m²) with FEV1 2.2(0.2 L (68%) predicted) and FEV1/FVC 82(5%) with significant hypoxia, PaO2 82(11 mmHg and PaCO2 47(8 mmHg). At baseline, the MIGET measure of perfusion to low V/Q units (log SD Q) was increased at 0.70(0.35) (normal <0.60), with increased shunt in 3 patients (3.3(3.9)). The MIGET measure of ventilation to high V/Q units (log SD V) was normal (0.54(0.11)). After 4 months of treatment, PaO2 had increased to 620(9 mmHg (p=0.06, paired t-test) and PaCO2 had fallen to 42(8 mmHg (p<0.01). Alveolar ventilation (VA) had increased in all, 7.3(1.1 L/min to 8.7(0.8 L/min (p<0.05) and PaCO2 had fallen to 41(8 mmHg (p<0.05) and 1.6(0.9% (p<0.08) respectively. The increase in PaO2 was due to both reduced V/Q inequality (64%) and increased VA. Treatment of OSA and OHS increases awake Va, reduces the perfusion to low V/Q units and decreases intrapulmonary shunt. This suggests that patients with OSA (even without OHS) have chronic awake hypventilation and that sleep-disordered breathing results in awake V/Q inequality. Treatment with nocturnal CPAP partly reverses these abnormalities.

Supported by the NH&MRC

Key words: OSA, MIGET, CPAP, hypoxia
Nominations for Awards: TSANZ/ALF John Read Prize Physiological Research

REPEATABILITY AND NORMALISATION OF DIAPHRAGM ELECTRO-MYOGRAM (EMG) SIGNAL STRENGTH IN HEALTHY SUBJECTS
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The root mean square of the diaphragm EMG signal (RMSdi) during inspiration has been used to quantify activation of the diaphragm during tidal breathing (Sinderby et al JAP 1998;85:2146-58). To examine the RMSdi response to hypercapnic ventilatory stimulation, its repeatability, and methods of normalisation, we measured breath-by-breath RMSdi, tidal volume, duration of respiratory cycle (Ttot), and end-tidal PCO2 in four healthy subjects (age [mean ± SD] 44.8 ± 13.5 yrs, BMI 28.1 ± 10.0 kg/m²) on two occasions during steady-state ventilation at seven levels of FiCO2 between 0 and 0.08 presented in random order. RMSdi was measured using a multi-electrode oesophageal catheter and controlled for signal contamination and diaphragm position. We also measured RMSdi obtained during a slow inspiration from FRC to TLC (RMSdimax), electrocardiogram R wave amplitude at the oesophageal electrode pair closest to the diaphragm and thickness of the costal diaphragm by ultrasound. We found that (a) the coefficient of variation of RMSdi over 10 breaths at peak ventilatory stimulation (FiCO2 0.08) ranged from 0.07 to 0.15, and this coefficient improved only marginally when a greater number of breaths were analysed, (b) RMSdi increased progressively with FiCO2 in all subjects, (c) the repeatability of RMSdi improved after normalisation with either RMSdimax or R wave amplitude, (d) differences in RMSdi between the subjects were eliminated after normalising with RMSdimax and Ttot (p = 0.10, ANOVA) and (e) RMSdi was not proportional to thickness of the costal diaphragm. We conclude that neural drive to the diaphragm in healthy individuals can be measured using the mean RMSdi over 10 breaths during steady state ventilation, and can be normalised by dividing it by the RMSdi during a breath from FRC to TLC and the duration of the respiratory cycle.

Supported by the NHMRC, Medical Research Fund of WA and SCGH Research Fund.
UPPER AIRWAY EXTRALUMINAL TISSUE PRESSURE IN RABBITS
Kristina Kairaitis, Sarah R. Garlick, Jason P. Kirkness, Terence C. Amis and John R. Wheatley.
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Pharyngeal patency depends upon the balance of forces acting across the upper airway walls. While the influence of intraluminal pressure on upper airway patency has been studied extensively there is little information describing upper airway extraluminal tissue pressure (ETP). Methods: We studied 7 adult, male, supine, anaesthetised, spontaneously breathing, New Zealand White rabbits. ETP was measured with a pressure transducer tipped catheter (MPC segment) was studied. Significant change in ETP with head change mean ETP, however, mouth opening to 2cm increased mean ETP to the upper airway. This mean force of 155.4 (35.4) g was extrapolated over adm ission (mean 90, range 50-250). There is dispersal by the three enzyme technique. ETP was positive in all rabbits (6.1 (1.7 SEM), range 1.2-13.5 cm H2O) and varied from 5.1 (1.8) cm H2O with the same frequency as respiration. There was no significant change in ETP with head flexion from 30° to 90°. However, further flexion to 7° resulted in a significant increase in ETP to 7.7 (1.9) cm H2O (ANOVA, p<0.05 compared to 30° and 50°). Mouth opening (no mask, head position of 70°) to 1cm (between the upper and lower incisor teeth) did not change mean ETP, however mouth opening to 2cm increased mean ETP to 10.1 (2.5) cm H2O (p<0.05 ANOVA, compared with mouth closed). No significant effect of mouth opening was observed with other head positions (p<0.05). Following tracheostomy, caudal displacement of the trachea with a mean force of 156.4 (25.4) g resulted in a significant increase in ETP from 11.6 (5.4) to 7.7 (5.5) cm H2O (n=6, p<0.05 Wilcoxon signed rank).

Conclusions: In rabbits, ETP is positive and thus exerts a collapsing force on the upper airway. This force is increased by head flexion and mouth opening, and decreased by caudal traction on the trachea.

Supported by: NH&MRC

Key words: Cystic fibrosis, sputum, cytokines, cytokology

Nominations for Awards: Nil

SPUTUM CYTOMETRY AND IL-8 IN CYSTIC FIBROSIS (CF) INPATIENTS.
Dakin CJ,1 Henry R1,2, Wang H,1 Morton J1,2.
1. Department of Respiratory Medicine, Sydney Children’s Hospital, Randwick, 2031.
2. School of Paediatrics, UNSW, Randwick, 2031.
There is considerable current interest in measuring inflammatory cytokines in CF respiratory secretions. In CF infants, IL-8 has been shown to correlate with infection. Small studies on CF sputum have failed to show similar correlations. The aim was to study the relationship between duration of treatment, lung function, sputum cytology and IL-8 in CF inpatients (representing a relatively homogeneous group of those with bronchiectasis).

Methods: Prospective standardised collection of spontaneous sputum samples at least 8 days apart during admission for pulmonary exacerbation. FEV1, and FVC were recorded. Sputum processing was selective, with dispersal by the three enzyme technique. IL-8 kit assay. Results: 26 admissions of 19 patients, 9 boys, with mean age 13.4 years (8-19 years). Mean of 10 days between data points (range 7-34). FEV1 mean at admission 59% predicted (27-97%) and discharge 67% (23-99%). Sputum total cell count (TCC) mean fell non-significantly during admission from 32 to 20 x 10^9/ml (+/-32sd). IL-8 levels were all very high, but showed no change over admission (mean 90, range 30-159 ng/ml). IL-8 level correlated with sputum TCC (r=0.49, p<0.005), neutrophils (0.47, p=0.016) and macrophages (-0.42, p=0.028), however IL-8 values for 42% of the samples were extrapolated from the standard curve. IL-8 did not correlate with FEV1 or FVC. As previously shown, TCC correlated with FEV1 (r=-0.43, p=0.001) and FVC (-0.48, p<0.0001). Conclusion: In CF inpatients with established inflammation sputum IL-8 levels were very high. They did correlate in the expected directions with cell counts, but not with pulmonary function or in-hospital treatment. In contrast, sputum cytology and pulmonary function were shown to correlate in the same sputum samples.

Key words: Cystic fibrosis, aputum, cytokines, cytokology

Nominations for Awards: Nil

ASYMPTOMATIC OBSTRUCTIVE SLEEP APNOEA CAUSES NEUROBEHAVIOURAL DYSFUNCTION
Maree Barnes1, Natalie Tarquini1, Siobhan Bankes2, Krystyne Camp1, Andrew Kennew2, R. Douglas McEvoy5 & Rob Pierce1.
1. Department of Respiratory Medicine, Austin and Repatriation Medical Centre, Victoria 3084 and 2. Sleep Disorders Unit, Daw Park Rehabilitation Hospital, South Australia 5041
Introduction: Completely asymptomatic patients may have sleep disordered breathing (SDB), but the severity of the disorder and the incidence of SDB is not clear. Aim: To determine the incidence of SDB and neurobehavioural dysfunction in asymptomatic subjects. Methods: As part of a study looking at neurobehavioural function in patients with obstructive sleep apnoea, 23 subjects were recruited as normal controls. A standard script was used to eliminate those who had any symptoms of SDB, including snoring and breathing problems while asleep, and those who had any psychiatric or other medical problems. These subjects then underwent overnight polysomnography, a Maintenance of Wakefulness Test (MWT) and neurobehavioural assessment.

Results: The 18 males and 5 females had a mean (SD) age of 47.3 (8.1) years, body mass index 27.6 (3.4) kg/m2 and abdominal-glu tal ratio was 0.89 (0.05). The mean (SD) respiratory disturbance index (RDI) was 9.6 (7.3), ranging from 0 to 34. The minimum sleep arousal index (Al) was 14.8 (8.3). Mean (SD) MWT sleep latency was 37.7 (4.4) minutes and the Epworth Sleepiness Scale (ESS) score was 5.9 (3.2) in 17 of 23 subjects had a normal ESS and MWT. Neurobehavioural assessment was abnormal in up to 5 patients in all areas tested, except verbal fluency (COWAT) which had a reduced score in 10 subjects (43.5%). There was no statistically significant correlation between the RDI and neurobehavioural results; there was a significant correlation between Al and abdominal-glu tal ratio (R=0.50, p<0.04), but not BMI. The MWT score correlated significantly with the Psychomotor Vigilance Task reaction time (R=0.50, p=0.03) but not with the ESS score (R=0.03, p=0.87). The ESS correlated significantly with the digit symbol substitution task (R=0.42, p=0.05), a test of general cognitive ability.

Conclusions: 1. Subjects who are screened to exclude symptoms of sleep disordered breathing may have mild to moderate obstructive sleep apnoea. 2. There was no statistically significant correlation between RDI and neurobehavioural dysfunction in these patients. 3. Daytime sleepiness correlates with vigilance and general cognition.

Supported by the NH&MRC and the University of Melbourne

Key words: Obstructive sleep apnoea, neurobehavioural dysfunction

PREDICTING OXYGEN DESATURATION DURING SLEEP IN PATIENTS WITH CYSTIC FIBROSIS
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Previous studies have suggested that an awake respiratory event (AWE) can predict nocturnal desaturation in patients with cystic fibrosis (CF). This study was performed to evaluate predictors of sleep disordered breathing. Methods: Full diagnostic sleep studies performed in 21 patients, selected with an FEV1<65% predicted who were in a stable clinical condition. Polysomnography, lung volumes, and maximal inspiratory and expiratory pressures were measured. Arterial blood gas (ABG) measurements were taken in the afternoon and immediately upon awakening. Results: 26.5±8(mean±SD) years, BMI 20±2kg/m², FEV1, 33±5% predicted, RV/TLC 58±10%, awake PaΩ, 47±1mmHg and PaCO2, 44±5mmHg. Twelve out of 21 patients spent >10 % of total sleep time (TST) with SpΩ 10%, whereas 15 out of 21 patients spent >10 % of RSM sleep time SpΩ 10% and the mean. Three of 9 patients with an awake resting SpΩ 84% had a TST average minimum SpΩ (the average of the minimum SpΩ per 30 second epoch of sleep) <90% and 11 of 13 patients with resting SpΩ 94% had a TST average minimum SpΩ 90%. All 21 patients had a absolute minimum SpΩ <80%. Both the PCO2 is turn sleep SpΩ and TST average minimum SpΩ correlate with awake resting SpΩ (r=0.76, p<0.0001; r=0.72, p<0.0001) and PaΩ (r=0.78, p<0.0001 both). FEV1, % predicted and PImax % predicted had the strong correlation with the lung function parameter percentage of minimum SpΩ during TST (r=0.51, p<0.05; r=0.47, p<0.03). No relationships were seen between nocturnal oxyhaemoglobin desaturation and lung volumes. A significant difference was seen in PaΩ from the evening (44±5mmHg) to the morning (46±6mmHg) ABG measurement (p<0.05). Conclusion: The significantly elevated PaOs suggests that respiratory acidosis may be the result of increased inspiratory effort.

Grant Support: NH&MRC

Key words: cystic fibrosis, sleep, hypoventilation.

Key words: Cystic fibrosis, sleep, hypoventilation.

Nominations for awards: No

Wednesday April 12 – Cystic Fibrosis SIG Orals
(1500-1630)
RESPIRATORY SYMPTOMS, AIRWAY INFECTION AND LUNG FUNCTION IN INFANTS WITH CYSTIC FIBROSIS

Gillian M. Nixon, David S. Armstrong, Rosemary Carzino, Keith Grimwood, Colin F. Robertson.

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Airway infection, inflammation and respiratory symptoms may occur in infants with cystic fibrosis (CF) from the first few months of life. To explore the relationship between airway infection, lung function and respiratory symptoms, we conducted a cross-sectional study in 41 children with CF (median age 17 mo) who had bronchial lavage and lung function measurement under general anaesthesia. Forced expiratory volume in half a second (FEV$_{0.5}$) was determined by the raised volume rapid thoracic compression technique. A colony count $>10^6$ CFU/ml bronchial lavage fluid and/or a differential neutrophil count $>50\%$ was considered positive for airway infection/inflammation. A healthy control group (n=8, aged 5-32 mo) had lung function testing prior to elective surgery. Results: 18/41 (44\%) children had airway infection, 56\% of whom were asymptomatic. Conversely, 7/23 (30\%) infants without airway infection were symptomatic. Mean FEV$_{0.5}$ (95\%CI) adjusted by analysis of covariance for height for those with and without infection was 215ml (187, 243) and 244ml (219, 289) respectively. Mean FEV$_{0.5}$ for the control group was 280ml (95\%CI 239,321). The difference between the groups was significant (p=0.04). No correlation was found between FEV$_{0.5}$ and markers of inflammation. Symptomatic children had lower lung function, regardless of the presence of infection (p=0.004).

Conclusions: Airway infection in infants with CF is associated with lower lung function but the presence of respiratory symptoms is more predictive of lower lung function than infection status. The primary defect in CF or other factors affecting airway calibre may lead to impairment of lung function and respiratory symptoms in the absence of infection.

G. Nixon is supported by the Grand Lodge of New Zealand Freemasons.

Key words: Cystic fibrosis, Infant, Lung function, Infection, Cough.

IRON DEFICIENCY IN CYSTIC FIBROSIS: RELATIONSHIP TO DISEASE SEVERITY AND PSEUDOMONAS AERUGINOSA INFECTION.

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Introduction: Iron deficiency (ID) is common in cystic fibrosis (CF) and is normally attributed to gastrointestinal factors and chronic inflammation secondary to sino-pulmonary sepsis. Hypothesis: Pseudomonas aeruginosa (PA) requires iron for proliferation and we hypothesise that ID in CF might be directly related to PA infection and severity of lung disease.

Methods: We measured iron status and several systemic markers of inflammation in 31 CF patients (median age 27 years, range 21-36 years) and assessed the relationship to FEV1%predicted, daily sputum volume and degree of pancreateic enzyme supplementation. Additionally, we measured the sputum concentrations of total iron and ferritin in an unselected subgroup of 13 subjects. Results: Seventy percent of subjects studied were ID (serum iron $\leq$7µmol/L &/or transferrin%sat. $\leq$16%). Significant relationships existed between serum iron, transferrin%sat., C-reactive protein (CRP) & ferritin:CRP ratio and FEV1%pred. (r=0.5, r=0.4, r=0.7, r=0.7 respectively, p<0.05). The volume of sputum expectorated daily was strongly associated with FEV1%predicted, transferrin%sat., and serum ferritin:CRP ratio (p<0.05). No relationship existed between ID and pancreatic supplementation. Sputum concentrations of total iron (median 63µmol/L, range 17-134 µmol/L) and ferritin (median 5038 µg/L, range 589-6982 µg/L) exceeded normal plasma levels and negatively correlated with FEV1%predicted (r=0.6, r=0.5 respectively, p<0.05).

Conclusions: ID in CF patients appears to be directly related to the severity of suppurative lung disease. Iron loss into the airway may facilitate PA infection and contribute to iron deficiency.
This study examined the effect of inhaled budesonide on blood eosinophils (EO), serum eosinophil cationic protein (ECP) and eosinophil protein X (EPX) in subjects with poorly controlled asthma (60 atopic) receiving inhaled budesonide twice daily by Turbuhaler®. Budesonide dose was 3200 or 1600µg/day for 8 weeks, then 1600µg/day for 8 weeks, then budesonide dose was titrated over 56 weeks. Airway hyperresponsiveness (AHR) was determined by eNO levels and AHR. Higher baseline EO, ECP and EPX levels were lowest at Week 8, but AHR continued to improve to Week 72. EO was lower at Week 8 for 3200µg cf. 1600µg starting dose (0.07 cf. 0.12x10⁹/L, p=0.02). There were positive correlations between baseline EO and both final FEV₁ (%predicted) (r=0.45, p<0.001) and final PD₂₀FEV₁ (r=0.43, p<0.001). This study shows that maximal reduction in peripheral inflammatory markers occurs after 8 weeks budesonide. Baseline blood eosinophil count, but not serum ECP or EPX, appears to predict better outcome in lung function and airflow hyperresponsiveness in subjects with poorly controlled asthma who receive inhaled budesonide treatment. Supported by AstraZeneca Sweden, AstraZeneca Australia and NHMRC.

**Key words:** asthma, inflammation, eosinophilia, ECR EPX

**Nominations for awards:** nil

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**USE OF INDUCED SPUTUM TO SELECT ADD-ON THERAPY IN PERSISTENT ASTHMA: A RANDOMISED TRIAL OF SALMETEROL IN NON-EOSINOPHILIC ASTHMA**

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Both long-acting β-agonists and inhaled corticosteroids (ICS) are effective add-on therapy in persistent asthma. Clinicians usually make empiric choices between these 2 different classes of drugs. Induced sputum identifies a group with persistent asthma but suppressed inflammation (non-eosinophilic) asthma in whom we hypothesised that Salmeterol (S) may provide better asthma control than ICS. 78 adults with stable symptomatic asthma were recruited and those with suppressed eosinophilia (E<5%, n=33) entered a 1 week run-in period followed by concealed random allocation to add-on therapy with fluticasone 500µg/day (F) or S 50µg/day with double-blind evaluation of the treatment effect after 1 month. Baseline airway responsiveness (AR) was moderately reduced, mean PD₂₀ was 5.75µmol, and improved 2-fold to 11.5µmol with S (p<0.05), whereas F led to no change in AR (7.51µmol, p=0.05). Sputum eosinophil cationic protein (ECP) was high at baseline (2519µg/ml) and was not suppressed by therapy (S=3673, F=2258). Sputum E at baseline was 1.3% and remained unchanged after S, but fell to 0.6% after F (p<0.05). Peak flow improved by 28L/min with S (p<0.01), but was not altered by F (1.1L/min), Daily symptoms and β-agonist use were reduced by S (1.33 puffs/day, p=0.05), but not by F. Quality of life improved 0.8 units with S (p<0.05) and 0.4 units with F. We conclude that in adults with persistent asthma, induced sputum can define a group with persistent AHR but suppressed eosinophilia. Salmeterol provides better asthma control than ICS in these patients. Induced sputum can help choose add-on therapy in persistent asthma.

Supported by Glaxo-Wellcome, Australia

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**EXHALED NITRIC OXIDE IS RELATED TO ALLERGIC SENSITISATION TO HOUSE DUST MITE AND CLADOSPORIUM**

Sara H. Downs, Jorg D. Leuppi, Sue R. Downie, Guy B. Marks, Cheryl M. Salome
Institute of Respiratory Medicine, University of Sydney, NSW, 2006

The concentration of nitric oxide in exhaled air (eNO) is associated with atopic and may also be a measure of airway inflammation. Individuals allergic to pollen and fungi have been reported to have more symptoms during seasons when the levels of the aeroallergens in ambient air are high. Aim: To determine if the association between eNO levels and sensitisation to specific allergens is the same in summer and winter. Methods: Skin prick test results for five allergens in 266 atopic children from Wagga and Moree were related to concentration of eNO in winter and summer 1998. At the skin prick test, a wheal size >3mm was defined as being sensitised. Exhaled air was collected in a 3L wine cask bag and the NO content measured by chemiluminescent analyser. Results: The proportion of children sensitised to house dust mite was 64.3%, to Alternaria was 43.4%, to rye grass pollen was 53.5%, to Cladosporium was 23.4% and to cat was 18.5%. House dust mite and Cladosporium were significant predictors of eNO in both summer (<0.001) and winter (<0.001); between winter and summer eNO increased in Moree (<0.001) and decreased in Wagga (<0.001). Sensitisation to house dust mite, Cladosporium, Alternaria, rye grass or cat were not significant predictors of change in eNO in either town, although a negative association between Alternaria sensitisation and change in eNO in Wagga was of borderline significance (p=0.03). Conclusion: In this sample of atopic children, eNO was related to sensitisation to house dust mite and Cladosporium. The direction of seasonal changes in eNO differed in the two towns, but were probably unrelated to allergic sensitisation. The factors which determine seasonal change in eNO remain unclear.

Supported by: Swiss Respiratory-, Scientific- and Novartis- Foundation, NHMRC, Liddy Ackin Trust, RPAH

**Key words:** Asthma, exhaled nitric oxide, skin prick test, allergy

**Nomination for Awards:** none
PERCEPTION OF ASTHMA: USEFULNESS OF A 10 YEAR PEF DIARY IN ASSESSING THE EFFECTS OF TREATMENT - A SINGLE CASE STUDY

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Asthmatics can be classified as good or poor perceivers of airway function, either in the laboratory or in the community. In a study done in 1988 - 90, good perceivers were identified as having a significant negative correlation of visual analogue score (VAS) against cued PEF. Only ten of 300 patients were recording daily PEF using a Mini-Wright meter. We report a case of a good perceiver who has maintained a PEF and treatment diary card from first assessment in 1989 to re-assessment in 1999. Methods: The male patient, aged 66 in 1989, had known asthma. Perception of asthma was assessed in 1989 and 1999 using a turbie PEF meter up to 4 times daily for 14 days. The readings of PEF were not visible to the patient. The diary card, kept by the patient, showed twicedaily PEF. The variability of PEF and the effects of stated treatment for each day were analysed. Results: In 1989, PEF ranged from 30% to 107% predicted and VASmax was 93mm. VAS and PEF were significantly correlated (r = -0.82), with a slope of -1.03 mm% l. In 1999, PEF ranged from 87% to 120% predicted and VASmax was 22mm. VAS and PEF were significantly correlated (r = -0.33), with a slope of -0.21 mm% l. Variation in PEF was up to 70% prior to March 1990, with PEF ranging from 180 to 460 l.min-1, with inhaled S2-agonists being the primary treatment. In March 1990 Becloforte improved PEF from a mean of 358 ± 53 l.min-1 to 425 ± 31 l.min-1. Subsequently the variation in PEF was maintained to about ± 20%, with PEF ranging from 405 to 520 l.min-1. Seven major reductions in PEF were observed (APEF > 75 l.min-1), some requiring medical intervention. Conclusion: The changes observed in perception demonstrate the probable effects of inhaled corticosteroids on perception of asthma, with a reduced slope compared to that in 1989. The control of asthma is clearly improved, with marked reduction in PEF variability. The diary card has provided a unique insight into the variation of PEF and the requirements for treatment over 10 years in this patient.

Key words: Perception, Asthma

AN OBSERVATIONAL STUDY OF MONTELUKAST IN ASTHMA

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Aim: To assess the effects of adding montelukast sodium (Singulair, MSD) to existing treatment in the control of asthma. Methods: Observational study. Patients were enrolled at the discretion of their physician, if their asthma was inadequately controlled on current treatment. Details of treatment and a symptom-based questionnaire were completed. FEV1 and PEF were recorded. Montelukast 10 mg (5 mg in children) was added to current treatment. Patients were reviewed twice over a 12-week period. Results: Study population: n = 616. The data for 132 completed patients have been analysed. Age range: 2-91 years; 77% adults; 23% children; 62% female. 97% of patients had moderate to severe, frequent episodic or persistent asthma, and most were taking inhaled corticosteroids and long-acting β2-agonists. Physicians reported that 69% of patients had a moderate to substantial improvement while 25% had no improvement with montelukast. Post bronchodilator PEF increased from a mean of 331 to 362 l.min-1 in adults (n=64), improvement was reported in: symptoms in the past week, and, in the past 4 weeks, emergency visits to a hospital or a GP, days lost from work or school, oral steroids, and overall patient satisfaction with preventive medication. 17% (102/618) of patients discontinued treatment and 4% (23/618) experienced side-effects. Conclusion: 69% of patients with moderate to severe asthma demonstrated a sustained and clinically-relevant improvement in their asthma with the addition of montelukast to existing treatment for the 12-week period.

Supported by: A grant from Merck Sharp & Dohme (Australia) Pty Limited

Key words: Montelukast sodium, Singulair, severe asthma

BRONCHIAL LIABILITY: FEV1 IS BETTER THAN PEF FOR THE DIAGNOSIS OF ASTHMA

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Serial measurements of airway calibre are used in the diagnosis and management of asthma. Traditionally PEF is used to calculate Bronchial Liability (BL) as: (highest daily PEF - lowest daily PEF)/highest daily PEF. FEV1, is less effort dependent and more reliable than PEF, and has been shown to reflect flow in both large and small airways. Portable data storage spirometers now maxes serial FEV1, measurements possible. Aim: Determine the measurement of airway calibre (FEV1, or PEF) and calculation of BL that best separates normal subjects from those with asthma. Method: On the basis of asthma questionnaire, spirometry and methacholine challenge, 25 well-defined asthma and 25 normal subjects were identified. All subjects then performed serial spirometry, recorded 7 times per day for 4-7 days using an electronic data storage spirometer (Micromedical DiaryCard, UK). Only sessions where spirometric data met ATS acceptability and reproducibility criteria were used in subsequent analysis. BL indices of overall variability, within-day variability, between day variability and circadian variability for FEV1, and PEF were calculated, and the upper limit of the normal range (95th percentile for normal subjects) determined for each index. Results: The traditional method of determining BL using daily amplitude in PEF had an upper limit of normal of 18.2% and correctly identified only 50% of subjects with asthma. By contrast the coefficient of variation of FEV1, from all sessions (CovFEV1), best separated the asthma from the normal group. In the normal group CovFE1 had an upper limit of normal of 4.5%. Values in excess of this level were strongly suggestive of asthma (sensitivity = 92%). For all indices of BL, FEV1, provided a significantly better measure than PEF (p<0.01). Where the quality of spirometric data can be assured, FEV1, proved more sensitive than PEF in separating the asthma and normal groups for all indices of BL. The index of BL providing the greatest sensitivity in the detection of asthma was CovFE1.2

RECOVERY FROM AN ASTHMA EXACERBATION FOLLOWING A SINGLE HIGH DOSE OF INHALED CORTICOSTEROIDS - A PILOT STUDY

Sue R. Downie, Joerg D. Leuppi, Cheryl M. Salemo, Ann J. Woolcock.
Institute of Respiratory Medicine, University of Sydney NSW. 2006.

The introduction of high dose inhaled corticosteroids (ICS) can lead to rapid improvements in lung function and asthma symptoms. A single dose of 2400µg of Budesonide can reduce airway responsiveness and sputum eosinophils within 6 hours. Aim: To determine if a single dose of 3200µg of Budesonide improves recovery from an asthma exacerbation. Methods: 19 Asthmatics with asthma exacerbation following withdrawal of ICS were randomised to receive either usual care (a doubling dose of ICS) plus placebo, or usual care plus a single dose of 3200µg budesonide, in a double-blind manner. Subjects monitored PEF, symptoms and rescue β-agonist use daily for 4 weeks. PEF was expressed as the lowest reading in each week as a % of the best reading in the four weeks pre exacerbation (PEF Low%high). Symptom scores incorporated symptoms and β-agonist use, and had a range of 0 to 8. Results: The budesonide group had significantly lower symptom scores and higher PEF (Low%high) in the first week after exacerbation than the placebo group. Both groups had recovered to similar levels by week 4. (mean ± 95%CI):

| Symptom Score | Mean PEF (Low%High) |
|---------------|---------------------|
| Budesonide    | Placebo             |
| **Exac.**     | 2.2 ± 0.9           | 2.6 ± 0.6            | 0.53       | 84.9 ± 3.3         | 76.1 ± 7.6       | 0.08     |
| **Wk 1**      | 1.3 ± 0.7           | 2.5 ± 0.5            | **0.008**  | 89.4 ± 2.9         | 81.7 ± 3.6       | 0.006    |
| **Wk 4**      | 0.2 ± 0.2           | 0.4 ± 0.4            | 0.4        | 90.3 ± 3.49        | 90.3 ± 3.3       | 0.99     |

Conclusion: Asthma exacerbations treated by doubling the dose of ICS resolve more rapidly with the addition of a single high dose of 3200µg of budesonide. The effect is most marked during the first week after the exacerbation, when it is most likely to reduce morbidity due to the exacerbation. Supported by SNSF, Novartis-Found. NHRFC, Aust. ARDS-Assoc.

Key words: Asthma, exacerbation, high dose ICS.

Nominations for awards: Nil
**A CLINICAL TRIAL OF AIR IONISERS IN THE TREATMENT OF ASTHMA**

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Air ionisers employ the generation of potential differences in the kilovolt range to produce negatively charged particles. These particles emit hydration, mobile and highly reactive. Air ionisation has been associated with altered serotonin metabolism in human and animal experiments. It is an effective means of precipitating airborne particles including particulate, airborne allergens and microorganisms, however, the effect of the use of these devices upon the clinical condition of asthmatics is the subject of controversy. This study aimed to assess the effect of nightly negative air ionisation (estimated 250 000 negative ions/ml at 1 metre from emitters) upon measures of asthma in 53 adult subjects (28 active, 25 placebo).

**Method:** A double-blind, placebo-controlled, study design with two parallel groups was utilised. Following a 1 week run in, subjects used active ionisers or sham devices for 9 weeks. Lung function (pre and post bronchodilator FEV₁, FVC, FEF₂₅-₇₅%) and Asthma Quality of Life were assessed in interviews at 5 week intervals. Subjects recorded peak flows, medication usage and symptoms twice-daily. Total plasma serotonin concentrations were also measured.

**Results:** There was a significant difference found between groups in the Social Distraction subscale. The active group showed less of an increase (1.68, p=0.040) after sex adjusted analysis, suggesting a detrimental effect of air ionisation upon Quality of Life. Short acting bronchodilator usage increased more in the active group (1.82 doses per day, p=0.19) between weeks 5 and 6 than in the placebo group. Lung function scores were not significantly different between groups, although there was a trend for decreased FEV₁ and increased response to bronchodilator in the active group. Plasma 5-HT was increased in the active group by 101.5 nmol/L (p=0.43) after 9 weeks of treatment.

**Conclusions:** These results suggest that there may be a detrimental effect of the nightly use of air ionisers in asthma treatment. It is essential that further investigation of these effects be undertaken in well controlled patients to establish if the negative air ioniser usage is truly a risk factor for asthma exacerbations in the community.

**Key words:** asthma, air ionisation, clinical trial, serotonin

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**EFORMOTEROL: INFLUENCE OF DELIVERY DEVICE ON CLINICAL EFFECT**

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Longacting beta₂-agonists now have an established role as an adjunct to inhaled corticosteroids in asthma management. Eformoterol is available in two dry powder devices, Foradil Aerolizer® and Oxis Turbuhaler®. There has been no controlled study to date of their clinical effect. We compared the bronchodilator response, time to onset of response and time to maximum bronchodilator response following 12 µg eformoterol delivered by these devices. Nineteen nonsmoking asthmatic patients with a documented bronchodilator response were enrolled in the randomised, single-blinded, crossover trial. The severity of baseline airflow limitation ranged from mild (FEV₁ > 70% predicted) to moderately severe (FEV₁ 50-59% predicted). The patients were assessed on two separate study days at least one week apart. FEV₁ was measured for a total of 6 hours after a single dosage of eformoterol. Side effects were also recorded. Statistical analyses were performed using SPSS. The area under the FEV₁-time curve (AUC) was calculated for each device and evaluated by paired t-test. There was no significant difference in AUC between the devices. There were no significant differences in time to onset or time to peak effect. One of the three patients experienced side effects with each device which resolved within the study period. We conclude that there is no significant clinical difference between 12 µg of eformoterol delivered by either device.

**Key words:** eformoterol, bronchodilator

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**ADDITIONAL FORMOTEROL IS MORE EFFECTIVE AND SAFER THAN DOUBLING THE DOSE OF INHALED STEROIDS IN MODERATELY SEVERE ASTHMA**

Jankins C¹, Mitchell C, Scicluniano R, Rubinfeld A. On behalf of 16 Australian Centres. ¹Institute of Respiratory Medicine, Campbelltown NSW 2560

**Method:** A prospective, multicentre, randomized, doubleblind, parallel group study we compared the effectiveness of (A) adding formoterol (Foradil®)(FORM) dry powder inhalation 12mcg bid to beclometasone (BDP) 500mcg bd with (B) doubling the BDP dose to 1000mcg bd in asthma patients on BDP 1000mcg a day or equiv. Subjects: All had 2 of the following on 2 of the last 7 days of a 4 week run-in: daytime(DT) symptoms limiting activity; any nocturnal(NT) symptoms; use of at least 4 puffs of rescue bronchodilator(BD); diurnal variation in PEF of > 15%. There were no differences between groups in baseline characteristics, symptoms, PEF and 2 hour post waking urinary cortisol/creatinine ratios (UCCR) as a measure of adrenal suppression. The baseline values and changes at 12 weeks were:

|                      | A: FORM + BDP 1000 | B: BDP 2000 |
|----------------------|--------------------|-------------|
| MORNING PEF (l/min)  |                    |             |
| Mean                 | 100                | 350         |
| Change*              | -39                | +11         |
| EVENING PEF (l/min)  |                    |             |
| Mean                 | 100                | 380         |
| Change*              | -22                | +3          |
| DT SYMPTOM SCORE     |                    |             |
| Mean                 | 100                | 1.42        |
| Change*              | -0.93              | +0.45       |
| NT SYMPTOM SCORE     |                    |             |
| Mean                 | 100                | 0.69        |
| Change*              | -0.35              | -0.13       |
| DT BD USE (puff/day) |                    |             |
| Mean                 | 100                | 3.20        |
| Change*              | -2.27              | -3.89       |
| UCCR (nmol/mmol)     |                    |             |
| Mean                 | 97                 | 50.5        |
| Change*              | +3.5               | -3.4        |

*Changes in all variables differed significantly between groups(p<0.001).

**Conclusion:** FORM + BDP 1000 was more effective and resulted in less suppression of cortisol secretion than BDP 2000 in these symptomatic patients with moderately severe asthma

Supported by: Novartis Pharmaceutical

**Keywords:** asthma, formoterol, beclomethasone, adrenal suppression

**Nominations for awards:** nil

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**"AS IF I HAVE NOT TAKEN A FULL BREATH" OR "HYPERVERILATION SYNDROME" OR "SIGNING SYMPTOM DUE TO GORD AND CURED WITH PROPER TREATMENT"**

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Hyperventilation syndrome may be due to many causes, but gastrooesophageal reflex disease (GORD) has not been aetologically linked to date. 21 cases have been identified. Three are reported here. Each was diagnosed with GORD and each was cured with appropriate treatment.

**Case 1** (SE) A 25 year old Lebanese born female presented in May 1998 with a four year history of "as if I have not taken a full breath". She was sighing regularly. Lung function tests & CXR were normal. Clinical examination was normal apart from an indented tongue and obesity.

Gastroscopy showed a small area of reflux oesophagitis and biopsy showed H.pylori colonisation. She was treated with triple antibiotic therapy (Helicopack) for fourteen days. Her symptoms resolved and she remains symptom free after 18 months follow up

**Case 2** (JD) A 40-year-old male East Timorese refugee presented with a four-month history of "I can't breathe properly" especially when going upstairs. At night he woke with shortness of breath "as if I have not taken a full breath" and obtained some relief by drinking water. He also had a dry cough. Clinical examination revealed no abnormality except for repeated sighing. Lung function tests, CT scan and serum iron were normal.

Gastroscopy showed a deep oesophageal ulcer (grade 3) at the lower end of the oesophagus. He was treated with Losee HP7 followed by Omeprazole 20 mgs bd for 6 months and 16 months later he was "very well".

**Case 3** (SE) A 22-year-old Australian born male of Lebanese extraction presented in September 1998 complaining of "as if I have not taken a full breath" and sighing many times each day for 4-5 years. His wife feared that "my husband does not like me". Spirometry and CXR were normal.

Gastroscopy showed severe ulcerative oesophagitis (grade 4). He was treated with omeprazole 20 mgs bd for 6 months and at last follow up on 9/11/99 he said, "I am very well thank you. You cured me long ago".

GORD can cause the above mentioned symptom which is curable and physicians should be aware of it and treat accordingly.
Personal Best and Recent Best Peak Flow in Asthma Management - Implications for Asthma Action Plans

Helen Reddel, Guy Marks, Cheryl Salome, Christine Jenkins, Sandra Ware, Ann Woolcock, Institute of Respiratory Medicine, Campbelltown, NSW 2560

Many PEF-based asthma action plans suggest a change in treatment when morning PEF falls below a trigger point calculated from a reference value such as personal best PEF or predicted PEF. Recent guidelines suggest once daily PEF monitoring during good asthma control. Aim: To examine PEF reference values and simple PEF indices during inhaled corticosteroid treatment, using morning only and twice-daily values. Methods: 61 subjects with initially poorly controlled asthma recorded PEF electronically twice daily during 72 weeks of inhaled budesonide treatment. For each week, the lowest morning PEF (Low) was identified, together with highest PEF (High=recent best) and personal best PEF (PB= cumulative best PEF). PEF indices (Low%High, Low%PB, and Low%predicted) were examined at baseline (poor control) and at plateau (good control).

**Results:**

| PEF index median (%IQR) | Poor control | Good control | Level at good control, cf. Low%PB |
|--------------------------|--------------|--------------|-----------------------------------|
| Low%PB                  | 63% (48, 73) | 81% (76, 84) | p=0.0001                           |
| Low%High                | 83% (48, 73) | 89% (85, 92) | p=0.02                            |
| Low%predicted           | 49% (40, 66) | 82% (72, 95) |                                   |

**Conclusions:** This study shows that recent best, personal best and predicted PEF are not interchangeable as reference values in asthma action plans; recent best (High) is preferred as it does not need continuous PEF monitoring. A trigger point of <80% personal best in action plans would result in overtreatment. During good asthma control, indices of PEF variation are only slightly overestimated by recording PEF once daily in the morning.

Supported by AstraZeneca Swedan, AstraZeneca Australia and NHMRC

Key words: asthma management, asthma crisis plans, PEF monitoring

*N: Refer to page A18 for Table 10A*

Nebuliser and Pressure Output from the Mefar™ Dosimeter: Results from ECRHS Calibration Project

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The European Respiratory Health Survey (ECRHS) is a large multicentre longitudinal survey investigating the prevalence of asthma around the world. Mefar™ nebulisers and dosimeters are currently used in the ECRHS, to determine the level of airway responsiveness. We have demonstrated in the past that differences exist in the driving pressure developed by different Mefar™ dosimeters, this significantly changes aerosol output. Aerosol output can also significantly differ between batches of the same model of nebuliser. Due to these concerns over the accuracy of the Mefar™ system used in phase 1 ECRHS and its potential confounding effect on the results, we were commissioned by the ECRHS Coordinating Committee to calibrate all the nebulisers to be used in the second phase of the ECRHS (phase II). We measured the mean aerosol output from 366 new Mefar™ nebulisers manufactured in 2 batches. We also studied the effect of changing dosimeter driving pressure on aerosol output in the nebulisers (n=5). Nebuliser output was measured using a locally developed calibration method using lithium chloride. Nebuliser output was significantly different between the two batches (p=0.009). The mean ± (SD) aerosol output for batch 1 was 7.0 mg sec⁻¹ (0.8) and for Batch 2 was 6.3 mg sec⁻¹ (0.7). The determined mean of all 366 nebulisers was 6.4 mg sec⁻¹ (0.8) range 3.1-8.4 mg sec⁻¹. The aerosol output of 5 nebulisers studied was directly related (R²=0.99) to dosimeter driving pressure with range of 5.1 (0.7)-9.0 (1.3) mg sec⁻¹ between 150-250 KPa. These findings are important because we have shown that significant differences in aerosol output can occur at different driving pressures. These potential confounders could compromise phase II of the ECRHS. Therefore these differences in aerosol output should be taken into account during statistical interpretation of the final data.

Supported by the NHMRC

Key words: asthma, perception, symptoms, epidemiology

The Words to Describe Methacholine Induced Airway Narrowing in Asthmatics and Non-Asthmatics

Alyson Roberts and Cheryl Salome

Institute of Respiratory Medicine, University of Sydney NSW 2006

Symptoms of wheeze or chest tightness, reported in questionnaires, form part of the definition of asthma in epidemiological studies, but these words may have different subjective meanings. Aim: To determine if the appropriateness of the terms used to describe methacholine induced airway narrowing differs between asthmatics and non-asthmatics, or in a community sample, between subjects with reported wheeze and those who have not wheezed. Methods: 23 non-asthmatic and 19 asthmatic subjects underwent methacholine challenge (0.04-200 µmoles), to cause respiratory discomfort. They then marked a visual analogue scale (VAS) from ‘not at all’ to ‘hard to breathe’ to indicate their subjective sensations associated with airway narrowing.

**Results:**

- Asthmatics (23.5 ± 6.3%) had a significantly greater % fall in FEV1 than the non-asthmatic subjects (16.2 ± 4.6%; p<0.05).
- Asthmatics rated ‘I feel wheezy’ (68.2 ± 13.1%; p<0.001) and ‘I find it hard to breathe’ (61.4 ± 13.4%; p<0.001) as significantly more appropriate descriptors than did non-asthmatics. In the population sample, subjects with wheeze in the last 12 months rated ‘I feel wheezy’ (47.9 ± 13.8%) significantly more appropriate than did non-wheezers (24.0 ± 12.3%; p=0.014), regardless of whether they had airway hyperresponsiveness. Conclusion: Symptoms and non-asthmatics differ in the words used to describe sensations associated with airway narrowing. It is not known if this difference reflects different physiological changes in the airways. Subjects who report recent wheeze, consider ‘I feel wheezy’ to be a more appropriate term to describe induced changes than do subjects with no history of wheeze. This may have implications for the interpretation of symptoms recorded by questionnaire in epidemiology.

Supported by the NHMRC

Key words: asthma, perception, symptoms, epidemiology

Should Inhaled Corticosteroid Treatment "Start High" in Poorly Controlled Asthma?

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**Objectives:** To determine if short-term or long-term outcomes in subjects with poorly controlled asthma can be improved with a starting dose of inhaled budesonide higher than that recommended in international guidelines. Methods: A parallel-group study of 61 subjects with poorly controlled asthma, randomised to receive 3200 µg or 1600 µg budesonide daily by Turbohaler® for 8 wks (double-blind), then 1600 µg/day for 8 wks (single-blind), followed by 14 months of open-label budesonide dose titration using a simple clinical algorithm. Study design incorporated a written asthma crisis plan based on electronic PEF monitoring. Primary outcome variable for Wks 1-16 was change in airway hyperresponsiveness (AHR), and for the open-label phase, mean daily budesonide dose. Results: During Wks 1-16, subjects starting with 3200 µg/day were 3.8 times more likely to achieve remission of AHR (PD20 FEV1 <200) but those starting with 1600 µg/day, but other outcome measures did not differ significantly (e.g. increase in morning peak expiratory flow +134 cf. +127/L/min, p=0.8). Subjects achieving remission were less likely to experience an exacerbation (2/13 cf. 27/48, p=0.02). During budesonide dose reduction, there was no significant difference in mean budesonide dose (1327 µg/day cf. 1325 µg/day, p>0.3). By completion/withdrawal, there was no significant difference in overall improvement in AHR (+3.9 cf. +4.2 doubling doses, p>0.6) or in asthma control (median symptoms 0.0 cf. 0.0 days/wk, ²β-agonist use 0.0 cf. 0.1 occasions/day, p>0.8). Median compliance with electronic monitoring was 89% over the whole study. Conclusions: A high starting dose of budesonide in subjects with poorly controlled asthma caused more rapid remission of AHR, but tight control of asthma was achieved with both starting doses.

Supported by AstraZeneca Swedan, AstraZeneca Australia, and NHMRC

Key words: asthma, inhaled corticosteroids, airway hyperresponsiveness

Respirology (2000) 5, (Suppl.)
A meta-analysis has compared the efficacy of two commonly used inhaled corticosteroids, fluticasone propionate (FP) and budesonide (BUD), at the clinically equivalent dosing ratio of 1:2 in 1983 patients (1). All clinical efficacy measures showed greater improvements with FP than BUD. Limited data are available on the relative economic benefit of FP and BUD, particularly in Australia, hence an economic analysis has been conducted based on the meta-analysis. Methods: The economic analysis was conducted from the perspective of the Australian healthcare system. Costs to the healthcare system (eg. drugs, medical consultations, hospitalisations) were calculated by applying Australian unit costs to health care resource use recorded during the studies. Sensitivity analyses were conducted. Results: *improvement from baseline in Peak Expiratory Flow (PEF) of 6% or more of PEF predicted **days on which patients had no symptoms, no use of rescue medication, no disturbance in sleep pattern and an absence of adverse effects

### EVALUATING ASTHMA CARE IN AUSTRALIAN AND BRITISH GENERAL PRACTICES

**Ian Charlton**

**Aims.** To conduct a case control study comparing a nurse run asthma clinic with traditional Australian general practice asthma care and compare these results to a nurse run asthma clinic in the UK.

**Methods.** A case control study was conducted comparing patients attending a nurse run asthma clinic in Kincumber N.S.W. with control patients in neighbouring surgeries at Saratoga and Avoca. Eighty three patients who attended the asthma clinic were matched for age, sex and disease severity. Patient case notes were audited to determine the number of consultations with the doctor, courses of oral steroid and use of acute salbutamol nebulisations. These results were compared to a nurse run asthma clinic in Aylesham North Kent. Intervention. The nurse run asthma clinics in Australia and the UK were run in similar ways. Patients using inhaled steroids were invited by their GP to a clinic conducted by an asthma nurse. The nurse spent one hour explaining the mechanism, treatments, and self-management of asthma. This was reinforced with a peak flow meter and diary card. Patients were reviewed by the nurse at 12 weekly intervals. Patients could consult their own doctors at any time if they wished.

**Results** Practices and patients were similar in the study groups. Australian practices had a higher proportion of children compared to the UK (54% vs 30%). GP consultation times were longer in Australian practices (15 v 10 minutes). In the UK clinic 1.7 courses of oral steroids were prescribed in the months before the clinic versus 0.5 after (<0.001). Australian clinic: 0.4 before 0.3 after (p<NS). The percentage of patients who would like their doctors to talk more about their asthma was 70% in the UK patient group and 22% for the Australian control practice and 13% for Australian asthma clinic practice. The difference between Australian and UK groups was significantly different (<0.05).

**Conclusions** The Australian asthma clinic demonstrated appreciable advantages over well managed GP care. Patients attending the UK asthma clinic had greater morbidity than in Australia. After attending the UK asthma clinic the patients' asthma improved to a level comparable to the Australian asthma patients. The differences between the UK and Australia may be due to the progress general practice has made in the 5 years between the studies or the greater amount of time Australian GPs spend with their patients. Asthma clinics may be most appropriate where patient care is less than ideal or where doctors themselves do not feel confident in managing asthma at the level current guidelines recommend.

**HEALTH SERVICE UTILISATION AND ACTIVITY LIMITATION IN ASTHMATICS FROM A SOUTH AUSTRALIAN POPULATION**

**DJ Christopher, B Smith, D Wilson, AM Southcott R Ruffin, Dept of Respiratory Medicine, University of Adelaide, TQEII Campus, SA - 5011**

This study looks at the utilisation of the health services by the asthmatics in the community and the limitation to physical activity and work caused by the disease. We performed a survey of a representative adult population of 3010 South Australians. In these, face-to-face interviews recorded: demographic data, details of past medical diagnosis of asthma & other chronic lung diseases; asthma symptoms; medical services available to asthmatics and activity limitation on account of the disease. Quality of life was measured using standard quality of life measures.

### RESULTS

In 299 patients (9.5%) a diagnosis of asthma had been made by a doctor. Over a 12 month period, in comparison to the rest of the study population, a significantly higher number of asthmatics utilised the services of the general practitioner (59% vs 43.9%; P<0.001), the hospital (12% vs 7.7%; P<0.01) and the other health services (34.1% vs 24%; P<0.001) and were unable to obtain health services that they needed (12.4% vs 7.9%; P<0.007). Significantly more asthmatics were using medications for a chronic disease for more than 6 months in the previous 12 months, when compared to the rest of the population (50.5% vs 22.6%; P<0.001). A higher number of asthmatics were unable to carry out their normal duties on account of their disease (20.9% vs 14.7%; P<0.004) among those who were able to carry out normal activities, more asthmatics tended to cut down the activities or accomplish less (35.6% vs 19.2%; P<0.001). The quality of life scores were lower for asthmatics when compared to the rest of the population.

### Conclusion

Asthmatics in the community seem to have the need to utilise the health services more and the disease seems to impose significant limitation to activity and work.

**Key words:** asthma, health services, work limitation, quality of life

*This research was funded by The Queen Elizabeth hospital Research Foundation.*
QUALITY OF LIFE IN PERENNIAL ALLERGIC RHINITIS IN SYDNEY
Sue F. Downie, Morgan Anderson, Joerg D. Leuppi, Cheryl M. Salome, Janet Rimmer. Institute of Respiratory Medicine, University of Sydney, NSW, 2006.

House dust mite (HDM) allergen levels in Sydney are high by national and international standards. Although allergic sensitisation to HDM and rhinitis are common in Sydney, little is known about the impact of perennial allergic rhinitis on quality of life (QOL) in a high allergen environment. Aim: To compare QOL measures in HDM sensitised, rhinitis subjects and healthy non-atopic controls, over a period of one year. Methods: 40 rhinitis patients skin prick test positive to D.farinae or D.pteronyssinus, and 19 non-atopic controls were enrolled in a longitudinal one year study that involved QOL assessment at 3 monthly intervals. The disease-specific QOL questionnaire (Juniper, 1997) measures the effect of rhinitis on daily activity, sleep, non-nasal non-eye problems, practical problems, nasal and eye symptoms and emotions. Results: In all measures, the QOL was significantly worse in rhinitis patients than controls both in summer and winter. There were no significant differences between summer or winter. Compared to healthy controls, rhinitis subjects were not significantly more troubled by nose (p>0.001) and eye (p>0.001) symptoms, they were also more troubled by non-nasal non-eye problems (p<0.01) such as fatigue, poor concentration, headache and reduced productivity. In rhinitics who were sensitised to pollens and HDM (n=19), QOL measures did not differ significantly from those with HDM sensitisation only, and they did not have significant seasonal changes in quality of life. Conclusions: In a high allergen environment, perennial rhinitis has a significant impact on quality of life, and affects not only specific symptoms, but also non-specific measures of quality of life such as fatigue, poor concentration, headache and reduced productivity. Seasonal allergens appear to have little additional impact in the presence of high levels of perennial allergens.

Supported by Astra, Lund.

Key words: Perennial rhinitis, quality of life, house dust mite, allergens

Nominations for awards: Nil

ADULT ASTHMA RISK SCREENING QUESTIONNAIRE INVOLVING SEVERITY PREDICTS QUALITY OF LIFE
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An adult risk screening questionnaire (RSQ1), principally involving severity, has previously been shown at a score above 30 to predict attendance at hospital emergency departments. We are using a modified form of this questionnaire in a RCT of asthma clinics in general practice. From baseline data, we have used the RSQ to assess asthma severity as a predictor of quality of life (QoL). Methods: 12 general practices in Adelaide. The RSQ covered sleep disturbance, hospital admissions, number of GP's visited and use of oral steroids for asthma, and a patient's rating of the severity of their asthma. The St George Respiratory questionnaire (SGRQ) was used to measure QoL. Results: 167 adult asthmatics were recruited, with a mean (sd) age of 50.4 years (+ 16.7 years). 56 participants scored over 30 on the RSQ. Age, weight, number of co-morbidities, history of smoking, % predicted FEV1, and RSQ were independently related to the SGRQ score. A stepwise regression of these variables showed a RSQ score > 30 to be a good predictor of a SGRQ score after adjusting for number of co-morbidities and history of smoking (p < 0.001). On average, people with a RSQ score > 30 will have a SGRQ score 13.4 points higher (95%CI: 8.7, 18.2) than those with score < 30. This is a clinically significant difference. Conclusion: The RSQ, used as a measure of severity, is a good predictor of clinically significant differences in QoL in adult asthmatics, and is sufficiently brief to be useful in general practice, and also as an alternative to lengthy QoL measures in some research settings.

1Wkefield M, Ruffin R, et al. A risk screening questionnaire for adult asthmatics to predict attendance at hospital emergency departments. Chest 1997; 112: 1527-1533.

Supported by Commonwealth Department of Health and Aged Care

Key words: Asthma, severity, quality of life

DEVELOPMENT OF A QUESTIONNAIRE FOR ESTIMATING ADHERENCE TO ASTHMA MEDICATION
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The AMAQ (Asthma Medication Adherence Questionnaire) has been developed to estimate adherence to asthma preventer medication based on patients' attitudes and behaviours. Methods: Literature review and patient interviews were used to identify items that could measure traits and behaviours relevant to adherence, along with questions to record reported adherence. Items were trialled to assess appropriateness, clarity, and comprehensiveness, modified through several draft versions, and then presented to patients by a non-clinician, emphasising that non-adherence was known to be common, honesty was desired, and responses were confidential. Results were analysed using Factor Analysis to refine item clusters representing each domain (eg. perceived stigma, asthma severity), and Cronbach Alpha was used to reduce the number of items in each cluster and enhance reliability. Multiple regression was then applied to select and weight items to form a scoring method predictive of non-adherence. Results: Analyses were based on 26 subjects under 50 years of age (all patients over age 50 reported full adherence). Seven item clusters were selected to be predictive of non-adherence, eg. 'perceived stigma', 'subjective estimate of asthma seriousness', 'lack of control'. The model predicted preventer non-adherence with multiple R2= .69, R2= .81; Adjusted R2=.69, F(8,13)=68.8, p<.001. Conclusions: The AMAQ offers a survey instrument that estimates non-adherence based on reported attitudes to asthma medication. It also provides a systematic and comprehensive assessment of attitude factors and behaviours associated with non-adherence, and could be used to allocate subjects a priori to treatment groups in clinical trials to control for non-adherence effects.

Key words: asthma, medication adherence, questionnaire

Supported by Glaxo Wellcome Australia

SMOKING IN ADOLESCENTS WITH ASTHMA: PREMEDICATION TO PROMOTE SOCIAL PARTICIPATION
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There is little understanding about what most influences decision-making around smoking in young people with asthma. We aimed to examine the perceptions, attitudes and behaviours of adolescents with asthma, focusing on understanding the experiences and practices of smoking and its impact on asthma and medication use. Method: 90 young people (10-24 years) were recruited from 3 tertiary asthma clinics and participated in an in-depth interview that was recorded and transcribed. Content and thematic analyses were undertaken, with data management assisted by NUDiST. Results: 57 participants reported to be non-smokers, 11 classified themselves as smokers, 4 as former smokers and 7 as marijuana smokers. Smoking status was not detailed in 11. Across all age groups participants knew that smoking was bad for their health. However, nearly all smokers in the sample mentioned initial peer pressure, via constructions of "being cool", as contributing to their smoking. This was frequently despite acknowledging that smoking made their asthma worse. The smokers chose to presmedicate with reliever medications prior to social events where they knew that they and/or others would be smoking. This behaviour was paralleled among the non-smokers who premedicated prior to participating in social events where they expected to be exposed to passive smoke. Both groups viewed this as a reasonable means of participating in social activities without overly compromising short term health outcomes. These findings indicate that smoking (passive and active) is commonly experienced as an asthma trigger, but that in smoking adolescents, this knowledge is more influential in informing use of reliever medication than in stopping smoking. This suggests that smoking cessation strategies must be attuned to both social as well as health contexts.

Supported by the NHMRC and Asthma Victoria (Anna Jane Trust)

Key words: Asthma, adolescents, smoking, premedication

Nominations for awards: Nil
ADHERENCE IN ADOLESCENTS WITH ASTHMA: COMPARISON OF SELF REPORT WITH PARENTAL REPORT AND OBJECTIVE MEASUREMENT

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The extent of poor adherence with preventative medications for asthma is increasingly recognised. Adolescents are widely believed to be less adherent than older populations although there is little evidence to support this belief. The reliability of adolescent self report (AR) versus parent report (PR) of adolescent medication taking is unknown. We aimed to measure adherence with preventative asthma medications in adolescents and compare AR and PR of adherence with objective measures of adherence.

Method: 30 consecutive adolescents were enrolled following review at a tertiary adolescent asthma clinic. An electronic Doser was attached to all metered-dose inhalers (MDI) for one month. Telephone follow up with adolescents and parents (separately) identified AR and PR for the last 7 days and the total study period, using clinical approaches to optimise self report. Results: Mean adherence rates for preventative medication were 71% (last 7 days) and 78% (study period). However, adolescents were fully adherent on only 40.6% (last 7 days) and 53.4% (study period) of days. Extra dosing was identified throughout the study period, rather than rapid MDI emptying or 'dumping'. There was moderate association but weak agreement with AR over the last 7 days of monitoring only (CC = 0.26). PR showed poor agreement with objective monitoring over both time periods. PR agreed better with AR.

Conclusions: Mean adherence in this selected population of adolescents is as high as has been previously reported in any population with asthma. However, adolescents were fully adherent on less than half of all days studied. Adolescents reported medication use more reliably than parents over the last 7 days of monitoring.

Supported by Asthma Victoria (Helen Schutt grant)

Key words: Asthma, adolescents, adherence, electronic monitoring, self report.

Nominations for Awards: Nil

TEACHING ASTHMA MANAGEMENT IN FINAL YEAR MEDICAL STUDENTS: AN EVIDENCE-BASED APPROACH

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Asthma management plans and asthma education are incorporated into guidelines, yet teaching about asthma in medical school is seldom assessed. We studied asthma knowledge, confidence in asthma management, and effectiveness of an asthma education workshop.

Methods: Interactive teaching sessions on management of asthma and a practical session using asthma devices. Theoretical knowledge was assessed by a 20 item questionnaire, completed before the workshop at 2 wks. Practical knowledge was assessed by confidence scores in use of asthma devices (0-5; not confident – very confident) before, immediately after the workshop, and at 2 weeks. Results: Mean (SE) knowledge scores increased significantly from 64.4 (6.1%) to 74.2 (5.6%) (p<0.05, paired t-test) at 2 weeks. Students scored poorly in questions on: predictors of asthma mortality, nebuliser and Turbohaler use, asthma management plans, side effects of inhaled glucocorticosteroids, and physical signs in acute asthma. Confidence scores rose significantly for all practical aspects of asthma management (p<0.01; Wilcoxon matched pairs test), and declined at 2 weeks, but still remained significantly higher than baseline.

Mean (SE) scores:

|          | Pre   | Post  | 2 weeks |
|----------|-------|-------|---------|
| Discussing asthma | 3.3 (0.8) | 4.4 (0.8)** | 4.1 (0.7)** |
| Use of PR meter | 4.0 (0.9) | 4.6 (0.8)** | 4.0 (0.7)** |
| Use of MDI | 3.8 (0.2) | 4.7 (0.6)** | 4.3 (0.7)* |
| Use of spacer | 3.5 (0.2) | 4.7 (0.5)** | 4.3 (0.6)* |
| Use of turbohaler | 3.3 (0.9) | 4.7 (0.5)** | 4.1 (0.9)* |
| Use of nebuliser | 3.1 (1) | 4.6 (0.8)** | 4.0 (0.8)** |

Conclusions: Medical student knowledge about several important features of asthma care was poor. Our workshop increased knowledge and confidence in management of asthma.

Key words: Asthma, education, asthma devices

PEER-LED ASTHMA EDUCATION IMPROVES QUALITY OF LIFE IN ADOLESCENTS

S Shah, J Peat, G Cantwell, H Wang, P Sindsukave, R Henry, P Gibson

Asthma is a major health problem in adolescents. The Adolescent Asthma Action (Triple A) Program is the first peer-led asthma education program, which empowers young people to take control and improves knowledge and attitudes about asthma in the school community.

Aim: To establish the effect of the Triple A Program on quality of life (QoL) in a randomized controlled trial.

Methods: Students from six high schools in rural Australia. The schools were randomly allocated to either the intervention or control group. 1379 students from Years 7 (12.5yrs) and 10 (15.6yrs) completed the ISAAC video questionnaire to measure asthma prevalence. Students who reported sneezing in the last year (n=272, 86% R) completed the Paediatric Asthma Quality of Life Questionnaire and performed spirometry. Following the implementation of the program in the 3 intervention schools, these variables were re-assessed.

Results: Prevalence of recent wheeze was 25%. At baseline, most students with recent wheeze reported mild to moderate impairment of QoL due to asthma. FEV1 was 103% predicted and the FVC/VCF ratio was 89%. Total QoL scores after adjusting for year and gender significantly improved in the intervention group when compared to the control group (p<0.03) with 25% of students with asthma achieving a clinically relevant improvement, compared to 12% in the control group (p<0.01). This effect was greatest in Year 10 students and in females. Significant improvements occurred in the activities domain (41% vs 28%, p=0.03) and some improvement in the symptoms domain (26% vs 18%) and the emotions domain (27% vs 20%), however these failed to reach statistical significance except for males in the emotions domain (39% vs 19%, p=0.02). Lung function improved significantly in both the control and intervention groups. FEV1/VCF ratio remained stable over time.

Conclusion: The Triple A Program achieves a clinically and statistically important improvement in QoL, but not in lung function, in students with asthma. The challenge in the new millennium is dissemination and sustainability of the program.

ACTIVATION OF PROTEASE ACTIVATED RECEPTORS INDUCE CYTOKINE RELEASE FROM THE RESPIRATORY EPITHELIAL CELLS

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Asthma is a very common, chronic disease in both children and adults. The respiratory epithelium is important in asthma as it is the first line of contact inhaled allergens and contributes to the inflammatory response due to its ability to synthesise a range of pro-inflammatory products under the influence of a variety of stimuli. In this regard, we have shown that allergen house dust mite proteases are potent inducers. What is not clear from our studies, however, is how the mite protease induced effects are mediated at the cellular level. Recent identification of a novel family of G-protein coupled cell surface receptors which activate a variety of cellular functions, once cleaved by proteases, has been of particular significance in this study. Thus far, four PAR have been identified and differentiated on the basis of their activation by different proteases; PAR 1, 3 and 4 are activated by trypsin whereas PAR-2 and 4 is activated by trypsin.

We have for the first time shown the presence of PAR in airway epithelial cell lines BEAS-2B, A549, NCI-H332 and cultured human lung cells using specific antibodies. Further we have confirmed the presence of mRNA for these receptors. We used ELISA to determine the effect of the small peptides consisting of six amino acid residues, corresponding to the cleaved nascent N-terminus portion of the receptor of PAR-1 to -4 in activating the receptors on the release of the pro-inflammatory cytokines IL-8, IL-6, and GM-CSF from the lung epithelial cell lines. These results demonstrate that activation of PARs present on human airway epithelial cells will lead to the production of pro-inflammatory cytokines. Further, we have also shown that thrombin and tryptase are also capable of cleaving this protease-activated receptor. Thus, this study takes us a step closer to understanding the mechanism of action of the dust mite proteases and allergens on the lung epithelium.

Supported by the NHMRC & Asthma foundation WA.

Key words: Protease activated receptor, Cytokines, Allergy

Additional key words: Asthma, education, asthma devices

Key words: Asthma, education, asthma devices
NON-ALLERGIC PROTEINS FROM THE HOUSE DUST MITE - IMMUNE RESPONSES TO RECOMBINANT HOUSE DUST MITE FERRITIN IN ALLERGIC AND NON-ALLERGIC SUBJECTS

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The majority of proteins making up the house dust mite (HDM) are not allergens. Immune responses to these proteins may alter responses to HDM allergens by changing the cytokine milieu around antigen presenting cells.

Aims: To isolate and characterise HDM non-allergens, and to study the immune responses to recombinant non-allergens in allergic and non-allergic subjects.

Methods: A Dermapthagposidae pteronyssinus IgE library was screened with rabbit anti-HDM serum and antigenic clones screened for absence of IgE binding. A suitable clone was sequenced and expressed as a recombinant fusion protein. Immune responses to this protein were studied in allergic and non-allergic volunteers by immunoglobulin binding, peripheral blood mononuclear cell (PBMC) proliferative responses, and cytokine production.

Results: A DNA clone coding for ferritin, probably heavily chain, was isolated and a recombinant protein expressed using the pET vector. No IgE binding to the recombinant protein was seen from a battery of allergic sera. The protein induced significant PBMC proliferative responses (Mean proliferation (SE) 8811(1050) cpm vs control 1265(149) cpm (n=15, p<0.0001). There was no difference between allergic and non-allergic groups in proliferative responses. Stimulated PBMC produced significant IL-5 (Mean (SD) 106(20) pg/ml) and interferon-g (Mean IFN-γ 2077(751) pg/ml). There was no difference between allergic and non-allergic groups for either cytokine. Conclusions: House dust mite ferritin has been cloned, sequenced and expressed as a recombinant protein, which has the immunoglobulin binding characteristics of a non-allergen. Significant T-helper 2 type cytokine production is observed with PBMC stimulation. The classification of proteins as allergens or non-allergens may require more than just the ability to bind IgE.

Support: NH&MRC

Key words: House dust mite, allergy, recombinant, ferritin, non-allergen

Nominations for awards: Nil

INSECT VENOM IMMUNOTHERAPY - A 10-YEAR-REVIEW OF THE USE OF A “RUSH PROTOCOL” IN AN AUSTRALIAN TEACHING HOSPITAL’S ALLERGIC UNIT.

Westall GP, Czarny D, Thien FCK, O’Hehir RE, Douglass JA. Department of Allergy, Asthma & Clinical Immunology, Monash University Medical School, The Alfred Hospital, Prahran VIC 3181.

Purpose: To report the 10-year cumulative experience at the Alfred Hospital with a rush venom immunotherapy protocol used on patients who have presented with anaphylaxis after insect venom sting. Methods: Patients were referred to the allergy unit after a history suggestive of anaphylaxis following insect venom sting. Skin tests and RAST levels confirmed causative insects. Patients were treated over a 5-day period in a hospital setting with appropriate rescue medications. Results: The schedule consisted of: Day 1 (0.1-0.4-1.0-2.5-4 µg of venom), Day 2 (10-20-30-40 µg), Day 3 (50-60 µg), Day 4 (100 µg), Day 5 (100 µg). Results: 68 venom-allergic patients received a total of 73 courses of rush immunotherapy. 65 were treated with honey bee venom, 7 with yellow jacket venom (vespula sp.) and 1 with paper wasp venom (polistes sp.) The mean age was 38.02 years with a range 13-71 years. The severity of the initial sting was graded according to Müller’s scale: grade I (2.94%), grade II (16.18%), grade III (27.94%), and grade IV (52.94%). Of the 68 patients 24 were atopic and 10 were asthmatic. Of the 73 courses of VIT, complications occurred in 27 courses, of which 25 were hypersensitivity reactions. One patient was initially inadvertently given the incorrect venom (polistes instead of vesupula wasp venom), and 2 patients developed gram-negative sepsis presumably, from infected intravenous sites. During induction 13 patients (17.9%) developed severe generalised reactions. In all 949 injections were administered during the induction phase, and adrenaline was administered on 14 occasions (1.48%). During the maintenance phase severe hypersensitivity reactions necessitating the use of adrenaline occurred in 4 patients. As a consequence of repeat severe generalised reactions during maintenance, one patient was advised to discontinue immunotherapy.

Conclusions: The experience gained over 10 years of using a rush protocol during the induction phase of VIT suggests that this should continue to be performed in an in-patient setting with appropriate resuscitation measures. Of those patients receiving VIT, 89% were bee-allergic. This figure is different to that seen in Europe and the United States, where most patients are wasp-allergic.

CHILDHOOD ASTHMA AND EXPOSURE TO FORMALDEHYDE AND VOLATILE ORGANIC COMPOUNDS

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Young children spend most of their time indoors (80%-90%) and exposure to indoor air pollutants has been associated with increased acute respiratory disease morbidity, increased prevalence and incidence of respiratory symptoms and aggravation of asthma.

In a case-control study carried out in Perth, indoor environmental factors were studied in relation to respiratory illness in 192 children, aged between 6 months and 3 years old. Cases (N=88) were children who attended the Accident and Emergency Department at Princess Margaret Hospital and were diagnosed with acute asthma. Controls (n=104) were healthy children and identified from birth records through the Health Department. Information about respiratory conditions experienced by the child and characteristics of the home was collected in a self-administered questionnaire, completed by the child’s parents/guardians. Formaldehyde, nitrogen dioxide, VOCs, house dust mites, temperature and humidity were monitored in each household. Skin prick tests were performed on all children. The unconditional logistic regression model showed that VOCs exposure was a statistically significant independent risk factor for asthma with OR= 1.08 [95%CI: 1.01-1.15]. Furthermore, formaldehyde appeared to be a risk factor for asthma only among atopic children with OR=1.03 [95%CI: 1.01-1.05]. House dust mite levels were also a significant risk factor with OR=1.63, [95%CI: 1.08-2.48]. No association between asthma and nitrogen dioxide levels was seen. The study results showed that indoor environmental factors contribute as risk factors for childhood asthma.

Supported by the APAWS

Key Words: asthma, children, indoor environmental factors

Nominations for Awards: Nil

OUTPATIENT CLINIC DESSENSITISATION FOR ASPRIN SENSITIVE ASTHMA-RHINOSINUSITIS

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Background: Aspirin sensitive asthma is a distinct syndrome affecting about 10% of asthma patients. Rhinosinusitis is a significant co-morbidity in these patients with rhinorrhoea, anosmia and recurrent nasal polyposis. Aspirin desensitisation has been found to improve nasal symptoms as well as reduce steroid requirements, reduce need for repeated nasal polypectomies, and fewer emergency presentations for asthma. However, currently published desensitisation protocols are time and labour intensive. AIM: To develop a protocol of outpatient clinic desensitisation for aspirin sensitive asthma-rhinosinusitis suitable for a hospital or specialist ambulatory clinic.

Methods: Patients with asthma-rhinosinusitis with a history or suspicion of aspirin sensitivity were recruited from the Allergy Clinic of the Alfred Hospital. Baseline lung function was obtained and patients were included if FEV1 was greater than 70% predicted. Patients were challenged in the clinic commencing with oral aspirin 50 mg (half a Cardrin™ tablet) and observed for 2 hours with half hourly peak flow and symptom records, and FEV1 at the end of challenge. If the challenge was negative, the patient returned at weekly intervals, and challenged with 100, 200 and 300 mg until a positive challenge. If the challenge was positive, then the patient was maintained at that threshold dose of aspirin daily until the next visit when they would be challenged at the next higher dose. A validated rhinonconjunctivitis quality of life (RQOL) questionnaire was obtained before and after desensitisation. Results: 9 patients (5M,4F) with a mean age of 43±12 years and mean baseline FEV1 92±16 (% predicted) of were challenged. The threshold dose of a positive challenge was 50 mg for 3 patients, 100 mg for 4 patients and 200 mg for 1 patient, and 300 mg for 1 patient. The mean maximal fall in FEV1 was 12±9% with the lowest FEV1 reached being 69% predicted. One patient developed persistent urticaria after reaching 200 mg and was withdrawn. The RQOL score fell from a median of 74 (range 26-131) pre-desensitisation to 30 (range 9-136) post-desensitisation. Patients were maintained on aspirin ranging from 100 mg daily to 600 mg bd. Conclusion: Gradual aspirin desensitisation is safe and feasible within an ambulatory hospital or specialist clinic setting, with the use of daily maintenance aspirin between visits to maintain the threshold.
HOUSING FACTORS DETERMINING THE DISTRIBUTION OF ENDOTOXINS IN NEW ZEALAND HOMES

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Wellington Asthma Research Group, Wellington School of Medicine, Wellington, New Zealand; and Environmental and Occupational Health Group, Wageningen, Netherlands.

Recent reports suggest that bacterial endotoxin may be associated with asthma severity. Little is known about housing characteristics that influence the distribution of endotoxins in domestic dust. Endotoxin levels in dust were measured from a selection of houses with carpets in Wellington, New Zealand (n=74). Using standard methods, we sampled dust from the whole living-room floor. Endotoxin levels were measured using an LAL assay. Questionnaires were used to collect information on home characteristics. The geometric mean level of endotoxin on the whole floor was 28,352 endotoxin units per gram of dust (EU/g), (Geometric sd= 3.4). After adjusting for confounders, houses without insulation had significantly (p=0.008) higher endotoxin levels (39,064 EU/g, sd=4.0) than houses with insulation or a room or garage below the living room (18,672 EU/g, sd=2.3). Endotoxin levels were also independently higher (p=0.04) in houses situated on sloping ground (35,603 EU/g, sd=3.7), compared with houses situated on flat ground (20,252 EU/g, sd=2.7), and in carpets which had been steam-cleaned or shampooed in the last year (52,351 EU/g, sd=3.4), compared to carpets not steam-cleaned or shampooed (25,348 EU/g, sd= 3.3). [p=0.05]. Houses without insulation or situated on sloping ground may have higher levels of endotoxins because they are likely to be damp or have poor under-floor ventilation. These are characteristics of many Wellington homes and it is in these homes that endotoxin levels may affect respiratory health. The higher levels of endotoxins in carpets which have been steam-cleaned or shampooed may also be due to an increase in moisture within these carpets after cleaning.

ACKNOWLEDGMENTS: National Asthma Campaign and participating centre research assistants.

ASTHMA PREVALENCE IN THE INTERNATIONAL STUDY OF ASTHMA AND ALLERGIES IN CHILDHOOD (ISAAC) AND THE EUROPEAN COMMUNITY RESPIRATORY HEALTH SURVEY (ECRHS)

Soo Cheng, Neil Pearce, on behalf of the ISAAC Steering Committee and the European Community Respiratory Health Survey

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International and regional prevalence comparisons are required to test and generate hypotheses about the causes of increasing asthma prevalence worldwide. The International Study of Asthma and Allergies in Childhood (ISAAC) is the first such study in children and the European Community Respiratory Health Survey (ECRHS) is the first such study in adults. We have therefore conducted a comparison of the findings from these two surveys, for the 17 countries in which both surveys were undertaken. There was a strong correlation between the ISAAC and ECRHS prevalence data, with 64% of the variation at the country level, and 74% of the variation at the centre level, in the prevalence of "wheeze in the last 12 months" in the ECRHS Phase I data being explained by the variation in the ISAAC Phase I data. There was also generally good agreement in the international patterns observed in the two surveys for self-reported asthma (74% of country level and 36% of centre level variation explained), self-reported asthma before age 14 years (64% and 26%), hay fever (61% and 73%), and eczema (41% and 50%). These findings therefore add support to the validity of the two studies which provide a new picture of global patterns of asthma prevalence, and identify some of the key phenomena which future research must address.

Supported by the Health Research Council of New Zealand
Key words: asthma prevalence epidemiology

MELBOURNE STUDY OF CHILDHOOD ASTHMA, OUTCOME AT AGE 42

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In 1964, 295 wheezy children and 106 controls were recruited at age 7 years to determine the outcome of childhood asthma. A further 83 children with severe asthma were included in 1967 at age 10. The subjects have been re-evaluated each 7 years with clinical history, lung function measurements, BHR and atopy status. In this report, we present the results at age 42. To date, clinical history is available for 328 subjects and lung function for 238. At recruitment, children were classified as: C: controls; MWB, mild wheezy bronchitis (<5 episodes of wheezing with RTI); WB, wheezy bronchitis (>5 episodes of wheezing with RTI); A, asthma (wheezy unassociated with RTI); SA, severe asthma (persistent symptoms) At age 42, the subjects were reclassified as: W-no wheeze in the last 3 years; X-no wheeze in the last 3 months; Y—wheeze in past 3 months, < once per week; Z—wheezing in past 3 months, > once per week. Data in the table represent the outcome at age 42 for each of the groups at age 7 / 10.

| Classification | W | X | Y | Z | FEV1(%pred.) | FEF75-25(%pred.) |
|----------------|---|---|---|---|--------------|-----------------|
| C (n=81)       | 85%| 8% | 5% | 2%| 104%         | 86%             |
| MBW (n=57)     | 67%| 19%| 14% |0%| 108%         | 84%             |
| WB (n=73)      | 59%|12% |18% | 11%| 102%         | 83%             |
| A (n=88)       | 32%|18% |26% | 23%| 98%          | 70%             |
| SA (n=49)      | 12%|14% |29% | 45%| 86%          | 55%             |

These results show a good clinical outcome for childhood asthma into adult years with relative preservation of lung function. Only those with severe asthma in childhood have a modest reduction in lung function in adulthood. Overall, there has been little change in clinical status in the last 7 years and no further deterioration in lung function.

Supported by NATIONALBANK AUSTRIA and NHMRC
Key words: childhood asthma, outcome, lung function.
PREVALENCE OF ASTHMA IN RECREATIONAL SCUBA DIVERS

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Asthma is considered a contributory factor in SCUBA-diving related mortality and is present in up to 9% of deaths. Current asthma is regarded as a medical contra-indication to diving. Although routine screening aims to exclude asthmatics from dive training, some asthmatics are known to dive. The prevalence of asthma amongst divers, and in relation to diving mortality, is unknown. We aimed to determine the prevalence of asthma in a cohort of Western Australian recreational SCUBA divers. We sought to characterise their general health, to identify any diving related problems and to determine the beliefs of divers regarding the implication of asthma on dive safety.

Methods: Questionnaires were mailed to 982 divers who had either recently completed a PADI diving course, or who were members of the University of WA dive club.

Results: In the 540 (55%) respondents, the prevalence of current asthma was 9.7% (95% CI 7.1-12.3%). This was significantly different from the prevalence of 11.8% in Australian adults. Past asthma was present in 5.6% and a further 15.3% had symptoms suggestive of asthma. Most asthmatic divers reported only symptoms of mild airways disease. There were no significant differences in the general health of asthmatic and non-asthmatic divers. Asthmatics had not experienced any increase in diving related technical or health problems. Although most asthmatics identified asthma related diving risks, many continued to dive despite active disease.

Conclusions: The prevalence of current asthma in divers does not support the contention that asthmatics are over represented in diving deaths. Current screening is ineffective at identifying asthma and precludes education of asthmatics in the potential risks of diving.

Supported by the Asthma Foundation of WA.

Keywords: Asthma, SCUBA, diving

IS ALLERGEN EXPOSURE THE MAJOR PRIMARY CAUSE OF ASTHMA?

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In recent decades, a number of authors have argued that allergen exposure is the major primary cause of asthma, and that the global increases in asthma prevalence are due to increases in exposure to aeroallergens. We have assessed the epidemiological evidence in support of this hypothesis. No longitudinal studies were identified in which allergen exposure during infancy in a random population sample has been related to asthma risk after age six years. Two studies have been conducted in selected populations chosen on the basis of a family history of asthma or allergy; one study found a non-statistically significant association whereas the other study found no association. Many of the identified prevalence studies in children showed negative associations between allergen exposure and current asthma, and the weighted averages of the population attributable risks in children were 4% for Der p 1, 11% for Fel d 1, -4% for Bla g 2, and 6% for Can f 1. There was little change in these estimates in studies in which children whose parents had adopted allergen avoidance measures were excluded. Furthermore, evidence from population studies is equivocal and provides little consistent evidence that allergen exposure is associated with the prevalence of asthma at the population level. Population-based cohort studies are clearly required, but currently available evidence suggests that allergen exposure is at most a minor risk factor for the primary causation of asthma in children.

Supported by the Health Research Council of New Zealand

Keywords: asthma, allergy, atopy, epidemiology

INCREASED WEIGHT IN CHILDREN IS A RISK FOR SYMPTOMS AND MEDICATION USAGE FOR ASThma, BUT NOT AIRWAY HYPERRESPONSIVENESS.

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Obesity may be a risk factor for asthma in children. If so, the effect could be due to an effect of obesity on lung volume and thus airway hyperresponsiveness (AHR). Methods: Data from 5982 Caucasian children (8-11 years) from 7 large epidemiological studies performed in NSW were analysed. Subjects were included if data were available for height, weight, age and a measure of airway responsiveness (AR). Doctor diagnosis of asthma, history of wheeze, cough and medication usage in the last 12 months were obtained by questionnaire. Body mass index (BMI) kg/m², divided into quintiles per year age, was used as a measure of obesity. The highest quintile was defined as overweight. Dose response ratio (DRR) was used as a measure of AR. DRR(% fall in FEV₁,uol histamine)+3. Airway hyperresponsiveness was defined as a DRR ≥ 8.1. Adjusted odds ratios (OR) were obtained by logistic regression. Results: After adjusting for atopy, age, sex, family smoking history and family history, being overweight was a significant risk factor for cough in last 12 months (OR 1.35, 1.17-1.55, p<0.001) and medication usage for asthma in the last 12 months (OR 1.25, 1.08-1.44, p<0.002). Increased weight was not a risk for AHR (OR 0.89, 0.75-1.05, p=0.14), diagnosed asthma (OR 1.06, 0.92-1.21, p=0.44) or wheeze in the last 12 months (OR 1.11, 0.96-1.29, p=0.16). Conclusions: Increased weight in children is a risk factor for cough and medication use for asthma but not airway hyperresponsiveness.

This study was funded by The Asthma Foundation of NSW, Australia.
MICRONUTRIENT INTAKE AND CURRENT ASTHMA IN YOUNG ADULTS:
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Whilst the true role of diet in asthma remains unknown, it has been hypothesised that diet may be a risk factor for asthma. Current interest is focused on the protective effect of fresh oily fish (specifically, long chain omega 3 fatty acids) and Vitamin E intake and the possible deleterious effect of dietary sodium. Methods: 638 young adults participated in a community-based cohort study of dietary risk factors for asthma. Participants completed a detailed respiratory questionnaire and a subset (n=419) also completed a semi-quantitative food frequency questionnaire and underwent methacholine challenge to measure bronchial hyper-reactivity (BHR). Predictive models were developed with multivariate logistic and linear regression. Results: 81 participants (38.9 (SD 6.3) years, 49% male) were defined as having current asthma on the basis of self-reported wheeze in the past 12 months and BHR. They had a BMI of 26.6(0.9) kg/m² and 19% were current smokers. These characteristics did not differ significantly from those participants without current asthma (n=338). Dietary sodium intake was a significant negative predictor (OR=0.03, 95%CI=0.003-0.24), whilst tinned fish intake (1.5, 1.03-2.19), average portion size (4.6, 1.61-13.0) and total energy intake (10.6, 0.84-138) were independent predictors of current asthma. In a separate multiple regression model, dietary sodium was found to be a significant negative predictor of PD20 following adjustment for confounding variables (dietary cholesterol, atopy, and gender). Conclusions: Those with current asthma appear to consume more tinned fish and less dietary sodium, which may be consistent with dietary change consequent to asthma awareness and/or diagnosis. However, sodium intake was associated with BHR, suggesting that sodium may play a role in the dietetic aetiology of asthma.

Supported by the NH&MRC

Key words: Atopy, genetics, polymorphism

RECOMMENDED LENGTH OF BREASTFEEDING DOES NOT REDUCE THE SUBSEQUENT RISK OF CHILDHOOD ASTHMA
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Background/Methods: As part of the population – based ISAAC (International Study of Asthma and Allergy in Childhood) study conducted in Upper Austria we analyzed breastfeeding habits and the influence on the development of asthma, allergic rhinitis and eczema in children up to the age of 6 – 9 years. Results: 74.6% of the parents reported breastfeeding their infants: 25.9% were exclusively breastfed for less than 2 months, 25.9% for 2 to 4 months, 13.2% for 5 – 6 months (the recommended duration of exclusive breastfeeding) and 10.4% of the children were exclusively breastfed for more than 6 months. Smoking during pregnancy and low educational level were inversely related to breastfeeding and duration of exclusive breastfeeding. In comparison to children without family history of atopic diseases, risk and high risk children were exclusively breastfed more often and for a longer period of time. No significant reduction in the prevalence of lifetime diagnosis of asthma was found either for breastfed infants in comparison to those not breastfed (OR: 0.92; CI: 0.82-1.04), nor did the length of exclusive breastfeeding have any significant influence on asthma prevalence; breastfeeding reduced the risk of allergic rhinitis (OR: 0.83; CI: 0.74-0.94). For atopic eczema, breastfeeding and length of exclusive breastfeeding was associated with an increase in risk (OR: 1.23; CI: 1.13-1.34). Conclusion: A protective effect of breastfeeding was found only for allergic rhinitis. We found no significant effect of breastfeeding on asthma prevalence and even a negative influence on atopic eczema. Despite the otherwise undoubted advantages of breastfeeding for child nutrition, the importance of the recommended length of exclusive breastfeeding for allergy prevention should not be overemphasised.

Supported by Land Oberoesterreich and Department of Epidemiology, University of Vienna

Key words: breastfeeding, ISAAC, asthma, prevention, epidemiology

ASTHMA IS NEGATIVELY ASSOCIATED WITH GROWTH IN HEIGHT DURING ADOLESCENCE
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Introduction and aim: There has been concern about the effects of inhaled corticosteroids on the growth of children with asthma. Previous work has suggested that children with asthma who are not taking inhaled steroids grow normally (McCowan et al., 1998 BMJ 668-672). We have used data from the Belmont cohort to evaluate whether asthma is independently negatively associated with height and growth in height during adolescence and young adulthood.

Methods: A cohort of 8-10 year old children (n=718), living in Belmont, NSW, were studied at two yearly intervals from 1982-1992, and studied again in the period 1997-1999. At each survey, standing height was measured and information on wheeze and inhaled steroid use in the preceding 12 months was collected by questionnaire. The presence of airway hyperresponsiveness (AHR), defined as PD20FEV1 < 3.9 μmol, was determined by histamine challenge test.

Results: A history of wheeze in the last 12 months was associated with, on average, a 1.6 cm (95%CI 0.6 to 2.6) lower height but not with a lower growth in height (P > 0.45). The presence of AHR was associated, on average, with a 2.9 cm (95%CI 1.6 to 4.1) lower height and also with a lower growth in height (P<0.001). The number of subjects using inhaled or oral steroid in the last 12 months at each survey ranged from 2 to 28. Adjustment for steroid use did not affect the associations described above.

Conclusions: People with asthma are slightly shorter in stature than others during adolescence and young adulthood and this is independent of inhaled or oral steroid use.

Supported by: NH&MRC, Allen-Hanburys

Key words: Asthma, Epidemiology, adolescence

ASSOCIATION BETWEEN GENETIC VARIANTS OF THE MAST CELL CHYMASE GENE AND ATOPY IN PAEDIATRIC POPULATIONS.
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Atopic disorders are characterized by elevated serum Immunoglobulin E (IgE) levels and are dependent on the specific triggering of IgE-sensitized mast cells by allergen. Mast cell chymase (MCC) has an important role in allergic inflammation within the respiratory tract and dermis. A previous study identified a polymorphism in the MCC gene (1411.2), which can be detected by BstXI enzyme restriction, and reported an association between this polymorphism and eczema. The aim of this study was to identify whether there was an association between genetic variants in the MCC gene and atopic outcomes in two unselected paediatric populations. Population 1: 77 six year old subjects from a cohort of infants recruited from an Australian hospital antenatal clinic. Population 2: 135 children (mean age 9 years) from Venezuela. Phenotypic parameters included skin prick testing, serum total & specific IgE titre, blood eosinophil measurements and a questionnaire was administered to ascertain family history and environmental exposures in both populations. In addition, spirometry and histamine challenge were conducted on population 1. In the Australian population, an association was found between the BstXI polymorphism and specific IgE to mixed grass (p = 0.039), however, there was no association between this polymorphism and asthma, eczema or other atopic outcomes. In the Venezuelan population, the BstXI polymorphism was associated with a physician diagnosis of asthma (p = 0.005), but not associated with elevated serum IgE levels or skin prick reactivity. These findings suggest that variants in the mast cell chymase gene are relevant in the genetics of atopy.

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Key words: Atopy, genetics, polymorphisms, paediatrics
POLYMORPHISM SCREEN OF THE CC16 GENE PROMOTER REGION.

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The A38G polymorphism in the 5' non-coding region of exon 1 of the Clara cell secretory protein (CC16) gene has previously been associated with an increased risk of developing asthma and reduced levels of circulating CC16 protein. **Aim:** To screen the promoter region of the CC16 gene to identify other polymorphisms that may alter CC16 gene function. **Methods:** Sixty four children were selected for asthma from a tertiary hospital respiratory clinic and 44 controls were recruited from a suburban general hospital. DNA from each subject was used in PCR to amplify the 550bp CC16 promoter region. Two PCR products, 287 and 273bp in length, encompassing the CC16 promoter region were screened for mutations using single stranded conformational polymorphism (SSCP) analysis and heteroduplex analysis. DNA sequencing on a 10% random sample was used to confirm these results. **Results:** No polymorphisms were identified in the CC16 promoter region. **Conclusions:** The association between the A38G polymorphism, asthma and reduced plasma CC16 levels is most likely due to altered CC16 gene function caused by the A38G polymorphism and not another linked polymorphism in the CC16 promoter region.

Supported by the NH&MRC

Key words: Polymorphism screen, CC16, promoter, asthma.

Nominations for Awards: nil

β2 ADRENERGIC RECEPTOR GENOTYPES AND LIFE-THREATENING ASTHMA

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The β2 adrenoreceptor (β2AR) has key functions in asthmatic airways, and exhibits desensitisation and down-regulation with prolonged β2 agonist exposure in asthmatics. Functionally relevant β2AR polymorphisms have recently been characterised. Ile-164 reduces β2AR affinity for β2-agonists. Codon 1627 polymorphisms enhance down-regulation, reduce bronchial inflammation and increase nocturnal asthma. S'-leader cistron polymorphism reduces receptor density and expression. We hypothesised that these β2AR polymorphisms modify asthma severity. **Aim:** To examine β2AR polymorphisms as disease-modifying genes in asthma. **Methods:** We recruited 53 adults with life-threatening asthma (admission to ICU due to asthma), 127 mild asthmatics (no ICU admission) and 177 healthy anonymous blood donors. β2AR genotypes were determined using PCR. **Results:** Patients with life-threatening asthma had mean (SD) age 42 (18) years and 55% were female. The β2AR was associated with an odds ratio of 6.9 (95% CI 1.2-38.2) for life-threatening asthma (see Table). There was no association of codon 1627 or S'-leader cistron polymorphisms with life-threatening asthma.

| Allele       | Life-threatening asthma | Mild asthma | Blood donors |
|--------------|-------------------------|-------------|--------------|
| Ile-164 (variant) | 4 * (3.8%)               | 1 (0.4%)    | 2 (0.8%)     |
| Thr-164 (wildtype) | 102 (96.2%)             | 253 (99.6%) | 352 (99.4%)  |

* P=0.027 (Fisher's exact test) compared with other groups.

**Conclusions:** The β2AR polymorphism in the coding region of the β2AR gene was infrequent but increased the risk of life-threatening asthma. Correlation of β2AR genotype to asthma phenotype has implications for understanding the pathogenesis of severe asthma, predicting prognosis and individualising asthma management.

Supported by: The Prince Charles Hospital Foundation, The Asthma Foundation of Queensland, NH&MRC Medical Postgraduate Scholarship

Key words: Asthma, β2 adrenoreceptor, polymorphism

Nominations for Prizes:

ASSOCIATION STUDY OF CC16 AND CD14 POLYMORPHISMS IN AN UNSELECTED POPULATION ASSESSED AT AGE 8 AND 25.

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The genes for Clara cell secretory protein (CC16) and CD14 both contain common polymorphisms (A38G and C-159T respectively) that have been associated with asthma-related phenotypes and altered serum levels of CC16 and CD14 respectively. **Aim:** To investigate the relationship between CC16 A38G and CD14 C-159T and the atopic phenotype in an unselected cohort. **Methods:** 276 seven year olds were recruited from an unselected Australian population and followed-up at age 25. Assessment included questionnaire, spirometry, histamine challenge and skin prick test. Blood was taken at age 25 for DNA and total serum IgE. Genotypes were determined using restriction enzyme digestion, independent association analyses were done relating genotype to phenotype at age 8 and 25. **Results:** CC16: 14% were 38AA, 50% 38AG and 36% 38GG. There was no association between CC16 genotype and asthma-related parameters (asthma diagnosis, symptoms, bronchial hyper-responsiveness (BHR), wheeze + BHR) in subjects analysed at age 8 and 25. CD14: 28% were -159CC, 49% -159CT and 23% -159TT. At age 8 there was a 2.5 fold lower risk of one ≥3mm skin prick test in -159TT subjects compared with -159CC and -159CT subjects (95%CI=1.04-5.88, p=0.039). There were no associations between CD14 genotype and other atopic parameters. At age 25 there was no association between CD14 genotype and atopic parameters. **Conclusion:** A reduced risk of a positive skin prick test was found in 8 year old children with the CD14 -159TT genotype, but the association was of marginal statistical significance. No other associations were found between CC16 A38G or CD14 C-159T and asthma or atopic parameters in subjects age 8 or 25 years. These data suggest that these two polymorphisms do not have a significant role in inherited susceptibility to atopy or asthma in this population.

Funded by AstraZeneca

Key words: asthma, atopy, genetics, polymorphisms

FLUTICASONE PROPIONATE INHIBITS EOSINOPHILIA, GOBLET CELL HYPERPLASIA AND AIRWAY HYPERRESPONSIVENESS IN A MURINE MODEL OF ALLERGIC BRONCHOCONSTRICTION

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Asthma is a disease characterised by the presence of chronic airways inflammation, airway hyperresponsiveness (AHR) and airway wall remodelling (AWR). AHR remodelling explains a major part of AHR. We have previously reported that glucocorticoids inhibit the proliferation of human cultured airway smooth muscle (Br J Pharmacol 116, 3219-3226, 1995). **Aim:** To examine the effects of the glucocorticoid fluticasone propionate (FP) on the development of bronchoalveolar lavage (BALF) eosinophilia, AHR and AWR in a murine model of allergic bronchoconstriction. **Methods:** Male C57Bl/6 mice were sensitised by intraperitoneal (ip) injection of ovalbumin (OVA) on days 0 and 12, followed by 8 aerosol challenges (30 min) with a combination of OVA (5% w/v) and fetal calf serum (FCS, 5% v/v) on days 20-27. FP (0.03-1 mg/kg) was administered daily by ip injection at least 1 h before OVA/FCS challenge. Control mice were challenged with saline and received vehicle (3 mg/kg, 4% DMSO + 96% peanut oil) by ip injection. On days 19 and 27, airway responsiveness to aerosolised methacholine (MCh, 3-12 mg/L) was measured using non-invasive, whole body plethysmography (Phen). On day 28, the mice underwent BAL with sterile saline and cytospot preparations were stained with DiffQuic for eosinophils. **Results:** FP, at all doses tested (0.03-1 mg/kg), reduced OVA/FCS-induced increases in BALF eosinophilia. The threshold for inhibition of goblet cell hyperplasia by FP was 0.1 mg/kg whereas only 1 mg/kg FP significantly reduced OVA/FCS-induced AHR. **Conclusion:** These results indicate that FP inhibits AHR, BALF eosinophilia and goblet cell hyperplasia induced by repeated allergen inhalation with different potencies. Supported by Glaxo Wellcome (UK)

Key words: Airways hyperresponsiveness, fluticasone propionate, eosinophilia, goblet cell hyperplasia, airway wall remodelling

Nominations for Awards: Nil
A CROSS SECTIONAL STUDY OF EOTAXIN AND IL-5 IN THE BRONCHOALVEOLAR LAVAGE (BAL) OF ASTHMATICS ON DIFFERENT LEVELS OF INHALED CORTICOSTEROIDS.

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INTRODUCTION: Eosinophilia is a key feature of clinical asthma. Two important cytokines that play a role in eosinophil biology are eotaxin and IL-5, but human data are limited and especially their responses to inhaled corticosteroid (ICS) regimes.

HYPOTHESIS: There is an increase in IL-5 and eotaxin in asthma and that ICS decreases the levels of these cytokines.

AIMS: To measure eotaxin and IL-5 in the BAL of asthmatic patients on varied steroid doses and contrast those levels with non-asthmatic controls.

METHODS: We have developed sensitive (>30pg/ml) chemiluminescent ELISA techniques that can measure both eotaxin and IL-5 protein levels in BAL. These assays have been performed in a cross sectional study of 42 steroid naïve asthmatics, 53 asthmatics on a low steroid dose (>1000ug/day BDP), 25 asthmatics on a high steroid dose (>1000ug/day BDP) and 25 non-asthmatic controls, in which a standardised 3x60ml BAL had been performed.

RESULTS: Our findings are summarised in the figures below:

CONCLUSIONS: The above figures support our hypothesis that eotaxin and IL-5 are raised above normal levels in asthma. ICS appears to lower IL-5 expression to an intermediate level. In contrast raised eotaxin exhibits some resistance to steroid treatment across a range of doses. Future longitudinal studies will be required to investigate this further.

SUPPORTED BY: Glaxo Wellcome and NHMRC

KEYWORDS: BAL, Asthma IL-5, Eotaxin Treatment

THE EFFECT OF LOW DOSE THEOPHYLLINE ON CYTOKINE PRODUCTION FROM ALVEOLAR MACROPHAGES IN PATIENTS WITH MILD ASTHMA.

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Theophylline is still widely used in the treatment of asthma. There is increasing evidence that theophylline has anti-inflammatory effects.

Theophylline decreases the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and increases the production of the anti-inflammatory cytokine IL-10. We investigated the production of IL-10, TNF-α and GM-CSF from alveolar macrophages (AM) and whole blood, in a double blind placebo controlled crossover trial to assess the anti-inflammatory activity of low dose theophylline in 15 patients with mild asthma (mean age: 30.5 ± 2.1; FEV1 % predicted: 87.9 ± 8.1%; PO2 on methacholine: 86.8 ± 2.4%; PO2 on exhaled NO: 21.0 ± 2.9 ppb). AM were obtained by fibraroscopic bronchoscopy and bronchoalveolar lavage (BAL).

Following treatment there was no significant increase in the production of IL-10 either constitutively or following stimulation (LPS 10μg/ml, IL-1β 10ng/ml), nor an attenuation of TNF-α or GM-CSF production in AM. There was a significant reduction of BAL and sputum eosinophils following theophylline (3.5 ± 0.8 to 1.9 ± 0.25%, p<0.05 in BAL and 11.3 ± 1.6 to 7.9 ± 1.1%, p<0.05) but clinical parameters including lung function and airway hyperreactivity were unchanged after theophylline therapy. In whole blood, there was no significant increase in production of IL-10 either constitutively or with stimulation. These results suggest that low dose theophylline exerts an anti-inflammatory effect in patients with mild asthma, however this is not mediated through IL-10.

This study was supported by BYK Gulden.

A COMPARISON OF THE IN VITRO PERFORMANCE BETWEEN THE FORADILE® AEROLIZER® AND OXIS® TURBUHALER®

Hak-Kim Chan, Nora Y.K. Chew
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Eformoterol fumarate dihydrate is a long acting beta-2 agonist for bronchodilation in asthmatic treatment. To date, Foradile®Aerolizer® and Oxis®Turbuhaler® are the only dry powder inhalers available for the delivery of eformoterol. The two products differ in the formulation, the aerosol production mechanism and the device resistance to airflow. Our aim was to compare the in vitro performance of these two inhalers in producing the eformoterol aerosols. The particle size distributions of the two inhalers was assessed by a four-stage liquid impinger (plus filter) with a glass throat, at flows of 30 - 120 L/min. Eformoterol collected from the impinger was assayed by high performance liquid chromatography using UV detection at 240 nm. Fine particles are those ≤ 4.4 - 6.8 μm in the aerosols, depending on the air flow. At high airflow, 90 and 120 L/min, both inhalers produced similar amounts (4 μg) of fine particles in the aerosol per dose discharged. This fine particle mass is about 30% of the label claim. As the flow was decreased to 30 and 60 L/min, both inhalers produced significantly less fine particles (p < 0.05), with the Oxis® Turbuhaler® producing lesser amounts than the Foradile® Aerolizer®. At a 'comfortable' inspiratory effort of 40 cmH2O, the Foradile® Aerolizer® would produce a significantly higher fine particle mass in the aerosols. We conclude that the in vitro performance of the two inhalers for eformoterol was equivalent at high but not at low airflows.

Supported by Novartis Australia

Key words: eformoterol, dry powder inhaler, Foradile®Aerolizer®, Oxis® Turbuhaler

Nominations for Awards: Nil

EARLY INTERVENTION IN ASTHMA: EFFECTS OF FORMOTEROL/BUDESONIDE “EARLY INTERVENTION” TH2 IMMUNITY AND INFLAMMATION IN A MURINE MODEL MURINE ASThma.

Alastair A. Mannach, Jessica Jones, Sarah-Jane Beavitt, Alastair G. Stewart, Gary P. Anderson. Department of Pharmacology, University of Melbourne, Australia

Treatment with a combination of long acting beta-agonists and glucocorticosteroids can control asthma symptoms/exacerbations (1), and early steroid intervention may produce better long term lung function (2). However, in vivo both steroids and beta2-agonists suppress IL-12 synthesis and may therefore reduce Th2 immune responses to a TH2 immune response (3). A Th2 immune response is associated with most disease. As both steroids and beta2-agonists are presently used to treat asthma we examined their in vivo effects on the intensity of Th2 recall responses and eosinophilic inflammation elicited by ovalbumin (OA). Groups of 7-10 male 20g Balb/c mice received nothing (C), PBS vehicle (PBS), high dose (based on species equivalence estimates) daily exposure of formoterol (F, 50pμg/kg, sc), budesonide (30μg/kg, sc) or both (FB) 1 day prior to, and for 13 days after, primary sensitisation to OA (1μg in Al(OH)3, i.p.). The OA response was boosted 14 fold after primary sensitization to expand TH2 effectors, and the mice subsequently challenged with three exposures to OA (1μg in) on days 21, 22, and 23 to elicit recall, analysed on day 24. Eosinophilic inflammation measured in BAL, was not exacerbated compared to C (4.00±0.3 cells/ml - mean/SEM) and PBS (7.1±1.3 cells/ml) by F (6.64±0.6 cells/ml) and was suppressed by B or FB (0.7/0.2 E, 2.7±1.1 E cells/ml, respectively, p<0.05). Compared to C and PBS, F, B, and FB suppressed IL-5 and IFNγ levels in FACS sorted CD4+/CD8+ T cells obtained from draining lymph nodes and restimulated with anti-CD3 in vitro (IL-5: 450; 540; 190; respectively; IFNγ: 650; 1100; <100; <100pg/ml, respectively). In addition, B but not F or FB suppressed IL-5 production from anti-CD3 stimulated T cells from mixed BAL cultures. The data suggest that treatment with high dose parenteral F, B, or FB during emergence of TH2 immune response does not enhance the intensity of lung mucosal recall responses.

(1) Pauwels RA, et al. N Engl J Med 1997 337:1405-15; (2) Haastert T, et al., N Engl J Med 1991 325:368-72; (3) Panina-Bordignon P, et al. J Clin Invest 1997 100:1513-9.
EFFECT OF BUDENOSIDE ON PERCEPTION OF BREATHLESSNESS IN ASTHMATIC SUBJECTS

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The perception of breathlessness is an indirect determinant of asthma treatment, particularly with symptom based self-management plans. The effect of treatment on perception has received limited study. Aim: To determine the effect of inhaled budesonide on the perception of breathlessness induced by histamine challenge. Histamine challenges were performed at baseline and 8, 16, 24, 48 and 72 weeks. In 35 subjects the severity of breathlessness was recorded by Borg scores during challenge and perception was estimated as the slope of Borg/FEV,4kPa. Blood eosinophils and serum ECP were measured. Results: Slope Borg/FEV, increased significantly after 8 weeks budesonide, (0.1±0.02 to 0.175±0.03, p<0.0001). Perception remained significantly increased at all subsequent visits, but did not increase any further. Slope Borg/FEV, at baseline did not differ significantly between subjects on inhaled corticosteroids (ICS) at study entry and those not on ICS (0.11±0.03 vs 0.11±0.02).

The magnitude of change in perception in the first 8 weeks of treatment did not differ significantly between the two treatment groups, and was not related to changes in baseline FEV, or serum ECP. Conclusions: Perception of breathlessness is increased within 8 weeks by treatment with inhaled corticosteroids in asthmatic subjects. However, there is no further change during a year of good asthma control. The increase is not related to improvements in clinical or inflammatory markers. Altered perception during treatment with inhaled steroids may lead to underestimation of symptomatic improvement, with consequences for self-management.

Study support: NHMRC Australia, AstraZeneca Sweden and AstraZeneca Australia

Key words: asthma, perception, inhaled corticosteroids

CELLULAR LOCALISATION OF INTERLEUKIN-13 RECEPTOR IN NORMALS AND ASTHMATICS.

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Interleukin (IL-13) appears to be capable of inducing the entire allergic asthma phenotype. Goblet cell hyperplasia, mucus hyperproduction and subepithelial fibrosis have been demonstrated in response to IL-13 in murine models of allergic bronchoconstriction. However, there are no studies of the distribution of IL-13 receptor in human airways. We studied the localisation of the IL-13 receptorα1(IL-13Ra1) in the airways of a cohort of normals and asthmatics that have been followed prospectively with reassessment every 7 years since the age of 7 (H Owaidi et al, BMJ 1994; 309: 96-9) and have recently returned for extensive review (age 42 years) including basic lung function tests and bronchoscopy. Endobronchial biopsies were analysed Immunohistochemically for IL-13Ra1 from 10 asthmatics of varying severity and 6 nonasthmatic controls. Fibroblasts were isolated from separate biopsies taken at the same time and cultured in DMEM (20% FCS and bFGF 3mM) for up to 5 weeks to produce an explant culture. Second passage cells were immunostained for IL-13Ra1. IL-13Ra1 was detected in basa, perilial cells, eosinophils, mononuclear cells and fibroblasts within the biopsies. IL-13Ra1 was also identified in fibroblasts cultured from biopsy specimens. We conclude that the expression of the IL-13Ra1 on cells associated with key asthma pathology is consistent with emerging evidence of IL-13 in a role for perpetuating the inflammatory response in asthma.

This work was funded by NH&MRC Australia, Glaxo-Welcome UK.

THE RELATIONSHIP BETWEEN SUB-BASEMENT MEMBRANE THICKNESS AND AIRWAY WALL DIMENSIONS IN ASTHMA.

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Airway remodelling in asthma includes increased wall thickness, areas of smooth muscle and mucous glands and deposition of extracellular matrix proteins and results in altered airway function. It is thought to be due to airway inflammation and responds to therapy with inhaled corticosteroids. Measuring airway inflammation and remodelling may be necessary to optimise therapy. Airway dimensions can only be measured on whole transverse sections. Aim: To determine if the sub-basement membrane thickness (BMt), which can be measured on a bronchial biopsy, reflects changes in dimensions across the entire airway wall. Methods: Transverse sections of large airways (> 10 mm internal perimeter) from cases of fatal asthma (FA, clinically severe), nonfatal asthma (NF, mild) and control (C) cases (n=5 each) were examined. BMt was measured at X400 and related to the area of the inner airway wall (WA), outer wall (WAc), total wall (WA), smooth muscle (ASM), mucous glands (Agl), cartilage (Acart) and numbers of eosinophils (Eos). Results: The mean value for BMt was stable after 15 measurements, taken randomly round the inner perimeter at intervals of 0.1 mm. Mean BMt was 5 µm in C and increased in FA (17 µm) and in NF (7 µm) and FA (9 µm) cases. BMt correlated positively with WA (p<0.001), smooth muscle (ASM, p<0.001), mucous glands (Agl), cartilage (Acart) and numbers of eosinophils (Eos). BMt was related to BM length, muscle shortening, Acart, WA or WAc. These findings suggest that BMt is a marker of airway remodelling in asthma, particularly in severe cases and that changes in BMt may be useful to monitor asthma treatment.

Support: NH&MRC

Key words: Sub-basement membrane, airway remodelling, asthma

Awards: nil

Identification of Lyn Kinase as a Central Regulator of Severe, Persistent Asthma in Mice.

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The Src family tyrosine kinase, lyn, is currently thought to be a key therapeutic target in allergic asthma because it is essential for in vivo signalling by high affinity IgE receptors, the common β chain of IL-3, IL-5 and GM-CSF receptors and the B cell receptor complex. We used lyn knock-out mice (lyn-KO) (Hibbs et al, 1995) to test this hypothesis. Paradoxically, sensitized lyn-/- mice (C57Bl6X129;J) mounted profound, persistent eosinophilic inflammation to ovalbumin aerosols (tail-oad control 1.04±0.39x10^9 vs lyn 9.73±0.81x10^9 bronchoalveolar lavage eosinophils, n=1-12, p<0.001), and had serum hyper-IgE, mast cell hyper-degranulation and bronchial hyperresponsiveness to inhaled antigen. The intense eosinophilia was not due to enhanced eosinophil progenitors (CFU-eos) in bone marrow or spleen. Similarly, elevated IgE was not responsible because double knock-out in B (lym-/-lyn-/-) mice also showed increased eosinophilia. Although purified thoracic CD4+ lymphocytes secreted >10-fold higher levels of IL-4 and IL-5 (>100pg/mg2x10^6 cells, p<0.01), but not IFN-γ, ultrap Budding CD4+ T cells did not express lyn. However, lyn was highly expressed in the rare NK1.1+ natural killer (NK) cell population. Depletion of NK cells prevented development of the multi-trait asthma phenotype. These data represent the first example of a single molecular defect causing an asthma-like syndrome involving multiple, diverse and seemingly unrelated disease loci simultaneously. We propose that lyn links these diverse loci by a fundamentally important, undiscovered, biochemical mechanism governing asthma severity and progression, acting principally on the NK1.1+ lymphocyte subset.

Hibbs et al., (1995) Cell: 83:301-311

Funded by NHMRC

Key words: lyn, Th2, IgE, NK cell, eosinophil, inflammation,

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INHALATION INCREASES AIRWAY NARROWING IN ASTHMATICS.

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Introduction: Inhalation increases airway narrowing in normals reaching a plateau at 10 minutes (G. King et al, Am J Resp Crit Care Med 1999). Since the bronchodilator response to DI is impaired in asthmatics, we hypothesised that inhibition of DI would have less of an effect on airway narrowing during methacholine inhalation in asthmatics compared with normals.

Methods: We studied 4 male and 3 female asthmatics (age range 27-53 years) who received 5 x PC15 doses of methacholine given 5 minutes apart and measured FEV1 after each dose. On 4 separate days, they were given 2, 3, 4 or 5 doses in random order, but FEV1 was measured only at baseline and after the last dose. DIs were inhibited between times.

Results: Geometric mean PC15 was 2 μmol. When DIs were allowed, the maximum decrease in FEV1 occurred after 3 doses and was 22 ± 5.7% of baseline. When DIs were inhibited, % decrease in FEV1 was enhanced which became greater as the duration of inhibition of DI increased. The % decrease after the last dose was 32 ± 6.8% when DIs were inhibited compared with 19 ± 2.5% when DIs were allowed.

Conclusion: Inhibition of DI during methacholine inhalation in asthmatics increases airway narrowing by a similar degree in asthmatics and normals.

Support: Astra/MRC/PMAC Canada Fellowship.

Key words: Asthma, Airway smooth muscle, Deep inspiration

BRONCHODILATATION AFTER DI IS REDUCED IN ASTHMatics COMPARED WITH NORMALS ONLY AFTER GREATER DEGREES OF AIRWAY NARROWING.

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INTRODUCTION: It has been suggested that bronchodilatation after deep inspiration (DI) is reduced in asthmatics. The relationship between the magnitude of narrowing and amount of reversal has not been determined. We hypothesised that in normals, DI induced bronchodilatation is greater as narrowing increases whereas in asthmatics, the bronchodilatation falls to increase with greater narrowing.

METHODS: 16 normals and 16 asthmatics (airway hyperresponsiveness and wheeze) inhaled doubling doses of methacholine up to a maximum dose of 8 μmol. The difference between flow at 40% VC on complete (V40c) and partial (V40p) expressed as the % baseline V40p (V40DI) was measured, as was the decrease in V40p as percent baseline (ΔV40p). The relationships between V40DI and ΔV40p were examined using a mixed effects linear regression model.

RESULTS: The mean ±SEM % decrease in ΔV40p was 49 ± 4% in normals and 70 ± 3% in asthmatics (p<0.01) and for FEV1 it was 8 ± 1% and 21 ± 2% respectively (p<0.01). The linear regression slopes of V40DI vs ΔV40p were 0.55 (p<0.01) in normals and 0.06 (p>0.05) in asthmatics.

CONCLUSIONS: The reversal of bronchodilatation due to DI increases to match increasing airway narrowing in normals but does not similarly increase in asthmatics. This difference could be due to mechanical differences of the airway walls or functional differences in airway smooth muscle.

Support: Institute of Respiratory Medicine and NH&MRC Australia.

Key words: Asthma, Airway smooth muscle, Deep inspiration

EXPRESSION OF MATRIX METALLOPROTEINASES-2 AND -9 IN SERUM AND BRONCHOALVEOLAR LAVAGE FLUID OF ASTHMATIC PATIENTS.

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INTRODUCTION: Asthma is characterised by thickening of the basement membrane and altered mechanical properties of the airway. This may be caused by enhanced proliferation of bronchial smooth muscle cells and an accumulation of extracellular matrix (ECM). Matrix metalloproteinases (MMP) with gelatinolytic activity are key regulators of local remodelling of ECM and have been suggested to be involved in the pathogenesis of asthma. We investigated the expression pattern of MMP-2 and MMP-9 in the serum of healthy controls and in serum and bronchoalveolar lavage fluid obtained from asthmatic patients.

RESULTS: Based on enzymatic activity by gelatine zymography, the inactive pro-precursor of MMP-2 was highly expressed in asthmatic serum samples, while it could not be detected in controls. Similar, high amounts of active MMP-2 were present in asthmatic serum samples, while only a low expression of active MMP-2 was observed in controls. The MMP-9 pro-precursor was more often expressed in sera obtained from asthma patients, while only few controls expressed low amounts of the MMP-9 pro-precursor. Active MMP-9 was not detectable in any serum sample. Interestingly, the active forms of both MMP were highly expressed in bronchoalveolar fluid samples of asthmatics.

CONCLUSION: We observed a distinct expression of MMP-2 and MMP-9 in the serum and BAL of asthmatic patients. It is yet unclear whether the enhanced expression of these MMP contributes to disease progression or if it represents a remodelling process of the lung to reconstitute the structure of its ECM.

Support: Fairfax Family Foundation Grant.

Key words: Asthma, Airway mechanics, Matrix metalloproteinases

DEEP INSPIRATION (DI) PRECEDING HISTAMINE INHALATION PROTECTS AGAINST AIRWAY NARROWING BY REDUCING BASELINE AIRWAY SMOOTH MUSCLE TONE.

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INTRODUCTION: DI that precedes methacholine inhalation by 6 mins or less reduces airway narrowing. We hypothesized that the DI prior to histamine inhalation protects against airway narrowing by reducing baseline airway smooth muscle tone.

METHODS: Four normal subjects inhaled histamine in a dose estimated to decrease the FEV1 by 15%, under 4 different conditions; with and without DI for 10 mins preceding inhalation either with or without 80 mg ipratropium administered 25 mins before inhalation. FEV1 was measured 5 times after histamine inhalation.

RESULTS: When DI’s were inhibited before histamine inhalation, ΔFEV1 was greater compared to when DI’s were taken (30±3 cf 20±4, p<0.05, ANOVA). Pre-treatment with ipratropium decreased ΔFEV1 when DI’s were inhibited (30±3 cf 12±1, p<0.05) but had no effect on ΔFEV1 when DI’s were not inhibited.

CONCLUSIONS: Pre-treatment with ipratropium abolished the increase in ΔFEV1 caused by inhibition of DI before histamine inhalation. DI may protect against induced airway narrowing by reducing baseline airway smooth muscle tone.

Support: Institute of Respiratory Medicine and Astra/MRC/PMAC Canada Fellowship.

Key words: Asthma, Airway smooth muscle, Deep inspiration
EFFECT OF A LONG-ACTING \( \beta_2 \) AGONIST OVER 3 MONTHS ON AIRWAY WALL VASCULAR REMODELLING IN ASTHMA.

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There are little data regarding the potential effects of anti-asthma treatment on indices of airway remodelling such as airway vascularity in asthma patients. Methods: We studied 45 symptomatic asthmatic subjects who were receiving treatment with low dose inhaled corticosteroids and 28 non-asthmatic normal subjects as a control population. Subjects underwent bronchoscopy with airway biopsy and asthmatic subjects were then randomised to receive supplementary inhaled salmeterol 50µg bd, fluticasone propionate 100µg bd or placebo for 3 months. Biopsy of the airway was then repeated. The biopsies were analysed for vascular structures in the sub-epithelial lamina propria. Results: Sufficient biopsy material was available for analysis of vascularity in 34 of the asthmatic and 25 of the normal subjects. We confirmed that asthmatic airways had a significant increase in the number of vessels/mm² of lamina propria compared to normal airways (524±137 vessels/mm², n=34 vs 425±130 vessels/mm², n=25; p=0.004). As previously described decrease in vascular area with low dose ICS at baseline was evident (Ondra et al. Thorax 1999; 54: 286-290). There was a decrease in the density of vessels of lamina propria after supplementary treatment only in the salmeterol group compared to baseline (before, 535±153 vessels/mm² vs after, 400±142 vessels/mm²; n=12; p=0.04). There was no significant change in the fluticasone (n=11) or placebo (n=11) treatment groups.

Discussion: No treatments were associated with adverse affects on parameters of airway vascularity. The demonstrated fall in vessel number following salmeterol treatment may suggest an advantageous effect of long acting \( \beta_2 \) agonists on this manifestation of airway remodelling over the 3-month time scale of this study. This effect seems to be complementary to the action of ICS on airway vascularity.

Supported by: Glaxo-Wellcome, Australia. Key words: Asthma, airway remodelling, vascularity, treatment.

PLASMA PHOSPHOLIPASE A\(_2\) (PLA\(_2\)) ACTIVITY IN STABLE ASTHMATICS AND CONTROL SUBJECTS

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PLA\(_2\) represents a large group of enzymes that share as a common characteristic the capacity to hydrolyse fatty acids from the sn-2 position of glycerophospholipids. Hydrolysis of phospholipids by PLA\(_2\) provides the precursors for eicosanoid synthesis that is important in lung inflammation and asthma. We have determined secreted PLA\(_2\) activity levels in plasma of a cohort of 64 stable asthmatics (43 mild and 21 severe) as well as in 23 control subjects. Correlation between plasma PLA\(_2\) activity values and gender, age, atopy, % of predicted FEV\(_1\) and vitamin C levels were analysed. Variables were compared by either unpaired, two-tailed t-test or by linear regression analysis. PLA\(_2\) levels were significantly higher in males compared to females (p=0.0297). Levels of PLA\(_2\) negatively correlated with plasma vitamin C concentrations (r=-0.0330). Furthermore, negative correlation with vitamin C levels and asthma status was also significant (p=0.0066). Positive correlation between %FEV\(_1\) and PLA\(_2\) was observed in control and mild asthmatics (r=0.0420 and 0.0388 respectively) but no such correlation was observed in severe asthmatics (p=0.257). In male subjects PLA\(_2\) levels correlated significantly with age (r=0.0423) and atopic status (r=0.0481) while in females no significant correlation among these parameters was observed. Preliminary results of this study suggest that effects of dietary anti-oxidants and plasma PLA\(_2\) on lung inflammatory processes might be gender-dependent. Further studies are needed to characterize the relationship between vitamin C and PLA\(_2\) levels as well as the effect of gender on these measurements.

Supported by Asthma Foundation of Western Australia. Key words: PLA\(_2\), Asthma, vitamin C, gender. Nominations for awards: Nil

GLYCOLMETHYLACRYLATE EMBEDDING OF TISSUE CAN BE USED FOR MEASURING COLLAGEN III AND IV WITHOUT SIGNIFICANT LOSS OF ANTIGENICITY.

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Ten Hacken et al. (Mod Pathol 1997;10:1043-1046) suggested that antigenicity levels for cell markers decreased alarmingly over time in bronchial biopsy specimens that were embedded in glycolmethylacrylate (GMA), which has taken on 'gold standard' status in recent years. This raised the question of whether the same would occur when looking at indices of airway wall remodelling such as collagen III (scarring) and collagen IV (vasculature) staining. This prospective study was undertaken to see what changes occurred to levels of these collagens over time, as a prelude to a long term study of airway remodelling in asthma. Nasal polyps were collected from 8 patients and embedded in GMA after appropriate processing. Sections were stained for collagen III and IV (after etching in acetone for 15 minutes and then digesting in 0.001% trypsin to improve staining) and then scored using computerised image analysis where collagen IV yielded a score of vessel number expressed per mm of basement membrane and collagen III was expressed as percentage positive area. Survey sections were measured to 100 µm below the basement membrane. Scoring, staining and scoring were carried out at baseline (base, 1 day post polypectomy) and subsequently at 1 month (TP1), 2 months (TP2) and 3 months (TP3) after embedding. Mean SD are presented:

| Vessel no | Base | TP1 | TP2 | TP3 |
|----------|------|-----|-----|-----|
| Col IV    | 19.0±8.4 | 19.1±6.3 | 24.9±13.2 | 19.4±7.1 |
| Col III   | 0.8±0.05 | 0.5±0.3  | 0.5±0.3  | 0.7±0.2  |

CONCLUSION: Our results indicate that embedding in GMA does not appear to cause a systematic loss of antigenicity over time for collagen III and collagen IV. Key words: Glycolmethylacrylate, Nasal Polyp, Collagen III, Collagen IV, Supported by Glaxo Wellcome Australia.

PROLIFERATION CAPACITY OF BRONCHIAL SMOOTH MUSCLE CELLS IS ENHANCED IN ASTHMATICS

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Histopathological features of airways in patients with asthma include airway inflammation and bronchial smooth muscle cell (BSMC) hyperplasia. It is not yet clear if this is due to increased cell proliferation or delayed cell apoptosis. Establishment of primary human cell lines from the lung provides a unique basis to study pathogenetic mechanisms of lung diseases on a cellular level. To our knowledge no data are published on primary bronchial smooth muscle cells cultured from asthmatics. To investigate cell proliferation, BSMC from three patients with asthma were cultured and compared with BSMCs from non-asthmatic non-sensitised controls. Cells were grown under sterile conditions in RPMI supplemented with 10% fetal calf serum (FCS), 8 mM L-glutamine and antibiotics. Cells were seeded onto 24 well plates (1x10^4 cells/cm²) and grown until reaching a logarithmic growth phase. Cell cultures were kept in FCS free medium for 48 hours. Following serum deprivation cells were restimulated with 10% human serum (obtained from atopic patients with asthma or non-sensitised healthy controls). Cell counts were performed daily for the following 4 days. In addition, proliferation was assessed by [3H]-thymidine incorporation. Asthmatic cells grew more rapidly compared with controls. Cell growth increased by a mean of 87.3% if sensitised serum was used compared with an increase of a mean of 48.6% under non-sensitised conditions. Asthmatic cell lines exhibited a greater increase in cell proliferation under sensitised conditions compared with control cells.

Summary: In this study we found evidence that bronchial smooth muscle cells of patients with asthma grow faster compared with controls. This effect was more apparent if cells were grown under sensitised conditions. Increased cell proliferation might contribute to airway thickening and altered contractility, which is observed in asthma.
EXACERBATIONS OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA): A STUDY OF LABORATORY MARKERS

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Introduction: A reliable disease marker for acute exacerbations (AE) of ABPA is not available. Currently the diagnosis is made clinically based on symptoms, radiology, total IgE and eosinophil counts. IL-5 plays an important role in eosinophil accumulation in the airways of patients with ABPA.

Methods: We developed an assay to measure the isoforms of IL-5 R RNA in peripheral blood leukocytes. Patients were followed prospectively for 6 months. AE were diagnosed clinically and were managed by the treating physician. We serially measured total eosinophil count, total IgE, Aspergillus specific IgE and eosinophil cationic protein (ECP) RNA for the isoforms of the IL-5 R RNA measured in peripheral blood using RT-PCR with real-time PCR technology (Taqman).

Results: 9 AE were observed in 15 patients. All AE were treated with prednisolone. There was a significant correlation between eosinophil counts and disease activity (P<0.01). An increase in ECP with exacerbations was also observed, but was not significant (P=0.09). IgE was a poor marker of disease activity. While, as a group, there was no significant change in mean M/S eosinophil ratios with AE, in one patient the ratio varied inversely with eosinophil count.

Conclusion: Eosinophil counts, but not total IgE, were a reliable marker for AE in ABPA. We intend to carry out further studies on M/S eosinophil in a larger group, including the effects of corticosteroids on this ratio.

Key words: Allergic bronchopulmonary aspergillosis, Total IgE, interleukin-5.

THE EFFECTS OF SALIVARY CONTAMINATION ON SPUTUM CELL COUNTS: ESTABLISHING QUALITY CRITERIA

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Salivary contamination confounds the accurate interpretation of induced sputum cell counts in asthma. The acceptable levels of contamination and its effect on measurements are not well established. The aim of this study was to examine the effects of salivary contamination on cell counts and to establish quality markers that could be used to determine the adequacy of sputum samples. Healthy adults (n=6) provided samples of blood and saliva. Granulocytes were isolated using percoll gradient centrifugation and ammonium chloride lysis of red cells. Aliquots of saliva were added to the granulocyte suspension in the following concentrations (v%): 0%, 10%, 30%, 50%, 70%, 80% and 100%. A total cell count and viability were performed on the saliva-granulocyte suspension with cytospin slides prepared for differential cell counts and supernatant assayed for ECP. Saliva contained between 25 and 128 x 10^6/mL cells per mL, of which 25-44% were viable. The cellular differential of saliva contained 85 to 86% squamous cells, with the remainder being neutrophils. No eosinophils or lymphocytes were seen in saliva samples. The concentration of ECP in saliva ranged from 5 to 62ng/mL. The addition of increasing volumes of saliva to the granulocyte suspension had no significant effect on total and differential counts up to 50v%.

Granulocyte contamination at 70v% was associated with a squamous cell count of >50%. There was significantly reduced cell viability from 98.9% to 96% (p<0.01), eosinophil percentage from 15% to 7% (p<0.01), lymphocyte percentage from 1% to 0% (p=0.01) and ECP from 214pg/ml to 37pg/ml (p=0.01). There was no significant trend to neutrophils to increase with the addition of saliva (p=0.08). In conclusion, salivary contamination has little effect on the cellular differential until there are >50% squamous cells present. There are significant effects on fluid phase markers at all levels of contamination. We propose quality criteria for sputum samples based on cell viability and <50% squamous cells in order to minimise the confounding effects of salivary contamination. More research is required to control for the effects of salivary contamination on fluid phase markers.

Supported by NHMRC.

EFFECT OF ANAESTHESIA AND SURGERY UPON EXHALED NITRIC OXIDE AND CARBON MONOXIDE.

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Increased exhaled nitric oxide is associated with inflammatory changes in the lung and airway, and likewise elevated exhaled carbon monoxide is also associated with asthmatic inflammation in non-smokers. Volatile anaesthetic agents and intubation are known irritants of the major airways. These agents might therefore be expected to affect the regulation of nitric oxide synthases in the upper airway. We therefore studied subjects who were undergoing abdominal surgery, primarily gynaecological, to assess the changes in exhaled nitric oxide before and after surgery and a general anaesthetic. 36 subjects agreed to participate, 2 had asthma, 11 were current smokers. All had exhaled nitric oxide measured using a gas impermeable bag and a flow restriction to increase oral pressure to approximately 50cm of water, thus avoiding nasal contamination of the sample. Sampling was repeated 24-30 hours later as soon as the subject felt able to provide a specimen.

Results: Mean nitric oxide level before surgery: 15.1 +/- 9.5ppb; post surgery: 15.2 +/- 8.0ppb. Mean exhaled carbon monoxide levels before surgery (excluding smokers): 4.2 +/- 3.7ppm; post surgery: 4.9 +/- 4.1ppm.

None of these changes was significant when log transformed as appropriate and subjected to parametric statistical tests. Conclusion: Modern anaesthetic agents and abdominal surgery do not appear to affect exhaled levels of nitric oxide or carbon monoxide.

Key words: exhaled nitric oxide, exhaled carbon monoxide.

AIRWAY EOSINOPHILIA IS ASSOCIATED WITH WHEEZE BUT IS UNCOMMON IN CHILDREN WITH PERSISTENT COUGH AND FREQUENT CHEST CUMDS

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The role of eosinophilic airway inflammation in the variant asthma syndromes of cough and chest colds is not well defined. We tested the hypothesis that children with persistent cough and chest colds have increased sputum eosinophil, similar to those with wheeze. The parents of 390 primary school children completed a symptoms questionnaire. Children with wheeze (n=25), cough (n=12), recurrent chest colds (n=17) and no symptoms (control, n=24) consented to allergy skin prick tests, spirometry, combined hypertonic saline inhalation challenge with sputum induction, peak expiratory flow (PEF) and symptom diary over a 2 month period. Children with wheeze had significantly reduced PEF (p=0.001) and higher sputum eosinophils when compared to the cough, chest cold and control groups (Medians: 3.1% vs 0.5%, 0%, 0%, p=0.03). The prevalence of eosinophilic bronchitis (sputum eosinophils >2.5%) was 45% in the wheeze group which was significantly higher than the control group (9.35%, p=0.04). Eosinophilic bronchitis was present in two children with cough (17%) and two with chest colds (12%, p=0.05 vs control). In these groups eosinophilic bronchitis was not associated with ARH (p=0.05) but tended to be associated with rhinitis. Children with cough and chest colds reported greater exposure to environmental tobacco smoke. In conclusion, this community-based survey of children with chronic respiratory symptoms has shown that wheeze is a good discriminator for the presence of eosinophilic bronchitis: persistent cough and recurrent chest colds without wheeze should not be considered variants of asthma.

Funding: Asthma NSW, Community Health & Anti-Tuberculosis Assoc, NHMRC and NSW Health.
INCREASED EOSINOPHILIC AIRWAY INFLAMMATION WITH CHLAMYDIA PNEUMONIAE INFECTION IN ASTHMA
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Infection with Chlamydia pneumoniae (CP) is associated with increased asthma severity. The relationship between CP infection and airway inflammation in persistent or prior CP infection is not known. We sought to compare airway inflammation in asthmatics with and without serologic evidence of persistent or prior CP infection. Adults with symptomatic asthma were recruited and evaluated by clinical assessment, spirometry, and airway responsiveness to hyperoxic saline and induced sputum analysis. Serum antibodies (lgG, IgA) to CP were measured by MIF and subjects classified as seronegative (CP-neg; n=37), seropositive to lgG alone (CP-G; n=28), and seropositive to both lgG and lgA (CP-GA; n=53). Subjects had moderate severity asthma with mean FEV1 75% predicted and mean dose of beclomethasone 1300 mcg daily. * p < 0.05
Table 1
|                | CP neg | CP-GA | CP-G |
|----------------|--------|-------|------|
| Sputum eos%    | 4.1    | 2.6   | 6.9* |
| ECP ng/ml      | 1802   | 1718  | 6458*|
| IL-5, pg/ml    | 21     | 11    | 59*  |
| IL-6, pg/ml    | 60     | 94    | 223  |

Sputum neutrophils and total cell counts were similar between the groups (p > 0.05).
In conclusion, asthma with Chlamydia pneumoniae infection and CP seropositivity is characterised by an increase in the severity of IL-5 mediated eosinophil inflammation and eosinophil degranulation. An IgA response in association with IgG seropositivity to CP appears to protect against some of the inflammatory changes in asthma. Persistent CP infection may increase the severity of eosinophilic airway inflammation in asthma. Supported by Hoechst Marion Roussell

CHLAMYDIA PNEUMONIAE AND ACUTE ASTHMA: PREVALENCE AND EFFECT ON AIRWAY INFLAMMATION
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Chlamydia Pneumoniae (CP) causes acute respiratory tract infections and persistence of the agent is seen in chronic severe asthma. Aims: To determine the prevalence of acute or reactivating infection with CP in acute asthma and its influence on airway inflammation. Methods: Adults (n=54) presenting to the emergency room with acute exacerbations of asthma had a clinical assessment, spirometry and sputum induction, acutely and four weeks later. Paired serum samples were taken for Chlamydia pneumoniae (CP) IgG and IgA and tested using ELISA. Results: A total of 31% (n=17) of patients had positive IgA titres (≥1:4) and IgG titres (≥1:2). Conclusion: This work was funded by NH&MRC (Australia)

MODIFICATION OF ALLERGIC INFLAMMATION WITH BACTERIAL LIPOPOLYSACCHARIDE
MK Tulic & PD Sly Clinical Sciences, TVW Telethon Institute for Child Health Research & University of WA Department of Paediatrics, Perth WA 6008 Aims: To determine the influence of infective inflammation on response to allergen we have administered nebulised lipopolysaccharide (LPS a) during the primary sensitisation phase, b) during allergen challenge or c) between the acute and late phase of the allergen response using an in vivo animal model. Methods and Results: During the primary sensitisation of PAG rats to ovalbumin (OA), a single aerosol challenge of LPS (500 ng/ml) given day −1 or up to day 4 after sensitisation, completely abolished allergic sensitisation, resulting in no increase in IgE or response to OA challenge. Presence of LPS (0.5, 5 or 50 ng/ml) with OA in the same nebuliser during allergen challenge resulted in an immediate decrease in lung function (time-to-peak decreased from 10.0±0.9(SEM) to 2.5±0.2 minutes (n=6, P<0.01) but abolished late-phase hyper-responsiveness, cellular influx and vascular leakage (assessed by Evans Blue dye) in a dose-dependent manner (n=6, P<0.01). Exposure of sensitised animals to LPS, 18 hours post allergen challenge also inhibited the late-phase hyper-responsiveness when measured at 24 hours (n=5, P<0.05) but further exacerbated the OA-induced neutrophil influx and Evans Blue leakage (n=5, P<0.01). In the later group of animals, aminoguanidine (NGS-selective: 100mg/kg sc) was effective in reducing the cellular influx and vascular leakage (n=5, P<0.01) whilst L-NAME (NGS-selective: 100mg/kg sc) potentiated the allergen-induced hyper-responsiveness (n=5, P<0.01). Conclusion: These results suggest that the modification of allergic response by LPS is dependent on the dose and timing of exposure. Whilst LPS exposure prior to sensitisation inhibits IgE production and hence the development of allergic inflammation, exposure post allergen challenge further exacerbates OA-induced cellular inflammation in rats. In this model, nitric oxide production by iNOS plays a major role in the migration of inflammatory cells and vascular permeability following allergen challenge while that produced by eNOS limits bronchial hyper-responsiveness. Supported by The Asthma Foundation of WA and NH&MRC Key words: allergic inflammation, bacterial infection, sensitisation, nitric oxide

IL-13 ACTIVATES HUMAN CULTURED AIRWAY SMOOTH MUSCLE THROUGH THE IL-13 Receptor
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Animal models have shown that IL-13, produced by activated CD4+ T H2 cells, plays a key role in the pathophysiological features of allergic asthma. The function of IL-13 in human cultured airway smooth muscle cells (HASM) has been elucidated by investigating the presence of the receptor for IL-13 (IL-13Ralpha1), its regulation at a transcriptional level and the effect of IL-13 on cell proliferation. HASM were grown to confluence in standard culture flasks and 8 chamber slides, and then serum-deprived for 24hr before a 30 minute pretreatment with either fluticasone propionate (FP) 1nM or 2-methoxyestrenol (2-Meo 10gM) prior to incubation in cytokine mix (TNFa 0.03nM + IL-1a 0.1ng/ml) or medium alone. Immunoperoxidase staining was used to determine the presence and location of the IL-13 Re1 (n=3). The expression levels of 2 mRNA transcripts for the IL-13 Re1 (4.2kb and 2kb) were assessed by northern blotting (n=6). DNA synthesis was assessed by incorporation of 3H-thymidine to determine the proliferative potential of IL-13 in the presence of the cytokine mix and IL-13 in the absence of the cytokine mix. DNA synthesis was assessed by incorporation of 3H-thymidine to determine growth potential of L-13 in the presence and absence of 5% FCS (n=6). IL-13Ralpha1 was detected in cultured HASM by immunohistochemistry. The increased staining intensity for IL-13Ralpha1 following addition of the cytokine mix was accompanied by redistribution of immunoreactive IL-13Ralpha1 from cytoplasm to a distinctly perinuclear location. The intensity and redistribution of IL-13Ralpha1 were reduced by pretreatment with either FP or 2-Meo. The level of the 2kb mRNA transcript was increased by the cytokine mix and decreased upon the addition of either FP or 2-Meo (89±5.0 % and 60±12% of the cytokine level, respectively). The 2-Meo of HASM was compatible with a functional influence of IL-13 on HASM.

This work was funded by NH&MRC (Australia)
LYMPHOID AGGREGATES AND HLA-DR EXPRESSION WITHIN THE AIRWAYS IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Asthma and COPD are characterised by persistent airway inflammation. We hypothesised that this results from persistent immune stimulation by activated cells in situ in smokers who develop COPD and in asthmatics. Lymphoid aggregates (LA) have been described in asthma and COPD. We hypothesised that these structures, if present, may represent a local site within the airway for antigen presentation and T-cell stimulation to occur. We counted the number of cases of COPD and asthma of varying severity with defined lymphoid aggregates and whether they expressed HLA-DR or not. Transverse sections of 3 or 4 large airways from controls (CO), smokers with normal lung function (SC), mild (FEV1<80%) and severe (FEV1<60%) COPD and mild (nonf - NFA) and severe (fatal - FA) asthma; n=8 in each group, were stained with HAM56 (macrophages) and anti-HLA-DR monoclonal antibodies. HAM56 was used to determine if HLA-DR+ cells within lymphoid aggregates were macrophages or not.

Figure 1

Compared with controls, the % of cases with defined LA’s was increased (p<0.05) in cases of FA, nCOPD and eCOPD. The percentage of LA’s staining for HLA-DR was increased (p<0.05) only in cases of fatal asthma. There was little HAM56+ staining in LA’s. The high percentage of cases with LA’s in FA, nCOPD and sCOPD suggests that they may play a role in the development of airflow obstruction. HLA-DR expression was increased only in FA, possibly due to an acute inflammatory stimulus. The findings suggest that lymphoid aggregates are related to severity of airflow obstruction and may provide a local site within the airway wall where antigen presentation can occur.

Support: NHMRC Australia.

Key words: Asthma, COPD, Inflammation, HLA-DR

Awards: Nil

PREVALENCE OF ATOPY IN PATIENTS WITH SARCOIDOSIS.

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Hypothesis: The prevalence of atopy is low in patients with sarcoidosis because their immune systems are skewed towards generating a TH1 type response.

Aim: To determine the prevalence of atopy in patients with sarcoidosis compared with normal controls.

Methods: Patients with a diagnosis of sarcoidosis not currently on treatment (n=98, 83F, age range 24-75) were prospectively recruited and data compared with historical controls from the European Community Health Survey (ECHS) (n=1257, 663F, age range 20-44). A history of asthma or allergy was determined by questionnaire derived form the ECHS. Atopy was defined as a serum specific IgE >35kU/L, to one or more of four common allergens.

Results: Patients reported a higher prevalence of asthma ever 21.4% vs 15.9% (p<0.05) but lower prevalence of nasal allergy 28% vs 38% (p=0.06). The prevalence of atopy was similar for both patients and controls 31.6% vs 34.8% as was the percentage of patients with a total IgE >100kU/L, 27.6% vs 30.5%.

Conclusions: Patients with sarcoidosis report similar prevalences of asthma and allergic symptoms and have similar prevalence of atopy. Further study of a subset of patients with acute or active sarcoidosis may be necessary to test the hypothesis.

Supported by the Health Research Council of New Zealand
REGULATION BY FORMOTEROL AND Budesonide of IL-8 and STEM CELL FACTOR (SCF) LEVELS IN HUMAN CULTURED AIRWAY SMOOTH MUSCLE (ASM)

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The combination of a long acting β2-agonist with inhaled steroid appears to be more effective in treatment of asthma than increasing the dose of steroid. It is possible that, inter alia, long acting β2-agonists have moderate anti-inflammatory effects in airway diseases that are complementary to or synergise with those of anti-asthma steroids. Aim: We tested the hypothesis that cytokine (IL-8 and SCF) levels in media of cultured ASM cells would be more sensitive to inhibition by the combination of β2-agonist and steroid than either agent alone. Methods: ASM cells were grown to confluence, then serum-deprived for 24h before treatment. Cytokine analysis of 48h incubation with 48/80, IL-1α and compound A23187 and compound 25M 2-SO4+1µM pyrithione resulted in suppression of NF-KB. Zn was detected by immunofluorescent visualisation of Zn5+37%). Neither budesonide (100 nM) nor formoterol (10 nM) affected basal IL-8 levels. Budesonide (1-100 nM) concentration-dependently reduced IL-1α-stimulated IL-8 release (IL-1α 100%; IL-1α+A23187 85%). Budesonide further reduced SCF release (56±5% control), while formoterol produced no further inhibitory effect, either alone or in combination with budesonide. Conclusions: These results suggest that ASM levels of IL-8 and SCF were reduced by budesonide alone and this action was not influenced by the long-acting β2-agonist formoterol.

Supported by Astra (Sweden)

Key words: Airway smooth muscle, formoterol, budesonide, IL-8, stem cell factor

Nomination for awards: Nil

AN INVESTIGATION OF HOUSEKEEPING GENE UTILITY FOR NORMALIZATION OF GENE EXPRESSION IN HUMAN CULTURED AIRWAY SMOOTH MUSCLE

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Interest is growing in the regulation of gene expression in human cultured airway smooth muscle (HASM) in relation to cell cycle, phenotype and cytokine production. The normalisation of gene expression by housekeeping genes uses the assumption that these housekeeping genes, such as tubulin or 23 kD Highly Basic Protein (23 kD HBP), or more commonly β-actin or glyceraldehyde-3-phosphate dehydrogenase (GAPDH), are expressed at constant levels. Aim: Our aim was to identify the gene which best meets the criteria for housekeeping: namely, that its level of expression be unaffected by different treatment regimens and that the variance of both its absolute levels and the variance of the normalised product of interest are minimised. Methods: We have used cDNA arrays (Atlas™ array) and northern analysis to pattern gene expression in mitogen-stimulated HASM in the presence and absence of anti-asthma agents. Results: The presence of multiple housekeeping genes in the array revealed that different mitogenic and drug treatments altered expression of certain housekeeping genes. These observations were confirmed by northern Analysis, a more quantitative reliable method than the array methodology. β-Actin was up regulated by thrombin (150% compared to control), conversely tubulin was down regulated by 2-methoxyestradiol (50% compared to control). Given that there was a significant difference in variance of the absolute levels of these two housekeeping genes across the different treatment regimens, these genes were not further evaluated. Although there was no significant difference in the variance of the absolute levels of either GAPDH or 23 kD HBP, the 23 kD HBP housekeeping gene had a significantly higher coefficient of variation (paired t-test, p < 0.0001) when used to normalized either cyclin D1 or p21CIP1 genes. Conclusion: The present study has shown that, in HASM, of the four housekeeping genes examined, GAPDH is the most reliable housekeeping gene when normalizing gene expression levels.

Supported by Glaxo Wellcome (UK), Amrad Operations Pty Ltd, NHMRC (Australia)

Key words: Housekeeping gene, human airway smooth muscle

Nominations for Awards: Nil

FLOW CYTOMETRIC ANALYSIS OF BRONCHIAL LAVAGE

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The characterisation of cellular infiltrates in bronchial lavage (BAL) is important in the diagnosis of a variety of lung disorders (Jeffery, 1998). In chronic bronchitis, the predominant cell infiltrate in BAL is macrophages and T cells. In chronic obstructive pulmonary disease (COPD), macrophages, neutrophils and CD8 positive T cells are present. Asthma is characterised by a marked eosinophil infiltrate and CD4 positive T cells. We describe a rapid multiparameter flow cytometric assay using fluorescently conjugated monoclonal antibodies to characterise cellular subtypes in BAL.

The use of standard control beads allows simultaneous analysis of absolute numbers of cells using a single platform assay, without the need for manual cell counts. There was good agreement between this automated counting method (counting 100,000 cells) and standard manual counting methods (counting 200 cells) to quantify absolute cell numbers. We conclude that the speed and accuracy of defining cell populations in BAL using flow cytometric techniques may aid in the differential diagnosis of lung disease. This technique would also be amenable to analysis of cell types in samples of sputum and bronchial brushing.

Reference:

Jeffery, P. (1998) Structural and inflammatory changes in COPD: a comparison with asthma. Thorax; 53: 129-136.
IL-4 AND TNF-α INHIBIT TGF-β PRODUCTION BY HUMAN LUNG EPITHELIAL CELL LINES: RELEVANCE TO COPD

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Human bronchial epithelial cells are known to secrete an array of inflammatory cytokines which play a role in immune responses in COPD. However, the regulatory mechanisms governing cytokine production in bronchial epithelia are largely unknown. TNF-α is a pro-inflammatory cytokine, known to be upregulated in COPD. IL-4 has been reported to induce IL-8 release by bronchial epithelial cells and to inhibit fibronectin release by these cells. TGF-β is an immunosuppressive cytokine, produced by many cells including airway epithelial cells and is involved in airway repair and fibronectin synthesis. We studied the cytokine interactions that might regulate TGF-β production using two epithelial cell lines (A549 and 16HBE). Cells were stimulated with various combinations of TNF-α and IL-4 (20ng/ml) for 24h. TGF-β and IL-4 production was measured by flow cytometry and immunohistochemical techniques. TNF-α significantly upregulated production of IL-4 from cultured epithelial cells. Unstimulated cells spontaneously released TGF-β. The production of TGF-β was significantly increased by PMA. TNF-α and IL-4 inhibited production of TGF-β by both epithelial cell lines. The inhibitory effect of TNF-α and IL-4 on TGF-β synthesis was additive. We conclude from our study that TNF-α induces IL-4 release from human epithelial cells and the inhibitory effect of IL-4 and TNF-α on the regulatory cytokine TGF-β in the bronchial mucosa, may contribute to the progression of the inflammatory response and decrease in repair processes in COPD.

IDENTIFICATION OF TH1 RESPONSE TO NON-TYPEABLE HAEMOPHILUS INFLUENZA BY FLOW CYTOMETRY

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Most adults are colonised with Haemophilus influenza, which is one of the major causes of respiratory infection. The role of the Th1 lymphocyte and in particular the Th1 helper (Th1 or CD4) cell, in the immune response to haemophilus infection has not been established. Th cell function can be assessed by the measurement of Th1 (IFN-γ) or Th2 (IL-4, IL-5) cytokines that are produced following antigen exposure. Aims: To measure whether healthy adults produce a Th1 or Th2 response when exposed to non-typeable haemophilus influenza (NTHi) in vitro, using flow cytometry to measure intracellular cytokine production. Methods: Flow cytometry has been described to measure intracellular cytokine production to cytomegalovirus (CMV) infection. This technique is performed by adding antigen and co-stimulatory antibody (CD28 and CD49) to whole blood, which is incubated for 6 hours. Red blood cells were lysed and leukocytes fixed, permeabilised and stained with immunofluorescent antibodies for CD4, CD69, IFN-γ, IL-2, IL-4, and IL-5. Binding of the antibodies to the cytokines is then measured using the flow cytometer. We validated this technique by screening 10 subject’s response to CMV antigen; 5 were responders with 0.83±0.28 of Th1 cells producing IFN-γ, consistent with a Th1 response. NTBI obtained from a child with conjunctivitis, was cultured on agar plates, washed and suspended at a concentration of 2.0 McFarlane units, heat inactivated and then disrupted by ultrasound sonication. 2 ml of blood was taken from 4 healthy male subjects. 1 ml of blood from each subject was exposed to 50µl of NTHi and the other ml served as a control. The response to NTBI compared with control was measured using flow cytometry. Results: Three of the six subjects produced a distinct Th1 response with 0.17% of Th cells producing IFN-γ, compared with control of 0.00%, with undetectable levels of IL-4 and IL-5. This result was comparable to that produced from the CMV group. This response was prevented by the addition of MHC-2 blocking antibody confirming the role of the Th cell. Conclusion: The results show that a Th1 response to NTHi can be measured by flow cytometry.

Key words: Haemophilus, Th1/Th2 cytokine response, flow cytometer

ANTI JO 1 ANTIBODY AND LUNG DISEASE

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Introduction: The anti Jo 1 antibody is known to be associated with adult dermatomyositis and polymyositis. A much smaller group of these patients present with lung disease. We reviewed this group of patients at our hospital.

Methods: A retrospective case review of patients with documented anti Jo1 antibody and lung disease. Demographic information, age at presentation, diagnostic investigations, treatment and progress were documented.

Results: 4 female patients aged 40-47 presented with respiratory symptoms. Three required open lung biopsies for diagnosis; two had organizing pneumonitis and one follicular bronchiolitis. One patient has an accepted high resolution CT diagnosis of organizing pneumonia. Three of the patients developed connective tissue diseases after the onset of respiratory disease (dermatomyositis (1), polymyositis (1) and one rheumatoid disease and one has no clinical manifestation of a connective tissue disease. Two patients developed respiratory disease before becoming positive for anti Jo 1 antibodies. All patients required treatment with corticosteroids and three were also treated with steroid sparing agents. Response was poor in all.

Conclusion: This review highlights this small but important group of patients with anti Jo 1 antibody and lung disease. In this group symptoms of connective tissue disorders may develop after the onset of respiratory disease. These patients often respond poorly to treatment.

DEVELOPMENT OF A NEW ASSAY FOR MEASUREMENT OF INFLAMMATION-RELATED PHOSPHOLIPASE A2 ACTIVITY IN HUMAN PLASMA

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Phospholipases A2 (PLA2) play crucial roles in diverse cellular responses, including phospholipid digestion and metabolism, host defense and signal transduction and providing precursors for eicosanoid generation. Mammalian tissues and cells generally contain more than one PLA2 enzyme, each of which is regulated independently and has distinct functions. Secreted PLA2 (sPLA2) found in plasma has been linked with inflammatory processes. One of the reported characteristics of the sPLA2 is its ability to bind to heparin. Using specifically designed affinity chromatography, sPLA2 was partially purified from human plasma samples. The resulting enzyme preparation was assayed with a newly developed activity assay using a chromogenic lipid substrate 4-nitro-3-(octanoyloxy)-benzoic acid. The products of the sPLA2 reaction were detected spectrophotometrically in a microplate assay. In optimized conditions the plasma sPLA2 reaction followed Michaelis-Menten kinetics. Mean of sPLA2 activities measured in plasma of 23 control subjects was 421.4±29.4 units [nmol of product formed in 1h per milligram of protein bound to the heparin column]. The amount of plasma needed for sPLA2 activity assay is relatively small (0.5ml) and the assay is rapid, simple and very reproducible (mean of standard deviation observed in measurements was 4.95%). The assay was successfully used to analyse sPLA2 activity in plasma from a cohort of 64 stable asthmatics (43 mild and 21 severe) and revealed a mean activity of 420.4±18.4 and 449.0±29.2 units respectively.

Supported by Asthma Foundation of Western Australia

Key words: PLA2, Asthma, plasma, assay.

Nominations for awards: Nil
IMPORTANCE OF GROWTH AND STRESS-RELATED SIGNALLING PATHWAYS IN HUMAN AIRWAY SMOOTH MUSCLE CELL PROLIFERATION

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Hyperplasia and hypertrophy of airway smooth muscle contribute to airway wall thickening and hyperresponsiveness in asthma. Understanding the intracellular signalling of airway smooth muscle proliferation may provide new anti-asthma drug targets. Aim: In this study, the relative importance of the activity of the two distinct families of MAPKs (extracellular signal-regulated kinase (ERK) and p38HOG) for the regulation of cyclin D1 levels and DNA synthesis was investigated using the inhibitors PD98059 (ERK) and SB203580 (p38HOG).

Methods: Cyclin D1 protein and mRNA levels were examined by western blotting, and by real-time PCR respectively. DNA synthesis was measured via BrdU incorporation into DNA.

Results: Both thymobin (0.3 and 3 U/ml) and bFGF (0.3 and 3 nM) increased ERK phosphorylation and activity levels, cyclin D1 at 20 h and DNA synthesis between 24 and 28 h after mitogen addition. Although PD 98059 (30 µM) reduced activity to baseline levels, it had no effect on cyclin D1 mRNA levels and reduced the increase in cyclin D1 protein levels in response to only the lower mitogen concentrations. PD 98059 completely prevented thymobin-stimulated DNA synthesis, whereas DNA synthesis in response to 100 nM bFGF was only partially inhibited (0.3 nM: 81 ± 11%; 3 nM: 57% ± 10% inhibition). Conversely, SB 203580 (10 µM) inhibited bFGF-stimulated DNA synthesis (0.3 nM: 56 ± 3.2; 3 nM: 52 ± 4.7% inhibition), but had no significant effect on thymobin-stimulated DNA synthesis. SB 203580 did not reduce mitogen-stimulated cyclin D1 mRNA or protein levels.

Conclusions: p38HOG contributes to the signalling of bFGF, but not thymobin-stimulated DNA synthesis through activity unrelated to the regulation of cyclin D1 levels.

Supported by GlaxoWellcome (UK) & NHMRC (Australia).

Key words: airway smooth muscle, signal transduction, extracellular signal-regulated protein kinase, p38HOG.

IRON OVERLOAD AND NO-DERIVED OXIDATIVE STRESS FOLLOWING LUNG TRANSPLANTATION.

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Background: The local generation of harmful reactive oxygen species (ROS) may contribute to the development of chronic rejection and irreversible airflow limitation (bronchiolitis obliterans syndrome - BOS) following lung transplantation (LT). Hypothesis:Chemically active iron and nitric oxide (NO)-derived radicals within the allograft may add to the oxidative burden. Methods: As a marker of potential iron load we determined the concentration of ferritin in bronchoalveolar lavage fluid (BALF) and assessed the relationship to haemosiderin-laden macrophages (HLM) in 14 stable LT recipients (sLTR) and 7 subjects with BOS. HLM were quantified using a haemosiderin-score (Hs). BALF nitrate and albumin concentrations were also determined as markers of nitric oxide-derived oxidative stress and microvascular leakage. Results: BALF ferritin levels and HS were significantly higher in sLTR than controls (p<0.01), but there was no difference between LT groups. There was a significant relationship between ferritin concentration and HS in LTR (r=0.7, p<0.01). There was a significant relationship between BALF nitrite and neutrophil (r=0.3, p<0.001), particularly in BOS (r=0.9, p<0.01) but only a weak relationship to BALF ferritin (r=0.3, p=0.02) and no relationship to BOS albumin. In BOS patients there was a trend towards higher BALF albumin levels compared with controls (p=0.07) and a significant relationship to BALF ferritin (r=0.8, p=0.05) but no such relationship in sLTR. Conclusions: Our findings suggest the lung allograft could be subject to significant iron-generated oxidative stress over time which may be exacerbated by NO and neutrophil-derived ROS. Microvascular leakage and plasma exudation may be an independent feature of established chronic rejection which potentiates the iron overload and contributes to further airway damage and remodelling.

ONCONSTATIN M (OSM) AND LEUKEMIA INHIBITORY FACTOR (LIF) INDUCE FIBROBLAST PROLIFERATION: MODULATION BY THE CYCLOOXYGENASE PATHWAY.

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Introduction: OSM and LIF are members of the IL-6 family of cytokines and influence the behaviour of a variety of cell types. OSM has been shown to upregulate the production of epithelial anti-protases and fibroblast-derived tissue inhibitor of metalloproteinase and also induces the release of collagen from fibroblasts. We have recently demonstrated the widespread distribution of LIF mRNA within the lung and its release from human lung fibroblast cultures (HFL-1).

Hypothesis: We hypothesised that OSM and LIF may play a role in airway remodelling by regulating fibroblast proliferation.

Methods: We examined the proliferative effects of stimulating HFL-1 cultures with OSM (0.2, 2 and 20 ng/ml) or LIF (0.5 and 50 ng/ml). Proliferation was assessed via an MTS assay and direct cell counts at 24, 48 and 72 hr.

Results: Both OSM and LIF enhanced the mitotic activity of HFL-1 in a time and dose dependent manner. Maximal proliferation in response to OSM was 42% above control and observed after 72 hrs, at a concentration of 2 ng/ml. Incubation with the cyclooxygenase 2 (COX-2) inhibitor nimueiseide (2 µM) or the MAPK inhibitor PD98059 (10 µM) enhanced the mitogenic effect of OSM above control by 33% and 71% respectively. In comparison, LIF exerted its maximal effect at 48 hr at a concentration of 50 ng/ml, reaching an 80% increase in proliferation above control, which declined to 25% by 72 hr.

Conclusion: These results demonstrate that OSM and LIF induce fibroblast proliferation and that for OSM at least, COX-2 release as well as signalling via the MAPK pathway may act to modify this mitogenic effect. These data support the hypothesis that OSM and LIF contribute to airway remodelling and fibrosis.

Supported by the NHMRC and the Raine Medical Foundation.

Key words: OSM, LIF, COX-2, fibroblasts, proliferation, asthama.

IDENTIFICATION OF THE BRAINSTEM REGIONS INVOLVED WITH COUGHING: A STUDY USING c-Fos IMMUNOHISTOCHEMISTRY.

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The central control of cough is thought to arise from an ill defined region within the brainstem. The aim of this study was to identify, using c-fos immunohistochemistry, affrent pathways which are activated by mechanical stimulation of the larynx and trachea. Methods: In pentobarbitial anaesthetised Wistar rats (n=7), the trachea was exposed and a small incision was made to insert a fine plastic tube to mechanically stimulate the larynx and trachea for 30 minutes. Rats who were similarly anaesthetised and whose trachea was cut but no tube inserted, acted as a control group (n=4). Rats remained anaesthetised for a further one hour before they were perfused and their brains processed for c-fos immunohistochemistry.

Results: c-Fos immunoreactivity was increased in a number of brain regions in the rats receiving mechanical stimulation (p<0.05, one-way ANOVA). These areas included the Koller-Fuse nucleus, the medial parabrachial nucleus (external part) and the nucleus of the solitary tract (nTS) (medial and lateral parts) which are involved with respiratory and autonomic functions.

Conclusions: The pattern of c-fos expression in the mechanically stimulated rats was similar to a previous study (Gestreau et al, J Neurosci 1997; 17:9340-9352) in which coughing was induced by electrical stimulation of the superior laryngeal nerve in cats. Our data suggest that stimulation of mechanoreceptors in the larynx and trachea activates neuronal pathways which project to nTS (medial and ventrolateral parts) in the medulla.

Key words: trachea, larynx, cough, c-fos, the solitary tract, rat

Nominations for Award: n/a
A NOVEL TECHNIQUE: PRIMARY FIBROBLAST CULTURES FROM TRANSBRONCHIAL BIOPSIES OF LUNG TRANSPLANT RECIPIENTS

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Long-term survival following lung transplantation (LT) is limited by the development of bronchiolitis obliterans (BO). Subepithelial fibrosis may be found in transtracheal biopsies (TBB) prior to the diagnosis of BO. In order to study this pathological change, we attempted to establish for the first time primary human fibroblast cell cultures from TBBs of LT recipients. One to two TBB samples of LT patients undergoing diagnostic or surveillance TBB were collected in sterile PBS supplemented with antibiotics. Biopsies were cut in 4 to 8 small pieces and placed onto 12 well culture plates or 25cm² culture flasks and cultured under routine conditions (21% O₂, 5% CO₂, 37°C). Culture medium consisted of RPMI 1640, 10% FCS, glutamine and HEPES. Fibroblast culture results of 50 consecutive TBBs were analysed. The 50 TBBs were performed in 30 LT recipients (13 CF, 8 emphysema, 4 PPH, 4 CFA, 1 VSD) who underwent bilateral (19), single (8) or heart-lung (3) transplantation. The indication for TBB were symptoms, a drop in FEV₁, and/or infiltrates on chest X ray in 27 and a surveillance or follow up procedure in 23 cases. The overall culture success rate was 54% (27/50) defined as cells reaching confluency to be further passage. The culture success was independent of the age, the transplant procedure, the underlying lung disease, the indication for TBB (symptomatic/surveillance/follow up), the result of histology in regard to rejection (A₁/A₂, B₁/B₂, versus B₁/B₂) and the BOS stage. Bacterial/fungal colonisation of the bronchial tree was frequent but showed no negative influence on cell culture results. Fibroblasts could be cultured from 48% (11/23) of samples with a clinical diagnosis of pulmonary infection (SAL/TBB result) and from 52% (12/23) TBBs of patients without infection.

Summary and conclusion: we have established a novel method of culturing primary human lung fibroblasts from lung transplant recipients. These cultures provide a unique in vitro model of human tissue to study pathogenetic mechanisms of bronchiolitis obliterans at an early stage.

WEGENER'S GRANULOMATOSIS DIAGNOSED IN PREGNANCY

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CASE: A 31 year old woman presented at 9 weeks gestation. Her past history included an episode of pericarditis 5 yrs previously with an aortic valve replaced, a history of sinusitis and nasal congestion which had required surgery. At presentation the patient had a 4 week history of night sweats and an asymmetric polyarthritis and a 1 week history of haemoptysis, dysphonia and intermittent epistaxis. Examination revealed a low grade fever and a number of tender, mildly swollen joints. Her nasal mucosa was erythematous and swollen.

INVESTIGATIONS: A CXR revealed bilateral pulmonary infiltrates. The cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) was moderately elevated (titre = 124 ANCA units, normal = undetectable) and the ESR was 106mm/hr. Renal function was normal. A biopsy of her nasal mucosa was performed. A diagnosis of Wegener's granulomatosis was made and pulse methylprednisolone was given. There was a prompt improvement in the patient's clinical condition with resolution of her haemoptysis and improvement in her voice and joint symptoms and normalisation of her inflammatory markers including the c-ANCA.

OUTCOMES: The patient wished to continue her pregnancy. In view of (a) the possible teratogenic effects of cyclophosphamide given in the first trimester of pregnancy and (b) of her prompt response to steroids and (c) the limited nature of her disease it was decided to withhold cyclophosphamide and to treat her with prednisolone and close observation.

Aim: To determine the outcomes and costs of an out-patient exercise program. Methods: 119 patients were referred during 1996. Eighty-five patients were assessed of whom 72 (63%) were referred for an exercise program. Exercise consisted of a 20-30min walk at 80-85% estimated peak oxygen consumption followed by a 30min exercise circuit. Outcomes included exercise capacity (field walking tests) and quality of life (QOL).

CONCLUSIONS: Significant benefits in exercise capacity and QOL were demonstrated following the 8 week program (p<0.05). The cost of this program was $249 per patient. The respective costs for the maintenance and LVRS programs were $427 and $766. Conclusions: Significant benefits in exercise capacity and QOL can be demonstrated from an out-patient exercise program and the cost of this type of program is modest.

Key words: Exercise training, pulmonary rehabilitation, costs, outcomes.

EXPRESSION OF CYCLOOXYGENASE IN HUMAN DENDRITIC CELLS.

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It has been proposed that dendritic cells (DC) play a key role in regulating the balance between Th1 and Th2 immunity possibly through release of prostaglandins (PGs), and cytokines such as IL-12 and IL-10. Thus, understanding the regulation of cyclooxygenase (COX) expression and PG synthesis in DC may shed important light on the induction & regulation of allergic disease. As little is known about the regulation of COX-1 and COX-2 in human dendritic cells (DC), the expression of these enzymes in DC and monocytes was assessed by immunocytochemical staining and by intracellular flow cytometry of permeabilised cells. COX-2 staining was detected at low intensity in only a small minority of freshly isolated blood DC and monocytes, but was dramatically upregulated following exposure to LPS (10ng/ml). Intensification of staining was apparent by 4h, and reached maximal levels within 24h, with 80-90% of cells showing COX-2 expression. Exposure of freshly isolated blood DC and monocytes to GM-CSF & IL-4 for 24h did not alter COX-2 expression, whereas monocyte-derived DC (obtained by culturing monocytes with GM-CSF & IL-4 for 7 days) exhibited intense COX-2 staining which was further enhanced by exposure to LPS. In contrast, COX-1 staining was detected at low-moderate intensity in the DC & monocyte populations studied, and its expression was not appreciably altered by LPS. These findings indicate that both COX-1 and COX-2 can be detected in human DC. The expression of COX-2 in DC varies in response to inflammatory stimuli and/or cellular maturation, and the influence of other cytokines and tissue derived factors needs to be explored further.

Supported by the NHMRC.

Key words: dendritic cells, prostaglandins, cyclooxygenase.

OUTCOMES AND COSTS OF AN OUT-PATIENT EXERCISE PROGRAM FOR INDIVIDUALS WITH CHRONIC LUNG DISEASE

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Exercise training is an established component of the management of patients with chronic lung disease, however there is little data regarding the cost of such programs. Aim: To determine the outcomes and costs of an out-patient exercise program. Methods: 119 patients were referred during 1996. Eighty-five patients were assessed of whom 72 (63%) who had completed the 8 week program for costing purposes.

Seven categories of service were considered including the 8 week program, the maintenance program and a program for lung volume reduction surgery (LVRS) patients. Analyses were based on 1898 physiotherapy salaries and the costs of consumables only. Results: Fifty-seven patients (56 males) completed the program (20.8% attendance). Mean (SD) age and FEV₁ were 85.5 (9.3) years and 41.4 (23.7)%pred. Significant improvements in exercise capacity and QOL were demonstrated following the 8 week program (p<0.05). The cost of this program was $249 per patient. The respective costs for the maintenance and LVRS programs were $427 and $766. Conclusions: Significant benefits in exercise capacity and QOL can be demonstrated from an out-patient exercise program and the cost of this type of program is modest.

Key words: Exercise training, pulmonary rehabilitation, costs, outcomes.

Posters — COPD

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PATIENT CHANGES IN HEALTH LOCUS OF CONTROL FOLLOWING PULMONARY REHABILITATION
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There are psychological benefits from Pulmonary Rehabilitation (PR). (Mahler, 1998). PR should improve perception of control over one's health, which in turn should benefit health related behaviour. Some studies have considered the influence of PR on self efficacy, but none has assessed the effects of PR on health related perceptions of locus of control. Aims: To evaluate effects of PR on psychological morbidity and locus of control.

**Method:** In a controlled design, 100 patients with COPD completed the condition specific version of the Multidimensional Health Locus of Control scale (MHLC), General Health Questionnaire (GHQ) and the COPD Self Efficacy scales. Results: T-tests for paired samples indicate that patients had a more internal health locus of control (HLC) following PR (pre PR mean=29.55, sd=8.50 vs post PR mean=34.87, sd=8.01, p<.001) and were less chance oriented (CHLC) (pre PR mean=24.16, sd=7.65 vs post PR mean=22.01, sd=7.17, p<.05). However, there was no significant difference in the likelihood of patients placing their health locus of control in the hands of powerful others (health professionals) (PHLC) (pre PR mean=38.24, sd=6.06 vs post PR mean=38.41, sd=5.61, p>0.05). Patients had significantly lower rates of psychological morbidity following PR (pre PR mean=6.42, sd=6.84 vs post PR mean=4.01, sd=5.49, p<0.00).

**Conclusions:** The results imply that PR helps respiratory patients recognize that self responsibility for actions influences their clinical state. They are less likely to leave symptoms to fate and more inclined to self monitor. PR appears to foster patient empowerment and self care.

**Key words:** COPD, pulmonary rehabilitation, health locus of control, self efficacy

EVALUATION OF AN OUTPATIENT PULMONARY REHABILITATION PROGRAMME
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Pulmonary Rehabilitation is an important part of COPD management. In 1994 a Pulmonary Rehabilitation Programme (PRP) was developed to reduce dyspnoea, panic and anxiety and improve exercise tolerance, confidence, disease management skills, knowledge and overall quality of life in COPD. The aim of this study was to evaluate the effect of the PRP on exercise tolerance, quality of life, and readmission for people with COPD.

**Design:** Cross-sectional analytic survey. Methods: PRP records were audited over a 54 month period. A 6 minute walk test with dyspnoea rating (BORG scale) and quality of life assessment (using CRDQ) were conducted pre and post at completion of week 7 PRP. A hospital records search for COPD admissions (DRG 177) between 1994 - 1998 was conducted and readmissions compared between those who were referred and completed the PRP and those who were referred but did not complete. Results: There were 316 referrals to the PRP of whom 172 (54%) completed the PRP. Exercise tolerance, perception of dyspnoea, and quality of life all improved significantly following participation in the programme. The 6 minute walk distance, mean(sd) improved by 65(137) metres from 283(157)m to 349(112)m following the PRP (p<0.000). Those that completed the PRP had a significantly reduced chance of hospital readmission (22%) compared to the non-completion group (48%) (p<0.05). Conclusions: A 7-week hospital based outpatient pulmonary rehabilitation programme improves exercise tolerance, perceived dyspnoea and quality of life in COPD. Participants who complete the PRP are less likely to be readmitted to hospital. Alternative care models may be needed for non-completers to reduce readmissions.

**Key words:** pulmonary rehabilitation, quality of life, exercise tolerance

OXYGEN THERAPY: CURRENT PRACTICE AND A PRESCRIPTION FOR CHANGE.
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Background: There is evidence for the efficacy of oxygen therapy in certain clinical situations. The aims of this study was to establish the current oxygen prescribing and oxygen saturation monitoring methods in the acute hospital setting and to develop a protocol for the effective and efficient use of oxygen therapy. Methods: An audit sheet and algorithm for oxygen use were designed. Using these sheets, patients on one acute medical (25) and one acute surgical (2) ward had a clinical assessment, which included a pulse oximetry. Analysis of each patient's medical history was performed. Results: 32% were administered oxygen with no indication. 32% had a documented SpO2 or SaO2 prior to institution of oxygen. 32% had oxygen applied by nursing staff with no medical staff order. 20% had no documentation of who ordered oxygen. Oxygen therapy was ordered on the drug chart in 12%. In terms of SpO2 monitoring, while on oxygen the frequency of assessment was 4-6 hourly in 68%, and in those off oxygen the frequency was >24 hourly in 32%. Conclusion: Oxygen is a drug and needs to be prescribed with the same care as other drugs. Based on literature review a protocol for the use and monitoring of oxygen therapy has been devised.

**Nomination for awards:** nil
EFFECTS OF PULMONARY REHABILITATION ON 12 MINUTE WALK DISTANCE IN LUNG VOLUME REDUCTION SURGERY PATIENTS

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Aim: The aim of the study was to evaluate the effect of an 8 weeks exercise programme prior to lung volume reduction surgery (LVRS) on the distance walked in 12 minutes (12MD) and to compare this with the 12MD following an 8 weeks and 6 months exercise programme post-operatively. Subjects: 25 patients with chronic airflow limitation referred to the pulmonary rehabilitation programme at Royal Prince Alfred Hospital for exercise training prior to LVRS were recruited. Methods: At initial assessment (A) all patients performed spirometry, two 12 minute walking tests (2 days apart) and completed the St George Quality of Life Questionnaire. Each patient was prescribed an individual exercise programme which included walking on the flat, stationary cycling, arm cranking, upper and lower body weight training, and treadmill walking up an incline. Reassessment at the end of eight weeks training (B) included the same measurements as at A. Patients resumed exercise training at an appropriate level 1-3 weeks post LVRS and were reassessed 8 weeks (C) and 6 months later (D). ANOVA was used to compare results at A,B,C and D. A p<0.05 was considered significant. All data are presented as means SD. Results: 25 patients with severe airflow limitation (mean FEV1 = 0.62 ± 0.16 L; mean FEV1/FVC ratio = 33.1 ± 10.4%) completed the 8 weeks training programme prior to surgery and 8 weeks training post-operatively. There was a mean increase in 12MD from A to B=36.5% (p<0.001) and from A to C = 22.2% (p<0.05). The subgroup of 11 patients who underwent 6 months post-operative rehabilitation were reassessed separately. Improvements in 12MD A to B=36.5% (p<0.001), A to C= 41.4% (p<0.05) and A to D=55.3% (p<0.001). Conclusions: Exercise training in patients with severe airflow limitation significantly improves 12MD. LVRS plus 8 weeks rehabilitation did not further significantly increase exercise capacity in the larger group of 28 patients. Significant improvements in 12MD at 6 months post-operatively in the subgroup of 11 patients suggests that eight weeks post-operatively may be too early to demonstrate peak changes in 12 MD following LVRS.

SIGNIFICANT FUNCTIONAL IMPROVEMENTS AND LONG TERM COMPLIANCE WITH A LOW INTERVENTION HOME BASED PULMONARY REHABILITATION PROGRAM

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Pulmonary rehabilitation programs (PRP) are an established intervention in chronic obstructive lung disease (COLD) with demonstrated efficacy in controlling symptoms and improving functional capacity and quality of life. Home based PRP (HPRP) offer the advantages of improved access, decreased cost and better long term compliance than hospital based programs. We carried out a prospective study to examine the effectiveness of a very low intervention HPRP.

Methods: 28 patients with stable COLD and breathlessness limiting daily activity underwent a 6 week HPRP. Lung function and functional exercise capacity (6 minute walk, endurance walk and maximal stair climb) were measured before and after the program. Exercise was prescribed using a simple algorithm based on performance in the initial functional exercise testing and performed daily at home. Supervision was limited to one initial home visit and a weekly phone call.

Results: The mean FEV1/FVC and FEV1 were 35.5% and 37.9% of predicted. 11 patients withdrew because of poor motivation, recurrent exacerbations or loss to follow up. In the 17 subjects completing the program all measures of functional exercise capacity improved significantly: mean six minutes walk by 44.4m (p<0.01); mean endurance walk by 484.1m (p<0.001); and mean stairs climbed by 10.8 (p<0.03). Lung function parameters and results of cardiorespiratory exercise testing did not change significantly. At mean 8.8 months of follow up 13/17 of subjects (76%) were still following a regular exercise program.

Conclusions: A simple and low cost HPRP can achieve results comparable to published trials of more intensive PRP as well as good long term compliance. Patients who withdraw may be selected for the more supportive environment of a hospital based PRP.

Key words: pulmonary rehabilitation, chronic obstructive lung disease, home, follow up

THE 24 HR EFFECT OF MANNITOL ON THE CLEARANCE OF MUCUS IN PATIENTS WITH BRONCHIECTASIA.

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Background & Aim: We have previously reported an acute increase in clearance of mucus after a single dose of mannitol in patients with bronchiectasis (Daviaskas et al. Am J Respir Crit Care Med 1999; 159(6): 1845-1848). In the present study we investigated, in addition to the acute effect of mannitol: 1) the 24 hr retention; and 2) the clearance rate 24 hours after inhalation of a single dose of mannitol in patients with bronchiectasis.

Methods: Clearance of mucus was measured on 3 consecutive days in 8 patients with bronchiectasis, age 29 to 70 years. On each day, following inhalation of 99mTc-sulphur colloid aerosol (6 μm), lung images were collected over 2 hours and at 24 hr. Mannitol (330±68) mg was inhaled from an Inhalator™ (Boehringer Ingelheim) only on day 2.

Results: The key findings of the study were that: 1) Mannitol helped patients to clear mucus within 2 hr that would otherwise have taken 24 hr to clear from the whole lung; and all defined regions (p<0.02) and 2) the 24 hr retention of mucus was greatly reduced in all regions when the patients had inhaled the mannitol (p<0.02). The clearance in the peripheral region at 24 hr was more than double the day mannitol had been inhaled compared to the day without mannitol (29.1±4.3 vs 13.4±4.6 %) (p<0.003). However, a single dose of mannitol did not change the clearance rate or lung function beyond 24 hr (p>0.2).

In conclusion, a single dose of mannitol increases clearance of mucus acutely and its effect may extend up to 24 hr. The optimum daily dose of mannitol and its long term clinical benefit need to be investigated.

The study has been supported by a NH&MRC grant.

COORDINATION OF BREATHING AND SWALLOWING IN INDIVIDUALS WITH COPD.

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Laryngeal penetration and subsequent aspiration of particulate matter such as food and gastric contents, has the potential to cause lung damage through direct injury and infection. The act of swallowing is intimately coordinated with ventilation in order to minimise this risk. The frequency of aspiration during swallowing in COPD may be increased, however the relationship between ventilation and swallowing in this group is yet to be elucidated.

Aim: This pilot study was undertaken to determine if there is (1) an increase in the incidence of laryngeal penetration and aspiration, (2) a decrease in the deglutition-apnoea interval and (3) a change in ventilation before and after swallowing (inspiration-swell-expiration: IES, exp-swell-exp EE, exp-swell-inh EIS and inh-swell-inh IIS) in patients with COPD.

Methods: A group of COPD subjects (median (SD) age 74 years ± 4, n=5, 3F:2M) with FEV1<0.75 predicted and a group of control subjects (71 years ± 6, n=4, 4F) were measured simultaneously. Results: 3 out of the 5 COPD subjects had either laryngeal penetration or aspiration while swallowing at least one of the 3 boluses compared to 0 out of 4 of the control group. There was a consistent respiratory phase difference between COPD and controls (figure1). Inspiration immediately post swallow was only noted in COPD subjects (odds ratio 15:1). No difference was observed in the deglutition-apnoea interval regardless of bolus size or the presence of aspiration (p=0.2-0.5). There was no evidence of arterial oxygen desaturation in any patient.

Figure 1.

| Ventilation associated with each swallow. |
|----------------------------------------|
| IES | EES | EIS | IIS |
| Controls | 83% | 17% | 0% | 0% |
| COPD | 20% | 20% | 60% | 0% |

Conclusions: There appears to be a greater incidence of penetration or aspiration in the COPD group compared to controls in this small group of subjects. This may be due to the increased incidence of inspiration directly following swallowing in the COPD group. There was no difference in the deglutition-apnoea interval.
A RANDOMISED CONTROLLED TRIAL OF NON-INVASIVE VENTILATION (NIV) IN ACUTE EXACERBATIONS OF CHRONIC AIRFLOW LIMITATION (CAL).

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There is growing evidence that NIV improves outcome in acute exacerbations of CAL. However, the application of this therapy in the ward setting, and its effect on hospital length of stay (LOS) remain to be established. Method: A prospective, randomised controlled trial of standard therapy (ST; i.e bronchodilators, steroids, O2, physiotherapy, ± theophylline) versus ST+NIV in patients presenting to the emergency department with acute hypercapnic (pCO2 >55mmHg) exacerbations of CAL. The primary endpoint was the need for intubation and secondary endpoints were lung function parameters, symptom scores (Borg scale) and LOS. Results: 10 patients (mean±sem age 75±6yrs) with severe acute exacerbations of CAL (FEV1 0.37±0.08L, pCO2 62±7mmHg, pH 7.33±0.03) were randomised to either ST (n=5) or ST+NIV (n=5). Half the ST patients failed treatment and were deemed to require intubation, versus none in the NIV group. Symptom scores, FEV1, FVC, pCO2, pO2 improved in all subjects by discharge, but the differences between treatment groups were not significant. The average LOS was shorter in the ST+NIV group (12±7 and 6±2 days, p=0.06). Conclusion: These preliminary data indicate that ward-based treatment with NIV is feasible in these acutely unwell patients, and further suggest that outcomes (including LOS) may be improved with such therapy. Further evaluation is required to verify these findings.

Key words: CAL, non-invasive ventilation, ward treatment

THE IMPACT OF HOME OXYGEN THERAPY ON THE DISEASE SPECIFIC QUALITY OF LIFE OF SUBJECTS WITH CHRONIC AIRFLOW LIMITATION.

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Chronic Airflow Limitation (CAL) is a major contributor to the burden of ill-health in Australia, and where hypoxia is present, can be treated with home oxygen therapy (HOT). At Flinders Medical Centre, a prospective longitudinal study has been undertaken to examine the impact of HOT on the quality of life of subjects with CAL. Methods: All eligible adult patients, aged less than 80 years, with a primary diagnosis of CAL, who met the prescription guidelines of the Thoracic Society of Australia and New Zealand were offered HOT and invited to participate. After baseline assessment subjects were followed-up at 3, 6 and 12 months from commencement of HOT. The disease-specific Chronic Respiratory Disease Questionnaire (CRQ) was applied. A mean change in score from baseline equivalent to 0.5 per question was considered clinically significant. Results: Follow-up was available for 115 CAL patients, (male:female 68:57), mean age 69.3 years, prescribed HOT from January 1991 to July 1999. Based on Guyatt’s clinically significant difference for the CRQ, 50% females experienced significant improvements in CRQ scores at three months, 42% at 6 months and 43% at 12 months with 21% patients experiencing significant deteriorations at 3 months, 22% at 6 months and 18% at 12 months. 41% males experienced clinically significant improvements at 3 months, 33% at 6 months and 42% at 12 months with 19% experiencing clinically significant deteriorations at 3 months and 6 months and 20% at 12 months. Conclusion: More CAL patients were able to demonstrate clinically significant improvements in their quality of life after commencing HOT than clinically significant deteriorations.

Key words: Chronic Airflow Limitation, home oxygen therapy, clinically significant difference
BARRIERS TO SUCCESS FOR AN EVIDENCE-BASED “ACCORD” GUIDELINE FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) – THE LITERATURE AND THE EXPERIENCE

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An evaluation of barriers and attitudes to best practice guideline use was conducted during a comprehensive multi-centre COPD management guideline implementation across three Adelaide metropolitan hospitals. Such guidelines to date have had a limited impact on clinician behaviour and patient outcomes. An evaluation of barriers is important in understanding what drives a clinician to use or not use a guideline. Methods: Focus groups of 30 health practitioners’ experience with the ACCORD were analysed using NUDIST software and structured according to the Triandis model, in terms of perceived consequences, emotions, facilitating and social factors. This analysis informed a 44-item questionnaire that was administered one-to-one to managed 3 or more COPD patients. The questionnaire included test-retest questions, was piloted (n=6), and modelled using multiple linear regression. Results: Social issues were identified in the focus groups primarily by senior medical staff and specialist respiratory staff, with nursing and allied health reporting more patient-care outcomes. 99 (85%) doctors completed the interview. There was greater guideline use on respiratory units than other units (p<0.01). Senior clinicians used the guideline less (p<0.02) and the 40-50 year age group were most resistant (p<0.01). Triandis modelling explained 49% of variance in intention to use and self-reported use of the best practice guideline. 1. Triandis HC Nebraska Symposium on Motivation. 1980; 27:195-259.

Supported by the NHMRC

Key words: Guidelines, barriers, COPD, attitudes, beliefs.

PREVENTING FRACTURES IN COPD, IS AT LEAST AS COST-EFFECTIVE AS TREATMENT OF POST-MENOPAUSAL HIP FRACTURES.

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Osteoporotic fractures cause significant morbidity, and people with asthma and chronic obstructive pulmonary disease (COPD) are at risk of increased fracture risk due to their long-term treatment with corticosteroids. COPD is associated with bone density reduction of 10% with associated increased fracture risk. Long-term fracture studies are difficult to conduct, whereas modelling studies can provide information for today. Alendronate has been shown to significantly increase BMD and reduce fracture rate in a number of patient groups. Almea: To model the cost-effectiveness of reducing fractures by screening the COPD population to identify those with reduced BMD, and treating with alendronate. Methods: Markov model incorporates data for presence/absence of COPD, gender, initial BMD & treatment response. Decision trees within the model generate annually over 30 years, probabilities of 4 outcomes: no event OR hip fracture OR dying OR institutionalisation. Data were derived from trials, population surveys, health utilisation data and life tables. Results: Costs per hip fracture, death prevented and life years saved were generated for treatment over 10, 20 or 30 years (to age 85). Table: Describes the number of Australian women with COPD and BMD Z score* <3 and also for normal women with Z = -1 -2. (Mean BMD in women who have had a hip fracture and are Pharmacy Benefits Scheme (PBS) eligible for alendronate.) Conclusion: Screening and targeted preventative treatment for women with COPD is at least as cost-effective as current PBS funded practice.

Key words: osteoporoses, hip fracture, COPD.

| Years Tx (treated) | Status | No. Tx in first year | No. alive, 85 yr old | Cost/care prevented | Cost/ death prevented | AUBL (Y saved) |
|-------------------|--------|----------------------|---------------------|---------------------|---------------------|---------------|
| 10 (75-85 yo)     | COPD   | 114-35-33            | $1,777              | $10,019             | $1,031              |
|                   | hip fracture | 7710-3882   | $3,032              | $10,019             | $1,031              |
| 20 (65-85 yo)     | COPD   | 98 – 15              | $920                | $4,012              | $293                |
|                   | hip fracture | 9248-3754   | $14,872             | $55,324             | $7,590              |
| 30 (55-85 yo)     | COPD   | 98 – 13              | $7,000              | $53,020             | $2,086              |
|                   | hip fracture | 12303-4633 | $38,392             | $148,864            | $17,262              |

* SDs below mean normal, age and gender matched BMD.

SYMPTOMATIC IMPROVEMENTS IN SOME PATIENTS NOT REFLECTED BY IMPROVEMENTS IN FEV; A SYSTEMATIC REVIEW OF THE EFFECTS OF SALMETEROL IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Patients with chronic obstructive pulmonary disease (COPD) often demonstrate little or no reversible airflow obstruction. A systematic review was therefore conducted to determine the effectiveness of long acting beta2-adrenoceptor agonists (LABAs) on lung function and health related quality of life (HRQL). Methods: Randomised controlled trials (RCTs) comparing treatment with LABAs (salmeterol and formoterol) for at least four weeks, with placebo, in patients with stable non-reversible COPD were identified and assessed according to Cochrane Collaboration guidelines. Results: Four RCTs were found which assessed the efficacy of salmeterol (two 16 week parallel group RCTs and two cross-over RCTs with four week treatment arms). A 16 week study of salmeterol 50 µg and 100 µg twice daily (b.d.) treatment demonstrated a weighted mean difference for the increase in FEV1, was 0.10 litre (95% confidence interval [Cl]: 0.05; 0.05) and 0.12 litre (95% Cl: 0.17; 0.05) respectively. HRQL was significantly improved, using The St George’s Respiratory Questionnaire, after 50 µg (b.d.), but not after 100 µg (b.d.). The cross-over RCTs did not show significant increases in FEV1 or morning and night time PEFR. No improvements were demonstrated in the Medical Outcomes Short Form 36, exercise tolerance (6 minute walk distance) and the incidence of COPD exacerbations. Salmeterol 50 µg (b.d.) was associated with reduced Borg Dyspnoea Scores (Peto Odds Ratio = 0.60, 95% CI: 0.40; 0.88).

Conclusions: Symptomatic improvements in terms of dyspnoea and HRQL were associated with limited increases in FEV1 in some patients with COPD after 16 weeks salmeterol treatment. The contribution to these improvements by a reversible airflow obstruction component in trial subjects is unknown.

Key words: chronic obstructive pulmonary disease, HRQL, salmeterol.

SECRETORY LEUKOCYTE PROTEINASE INHIBITOR MAY PROTECT THE LUNG AGAINST THE DEVELOPMENT OF EMPHYSEMA IN INDIVIDUALS WITH ALPHA-1-ANTITRYPSIN DEFICIENCY

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Background: We have previously speculated (Respirology 1997;2:91-95) that the variation in expression of alpha-1-antitrypsin (A1AT) deficiency is in part due to the presence or absence of other antiproteinases particularly those of small molecular size, eg, secretory leukocyte proteinase inhibitor(SLPI) (15KQ). Aim: To present two cases of A1AT deficiency which support this hypothesis. Case studies: Two patients are reported. Each underwent lung testing (spirometry, DLCO) and bronchoscopy with bronchoalveolar lavage(BAL). A1AP and SLPI were measured in both serum and BAL by standard techniques. Case 1: 51 yr old male with severe emphysema (PIZZ) and a past smoking history of 96 pk yrs. Case 2: 49 yr old female with normal lung function but A1AT deficient (PIZZ) and had never smoked.

Table: Smoking history, Serum SLPI mg/ml, Serum A1AT mg/ml, BAL A1AP mg/ml per Urea, BAL SLPI mg/ml per Urea, Lung function.

| Case | Smoking history | Serum A1AT mg/ml | Serum SLPI mg/ml | BAL A1AP mg/ml per Urea | BAL SLPI mg/ml per Urea | Lung function |
|------|-----------------|-----------------|-----------------|-------------------------|-------------------------|---------------|
| 1    | 36 pk yr        | 0.35            | 0.33            | 0.04                    | 1.05                    | AO; ↓DLCO     |
| 2    | Nil             | 0.35            | 0.46            | 0.32                    | 2.29                    | Normal        |

Normal values# (Mean ± SD)

|                | 1.87 ± 1.94   | 0.14 ± 0.08    | 0.48 ± 0.03 | 3.64 ± 1.94 |

# current/ex smokers, data submitted for publication

Conclusion: These results are consistent with the concept that SLPI in the presence of A1AT deficiency can protect the lung against the development of emphysema in the absence of cigarette smoking.
VATS INTRA-CAVITARY ABLATION OF GIANT BULLAE UNDER EPIDURAL FOR HIGH RISK PATIENTS
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Unlike lung volume reduction surgery, the benefits of surgery for giant bullae are not in dispute. However some patients have so little reserve that conventional surgery is not a viable option. Two such patients are presented below.

A sub-periosteal rib resection was performed, leaving the parietal pleura intact. Concentric purse-string sutures were then placed and lightly snugged to keep the bulla against the parietal pleura and the centre was incised with a scalpel.

The first patient survived 8 months, requiring oxygen on exertion. The other is fully active at 6 months without oxygen support.

The patients described could easily have been denied a surgical solution for their dyspnoea. This procedure achieves hospital discharge and good quality of life, without imposing risks of thoracotomy, anaesthesia or ventilator dependence.

Key words: Thoracotomy, emphysema, lung volume reduction surgery.

RISK FACTORS FOR CHRONIC RESPIRATORY DISEASE IN A RURAL ABORIGINAL COMMUNITY IN NORTHERN AUSTRALIA
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Life expectancy for Northern Territory Aboriginal women and men is, respectively, 19.5 and 18.2 years less than non-Aboriginal people. Of this excess mortality 10% in females and 7% in males is due to chronic non-specific lung disease. The incidence of chronic obstructive pulmonary disease in this community is two and a half times that in the country’s general population. The rapid spread of chronic obstructive pulmonary disease (COPD) in the community is a major challenge in diagnostic coding and admission detail. The proportion of chronic obstructive pulmonary disease (COPD) is defined by ICD-9 CM codes 492 & 496.

Aim: To assess and analyse the national data set on COPD hospital admissions, classified according to ICD-9. Results: Four years of data from the National Hospital Morbidity Database were examined, using ICD-9-CM codes 492 - 496 as the primary diagnosis. Most COPD cases were recorded within a residual category labelled ‘obstructive disease not otherwise specified’ (code 496). The proportion attributed to this category varied from one state to another (50% to 90%). The coding classifications within COPD also demonstrated variation in admission detail. The proportion of admissions for emphysema increased throughout the period (8% to 12%) while the proportion for chronic bronchitis decreased (24% to 19%). These trends were also reflected in mortality rates derived from the Australian Bureau of Statistics. The mean length of hospital stay varied across ICD codes, with emphysema (10 days, SEM: 0.2) being longer than chronic bronchitis (8 days, SEM: 0.2) (p<0.01). Using the number of diagnoses as a proxy for comorbidity, patients with emphysema have significantly more comorbidity than patients with chronic bronchitis (p<0.01).

Conclusion: The widespread use of a residual coding category generates both variation in recording because of unclear definition and a lack of information regarding sub-classifications of COPD. Retrospective analysis using ICD-9 coding definition for COPD patient groups is likely to provide improved outcomes due to the heterogeneity of the most utilised coding group.

Acknowledgements: Astra Pharmaceuticals provides financial support to AARI for Health Economics

Key words: COPD, ICD-9, epidemiology

ACCORD: THE PSYCHOLOGICAL MORBIDITY IN PATIENTS ADMITTED FOR COPD TO SOUTH AUSTRALIAN HOSPITALS.
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COPD is one of the leading discharge diagnoses for Australian hospitals. The reason for admission is not reflected in the Diagnosis Related Group (DRG) classification, but evidence from overseas and from Flinders Medical Centre (SA) suggest that psychosocial factors are an important contributing factor to admissions. Aim: The Adelaide Collaboration on Chronic Obstructive Respiratory Disease (ACCORD) Project Team developed and implemented evidence-based clinical practice guidelines for use in hospitalised COPD patients, with an aim of identifying more accurately not only physiological but also psychosocial morbidity. Methods: The ACCORD guidelines were implemented in three “active” (A) hospitals over a 6 month period. Patterns of admission and DRGs were tracked before and during the intervention period in both A and “control” (C) hospitals. Patients completed the 28-item General Health Questionnaire at admission, 6 weeks after discharge, and 6 months later; a total score over 5 is considered to indicate significant psychiatric morbidity. Results: Mental health (MH) DRGs were recorded in less than 6% of patients in the pre-intervention period. At admission 72.5% of 506 patients had GHQ scores over 5. Six weeks after discharge 56.2% of 283 patients had significant psychiatric morbidity, and at 6 months 51.1% had GHQ > 5. The age-matched prevalence of psychiatric morbidity is 12.8%. The main psychiatric diagnoses defined by the GHQ were Anxiety & Insomnia (55.7%) and Severe Depression (30.7%).

Conclusion: There is a high level of psychiatric morbidity in patients admitted for treatment of COPD to SA Teaching Hospitals. Neither the overall psychosocial impact of COPD nor the specific psychiatric diagnoses were coded. This under-recognition of psychosocial morbidity needs urgent attention.

Key words: COPD, hospitalisation, mental health, psychological morbidity
SYSTEMATIC ASSESSMENT OF CLINICAL PRACTICE GUIDELINES FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE [COPD]
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COPD is a condition of major morbidity and cost to society. Neither the extent of best practice COPD management guideline uptake in clinical settings, nor the impact on patient health outcomes is known. The quality of development of COPD guidelines is also in doubt. Therefore, our aim was to systematically review COPD guidelines to evaluate the quality of the process of development.
Methods: A key-word search was performed using "COPD" and "guidelines". Two reviewers independently evaluated the guidelines using the criteria of Ward1 plus medicolegal and ethical considerations on a three-point scale.
Results: Six national COPD guidelines (Thoracic Societies of Australia and New Zealand, Britain, USA, Canada and South Africa) and one international COPD guideline (European Thoracic Society) were identified. Inter-reviewer correlations (Kappa=0.7) showed good agreement. The guidelines were uniformly based upon a consensus approach, mostly with a medical model focus, rather than multi disciplinary, and were lengthy (up to 45 pages) and discursive. Only one had an executive summary suited to everyday practice. The papers did not reflect a systematic evidence-based approach to the collection, appraisal, collation or presentation of information. Most guidelines provided no indication of their level of evidence or methods employed to resolve differences of opinion. There was no evidence of their actual uptake. Ethical and medicolegal implications were not addressed. A single drug company sponsored 6 of the guidelines. Conclusions: COPD is common, and places great morbidity and cost burdens upon society, therefore management principles should follow leading, state-of-the-art, best-practice, evidence-based guidelines. However, in spite of guidelines being reported by major national bodies for over a decade now, most fail to meet the majority of Ward's criteria. Further, there is a lack of evidence of their uptake or any impact upon patient outcomes. There is a need to develop and evaluate independent guidelines, with multi disciplinary involvement, that will be readily adaptable for a range of clinical disciplines.
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Key words: COPD, guidelines, development, review, quality of evidence.

A COMPARISON OF SINGLE BREATH CARBON MONOXIDE TRANSFER FACTOR AND HIGH RESOLUTION CT (HRCT) IN THE DIAGNOSIS OF EMPHYSEMA.
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HRCT is the gold standard for the diagnosis of emphysema in patients with airflow obstruction. A reduction in TlCO is also an indicator of the presence of emphysema in this group of patients. A previous study demonstrated a poor correlation between reduction in TlCO and HRCT finding of emphysema in a subgroup of patients with very severe airflow obstruction (1). Nonetheless, in clinical practice, a reduction in TLCO is commonly interpreted as consistent with a diagnosis of emphysema. We wished to determine the relationship between the reduction in TlCO in the presence of severe airflow obstruction and the presence of emphysema on HRCT.
METHODS: We examined current or ex-smokers with irreversible airflow obstruction, FER <60%, FEV1<1.5 L, TlCO <15 mL/min/mmHg who had undergone HRCT. RESULTS: 95 out of 113 patients had reduced TlCO (mean = 37.5 %pred) and KCO (mean = 50.0 % pred) with HRCT evidence of emphysema, whereas 18 had reduced TlCO (mean = 53.9 %pred) and KCO (mean = 64.8 %pred) but no HRCT evidence of emphysema. CONCLUSION: These data suggest a reduction in TlCO does not necessarily equate with parenchymal abnormality in patients with severe smoking related airflow obstruction. The explanation for this reduction in TlCO in patients with severe airflow obstruction but no HRCT evidence of emphysema remains hypothetical. Ventilatory inhomogeneity leading to measurement error may be an explanation for this finding.
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THE CLINICAL UTILITY OF EAR LOBE ARTERIALISED CAPILLARY BLOOD IN THE ASSESSMENT OF PATIENTS FOR LONG TERM OXYGEN
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Introduction
The prescription of long term oxygen (LTOT) is underpinned by the measurement of arterial PO2, generally obtained by radial artery puncture. Cutaneous oximetry has not proved sufficiently reliable as an alternative. The use of ear lobe arterialised capillary blood has been proposed with several studies suggesting close agreement between arterial values. However, this technique is not widely used and the clinical utility remains uncertain.
Methods
Consecutive patients with chronic respiratory disease undergoing assessment for LTOT were invited to participate. Simultaneous radial artery and arterialis ed ear lobe sampling was performed and procedural difficulties and patient discomfort detailed. Agreement between arterial and arterialis ed PO2 was compared using the Bland and Altman method.
Results
One hundred patients were studied. Procedural difficulties (insufficient sample or air in sample) were similar for both procedures, however a clotted specimen occurred more frequently in the ear lobe arterialised sample. Seventy six sample pairs were available for comparison. Radial artery and arterialis ed PO2 were in close agreement with a mean difference 0.30 kPa (95% CI = -0.54 to -0.006). However, based on the arterialis ed earlobe sampling and using the absolute criterion (PO2 ≤ 7.3 kPa) for the prescription of LTOT, 10/57 (18%) patients would receive oxygen inappropriately. Conversely 6/19 (32%) patients would have been denied treatment. Radial artery puncture gave rise to significantly greater discomfort (p<0.0001) and level of concern (p<0.0001).
Conclusion
Although patient preference strongly favours arterialis ed ear lobe sampling, procedural difficulties and insufficient accuracy mean that ear lobe sampling cannot replace radial artery puncture in the assessment of patients for the provision of LTOT.

VALIDATION OF THE SELIM CHRONIC LUNG DISEASE QUESTIONNAIRE WITH OBJECTIVE MEASUREMENT
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The objective of this study was to evaluate the Selim Chronic Lung Disease Questionnaire (a severity rating based on symptoms) in patients with chronic obstructive pulmonary disease (COPD) and asthma by correlating the Selim score to objective measurements of severity. This open study was conducted in hospital respiratory outpatient clinics. Consecutive patients with COPD and asthma had responses to the Selim Questionnaire recorded: FEV1 and FVC were measured and a patient self rating of severity of illness was documented. The Selim Questionnaire is based on 6 questions related to dyspnoea, cough, wheeze and sputum production, and asks patients to rate these over the previous three month interval. This report is from the initial 65: 32 females and 23 males age range 20-79 years. A correlation has been demonstrated between FEV1 and the total Selim score (see diagram).

Furthermore, subgroup analysis has suggested that the questions relating to dyspnoea seem to correlate better with FEV1 and FVC than the questions relating to wheezing and cough. It is anticipated that further subgroup analysis will be performed on the basis of diagnostic groups viz. Asthma vs predominantly COPD. This research is funded by TQEH Research Foundation.
Key words: Quality of life, Selim Questionnaire, Chronic Obstructive Pulmonary Disease and asthma.
INTERLEUKIN-1 RECEPTOR ANTAGONIST AND TUMOUR NECROSIS FACTORα (TNFα) POLYMORPHISMS IN CYSTIC FIBROSIS

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Considerable variation exists in cystic fibrosis (CF) phenotype and severity, even amongst individuals with identical CFTR mutations. There is significant individual variation in host inflammatory response, with increased TNF-α and IL-1β concentrations in CF airways. Functionally relevant polymorphisms in cytokine genes have recently been characterised. The TNF2 polymorphism at position -308 of the TNF-α promoter is associated with TNF-α higher concentrations in vitro. Variable numbers of tandem repeats in intron 2 of the interleukin-1 receptor antagonist (IL-1Ra), an anti-inflammatory cytokine, lead to alleles which have been associated with inflammatory diseases. We hypothesised that these polymorphisms influence phenotype in CF. Aim: To examine TNFα promoter and IL-1Ra polymorphisms as disease-modifying genes in CF. Methods: We recruited 73 adults with cystic fibrosis and 168 healthy anonymous blood donors. Genotypes were determined using PCR. Results: CF patients (55% female) had mean (SD) age 35.4 (8.4) years, BMI 21 (3) and FEV 1 56 (22) % predicted. We found greater allele frequencies in CF than TNF2 19.9%, IL-1Ra*1 77.4%, IL-1Ra*2 21.9% and IL-1Ra*3 0.7%, which did not differ from controls. BMI was similar between TNF-α genotypes (1/1 20.8, 1/2 21.2, 2/2 19.8). FEV 1 was not different between TNF-α genotypes (1/1 57%, 1/2 53%, 2/2 67%). There was a trend to overrepresentation of TNF2 in adults with CF who required lung transplantation. IL-1Ra variants were not associated with BMI or lung function. Conclusions: Presently our data do not provide evidence for TNF-α and IL-1Ra polymorphisms as modifiers of BMI, FEV 1 or VC in CF. Recruitment is continuing to obtain adequate power and further detailed CF phenotyping, including key longitudinal clinical and physiological outcomes, is required to exclude an effect of cytokine gene polymorphisms.

Supported by: The Prince Charles Hospital Foundation

Key words: Cystic fibrosis, tumour necrosis factor-alpha, interleukin-1 receptor antagonist, polymorphisms.

DEFINING AN EXACERBATION OF PULMONARY DISEASE IN CYSTIC FIBROSIS (CF)

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Despite the importance of pulmonary exacerbations (PE) in CF in both clinical and research settings, published evidence or consensus is lacking about the variables used to define an exacerbation. Hospitalisation, a surrogate measure, relies on uniformity among clinicians in diagnosis and treatment of PE. Aim: To evaluate and compare consensus among clinicians about the variables considered helpful in diagnosing a PE requiring treatment. Methods: Two round Delphi consensus development. A comprehensive list of symptoms, signs and investigations used to define PE was compiled from published trials. A written self-administered questionnaire included the list in age appropriate groups to survey opinion about the helpfulness of each item, and the estimated proportion of patients admitted within a month of diagnosis of PE. Sent to all clinicians managing CF patients in Australia. A second round of the survey was sent, with summarised responses from the first, giving the opportunity to modify responses to develop consensus. Results: 1st round: Replies from 59/91 clinicians (66%), 41/60 (68%) from those managing children (C) and 18/31 (58%) from those managing adults (A). Responses of C and A differed for 7/32 variables (Mann Whitney, p<0.05). Clinic grouping did not show greater consensus among responses of C (Krukal-Wallis p=0.362), Consensus, >74% or <26% respondents rating a variable helpful/very helpful, was found in only 40% of variables listed. Estimated admission rate within a month of diagnosis was 61% (30-100%) for A and 48% (5-100%) for C. 2nd round: Replies from 55/51 (60%), from C 32/61 (52%), from A 23/31 (75%). Consensus increased from 50% of variables to 80% in C, and 63% in A. Conclusions: A lack of consensus was found among clinicians managing CF about the variables considered in diagnosing PE and the duration to admission of identified PE; suggesting inhomogeneity of management. Consensus increased following feedback of summarised responses. The resulting variables will be used to develop a clinical measurement tool.

Key words: Pulmonary exacerbation, cystic fibrosis, delphi. Nominations for Awards: Nil.

EVIDENCE BASED CHEST PHYSIOTHERAPY FOR INFANTS WITH CYSTIC FIBROSIS DIAGNOSED WITH NEWBORN SCREENING

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Newborn screening leads to early diagnosis and introduction of chest physiotherapy (PT) in young mainly asymptomatic infants. Infantile reflux is common in early life. Gastroesophageal reflux (GOR) is more common in CF. Aims: To measure (1) the acute effects of standard postural drainage (SPT) versus modified positions (MPT) on GOR and axiometry in very young infants with CF; while in different states of alertness (SOA) sometimes using non-nutritive sucking (NNS) for comfort; (2) the longer term effects of SPT vs MPT on respiratory status during infancy. Method: 20 infants (mean age 2.1 months) each had 2 sessions of SPT and MPT during 30hr osophageal pH monitoring. The number of reflux episodes (NRE) and axiometry were measured in SPT positions (supine flat, prone, left and right side lying with 30° head down tilt) and MPT positions (supine 30° head up, prone, left and right side flat). Different SOA and NNS were recorded. Thereafter infants were randomized to SPT or MPT for 12 months. Respiratory status, medical treatment and radiology were compared. Results: The NRE/hour for SPT, MPT and background (BG) were 2.5±1.6, 1.8±1.3 and 1.1±0.6; p<0.05. The NRE in each position during SPT vs MPT were: supine flat vs supine 30° head up: 20 episodes vs 12, p=0.067; prone 30° head down vs prone flat: 18 vs 9, p=0.03; right side lying (SRL) 50° head down vs SRL flat: 15 vs 9, p=0.01; left side lying (LSL) 50° head down vs LSL flat: 7 vs 11, p=0.01. The mean Sa02 during SPT vs MPT were: 98.54±1.60% vs 98.75±1.07%; and heart rate 141.97±11.48 vs 139±8.61 beats per minute. There was no evidence that use of NNS or falling asleep during treatment increased the episodes of GOR. In the longer term study, annual days with respiratory symptoms for SPT versus MPT groups were: cough: 116±37.56 vs 83±11.86, p=0.50; upper respiratory tract infections: 70±32.76 vs 37±24.91, p=0.03; wheeze: 41±32.46 vs 25±54.54, p=0.50; days on antibiotics: 116±88.56 vs 67±58.62, p=0.21. At mean age 2.5yrs, 86% of the infants in the MPT groups had perfect Brasfield scores of 25 versus 43% in the SPT group. Conclusion: MPT should be considered as the most effective and safe regimen for infants with CF based on current scientific evidence.

INFLAMMATION, INFECTION AND LUNG FUNCTION IN CLINICALLY STABLE INFANTS AND YOUNG CHILDREN WITH CYSTIC FIBROSIS (CF)

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There is a lack of comprehensive research into interactions between infection, inflammation and lung function in infants and children with CF. The aim was to study the effect of lower airway infection on clinical parameters, using functional tests (FPTs), and inflammation in clinically stable patients. Study design was a prospective cohort study of CF patients under 4 years, identified on newborn screening. Methods: A single general anaesthetic, with intubation and muscle relaxation for FPT's. Passive lung mechanics were measured by single breath occlusion passive deflation (computerised system), for compliance (Cr) and resistance (R), Functional residual capacity (FRC) and total lung capacity (TLC) measured by nitrogen washout. Lavage specimens (BAL) were obtained from right lower, middle and upper lobe bronchi for cytology, cytokine IL-8, and quantitative microbiology. Results: 15 children studied, 6 girls, all pancreatic insufficient. Mean age 27.3 months (range 12-42 months). Double .sf508 in 12/15. Prior respiratory admissions in 9/15, correlated with culture of Pseudomonas aeruginosa (Pa) (r=0.694, p=0.004), and IL8 level (r=0.538, p=0.039). Lower respiratory pathogens (>10cfu/ml BAL) were found in 7/15: Staphylococcus aureus (Sa) in 2; Pa in 4; and Sa, Pa and haemophilus in one child. Sa was only detected in children not taking prophylactic fluconoxil. Culture of any Pa, or Sa >10cfu/ml BAL correlated significantly with BAL total cell count (r=0.525, p=0.029), neutrophil % (r=0.92, p<0.001), and macrophage % (r=-0.75, p=0.001) and IL8 (r=0.72, p=0.001). Culture of Pa correlated with age adjusted Crs (r=-0.60, p=0.02), Crs/FRC (r=0.69, p=0.007) and FRC/TLC (r=0.75, p=0.003). Conclusion: In infants and children with CF the presence of pathogens in the lower airways correlated with levels of inflammation, respiratory system compliance and degree of air trapping.

Key words: Cystic Fibrosis, infant lung function testing, cytokines, infection. Nominations for Awards: Nil.
Cystic Fibrosis Conduction Regulator Gene Mutations: Do They Play a Role in the Aetiology of Allergic Bronchopulmonary Aspergillosis?

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Introduction: Allergic bronchopulmonary aspergillosis (ABPA) shares some important similarities with cystic fibrosis (CF); hence the possibility that genetic factors may play a role in pathogenesis. We aimed to determine the frequency of cystic fibrosis conductance regulator (CFTR) gene mutations in asthmatics with and without ABPA.

Methods: Patients were recruited prospectively from asthma clinic. A diagnosis of ABPA required satisfaction of 1 Department of Respiratory Services, Green Lane Hospital, New Zealand

Results: Of the 26 asthmatics SPT positive to A1, 36% (n=26) were positive to ABPA (n=31). Genomic DNA was screened for the carrier rate in ABPA cases and 2 hours after screening. Blood samples were collected every 30 min for 6 h by smoking through a straw into collection tubes. In CF patients 13C trilobin recovery was measured with and without PERT (usual dose for light snack), on different days in a randomised order, and compared to 13CO2 recovery from healthy subjects. Intra-individual variability was assessed in 7 healthy subjects by repeating the breath test on a second day (healthy 1 and 2). Values were % cumulative recovery of 13CO2 dose over 6 h. Data are median (IQR). Statistic: Mann Whitney U and Wilcoxon tests; *p<0.01 PERT vs no PERT).

Conclusion: The 13C trilobin breath test is a simple and reproducible method to assess fat absorption which reliably screens for severe fat malabsorption in adult CF patients. Further studies are needed to determine whether it is also useful in less severe pancreatic exocrine failure or monitoring the dose of PERT.

Key words: cystic fibrosis, malabsorption, 13C Trilobin breath test

Evaluation of Cystic Fibrosis Phenotypes: A Comparison Between the Clinical and the Faecal Collection Methods

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Cystic fibrosis related diabetes mellitus (CFRDM), attributed to ongoing pancreatic fibrosis and destruction of beta islet cells, complicates CF in 5-24% of patients, whilst impaired glucose tolerance (IGT) occurs in up to 75%. The onset of CFRDM is usually insidious and associated with respiratory and nutritional deterioration. There is minimal information on the role of impaired glucodynamic control in the period prior to the onset of CFRDM, nor its frequency in the paediatric population. Whilst implied, it remains unclear whether better management of the pre-diabetic stage will translate to slower progression to CFRDM or improved outcomes. Methods: A prospective analysis of glucose tolerance in the CF clinic at John Hunter Children’s Hospital, as the first data in screening all school-aged children in NSW. A fasting blood glucose (FBG), 2-hour oral glucose tolerance test (OGTT) and HbA1C were measured. Results: 30 children have completed screening from a clinic of 62 (18 too young, 4 lost to follow-up, 3 CFRDM, 1 pancreatic sufficient, 6 to be completed). Mean [95% CI] age was 12.77 years [11.44, 14.1], HbA1C 5.6% [5.45, 5.73], FBG 4.84mmol/L [4.4, 4.84] and 2 h OGTT 7.3mmol/L [6.82, 8.14]. 11/30 have evidence of IGT on testing with a 1.75g/m/kg (max 75g) OGTT, with 2 hour BG 9.65mmol/L [8.51, 10.82]. This represented an older age group, 14.5 compared to 11.8 years (p=0.047), but there was no significant difference in FBG 4.7 vs 4.6mmol/L (p=0.64) or HbA1C 5.7 vs 5.54% (p=0.31). Blood glucose at 2 hours after LactucaX® load was significantly higher, 9.85 vs 5.95 mmol/L (p=0.0001). Overall there was no influence of enteral feeding or liver disease, but there is a high probability of Type 2 error. Conclusions: In this small initial cohort of children, 37% have evidence of impaired glucose tolerance on OGTT, whilst only 3/11 had a HbA1C in the IGT range (6.1-7%). All patients with IGT had FBG <7.0mmol/L, including the 1 patient with an OGTT result in the CFRDM range (14.4mmol/L). Further evaluation is required of the true incidence of IGT in this population, due to uncertainty regarding influence on morbidity and progression to symptomatic CFRDM.

High Dose Intravenous Tobramycin Determined by Area Under the Curve is Well Tolerated in Cystic Fibrosis

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Background: Traditionally, tobramycin is administered at 5-7 mg/kg/24hrs to treat bronchiectasis in cystic fibrosis (CF) and monitored by trough/peak concentrations. However, patients with CF exhibit unique pharmacokinetics including increased volume of distribution and clearance, which limit the validity of conventional drug monitoring. Aims: to 1) establish effective doses of tobramycin in CF patients using the Area Under the Curve (AUC) method; 2) document safety by audiometry, urine examination and serum creatinine; and 3) examine determinants of dose requirements. Methods: Tobramycin was commenced at 10 mg/kg/24hrs and adjusted according to AUC 86-101 mg/l.hrs (Br.J.Clin.Pharmac. 1995;39: 605-609). Clinical (FEV1,FVC, heart rate, respiratory rate and oxygen saturation), inflammatory (neutrophils, platelet count, CRP, ESR), nutritional (weight, protein, albumin), audiometric and renal parameters were measured at baseline and day 10. Results: 15 patients (4 male) in 21 episodes of care, mean age 24 median 23 (SD 5.53) with mean FEV1 % predicted 43.3 median 35.19 (SD 21.47) at day 1 tolerated an average dose of 8.99 mg/kg median 9.14 (SD 1.76) without any recorded renal or ototoxicity. Patients achieved mean FEV1% predicted of 55.59 median 52.79 (SD 23.44) at day 10. By univariate analysis body mass index (BMI) p=0.0005, serum creatinine p=0.0004, FEV1% predicted day 1 p=0.01 and age p=0.02 explained 48%, 48%, 26% and 20% of the variability in dose requirements respectively. By multiple adjusted R-squared regression, 60% of dose variability explained by age, BMI and serum creatinine. Conclusion: Doses determined by AUC methods are higher, tolerated without increased toxicity and possibly superior to standard regimens. Determinants of dose include age, BMI, severity of lung disease and renal function.
THEORIES FOR MEDIATING AND NEGOTIATING AN IN-PATIENT STAY FOR FAMILIES AND PATIENTS WITH CYSTIC FIBROSIS
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Cystic Fibrosis is a life threatening chronic illness requiring many inpatient admissions for treatment. Reviews of the literature and discussions with staff and families reveal a complex array of difficulties associated with the long-term psychosocial management of a chronic illness. Families often bring unresolved issues from past admissions, which may be conflicting in regard to the general management of the illness while in hospital. Staff also speak of a loss of professional role when working with families that are seen to be ‘difficult’. A level of stalemate therefore often develops with both families and staff unsure about how they could work more effectively together. Systems theory, feminist and psychodynamic theory can be used to identify and analyse areas of conflict, and structure the process of mediation and negotiation between patients and staff. Systems theory examines the relationships between individuals, the way in which they communicate and the meanings that develop out of those interactions, as well as examining the organisation of the family. Feminist theory examines the structural influences on a family living with a chronic illness and Psychodynamic theory examines the intrapsychic processes of the individual such as the unconscious, the impact of past history on behaviour and object relations theory which examines the bond between child and parent. The use of these theories allows for the development of appropriate interventions to produce an effective outcome for all parties to the process. This in turn may assist families to cope with the demands of a chronic illness as well as potentially reducing unplanned patient presentations.

Key words: Cystic Fibrosis, Mediation, Negotiation

CLINICAL DIAGNOSIS OF CYSTIC FIBROSIS IN A SCREENED COMMUNITY: 1989-1998
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Introduction: In Victoria 95% of infants with cystic fibrosis (CF) are diagnosed in the newborn period because of a family history of CF, meconium ileus or newborn screening. Later diagnoses of patients born before screening was introduced or represent cases missed by newborn screening. The aim of this study was to examine the presenting features and genotype of patients diagnosed with CF on clinical grounds since the introduction of newborn screening in Victoria.

Methods: A retrospective review of patients attending the 3 CF centres in Victoria (2 paediatric, 1 adult) who were diagnosed with CF between 1989 –1998 following a referral for sweat testing on the clinical suspicion of CF.

Results: From 1989-1998, 56 patients were diagnosed with CF on clinical grounds, 47 were born before the introduction of newborn screening and 9 after (missed by screening). The principal clinical presentation of the 56 patients (age range 4 months-40 years) were as follows: failure to thrive (FTT)/statorrhea 18 (8 missed by newborn screening), productive cough [haemoptysis] 14, younger sibling with CF 6, rectal prolapse 3, atypical asthma 5, nasal polyposis 2, infertility 2, recurrent pancreatitis 2, lower respiratory tract infection 2 (1 missed by screening), chest pain 1, hepatosplenomegaly 1, appendicitis 1, dehydration 1. The mean age of the 18 patients with FTT/statorrhea was 2.2 (±2sd) years while the mean age of the 14 patients presenting with productive cough was 21 (±8sd) years. Nineteen patients were ASCT+/FS508 (mean age at diagnosis 3.5±3.1 (sd) years), 24 ASCT/-/FS508 other (mean age at diagnosis 12.1±14.8 (sd) years), 4 no genotype available.

Conclusions: Younger patients are more likely to present with FTT/statorrhea and following the introduction of newborn screening for CF there may be a lag period of 3-4 years when patients present. Later presentations are more likely to be due to respiratory complications but the range of clinical presentations is broad. Despite the presence of newborn screening for CF a sweat test should be performed if there is clinical suspicion of the diagnosis.

NEWBORN SCREENING FOR CYSTIC FIBROSIS IN VICTORIA: 1989-1998
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Background: Newborn screening for cystic fibrosis (CF) was introduced in Victoria in 1989. The primary screen is immunoreactive trypsinogen (IRT) measured from heel prick blood taken on day 4 of life. Babies with an elevated (>99th centile) IRT had either a second IRT measured at 4-6 weeks (1989-1990) or mutation analysis for ASCT/FS508 (1991-1998). Babies with an elevated second IRT or with one or two copies of ASCT/FS508 were referred for a sweat test to confirm the diagnosis of CF. The aim of this study was to review newborn screening for CF in Victoria over the first ten years of the programme (1989-1998) and examine the reasons for missed cases.

Method: We retrospectively reviewed the records of the Victorian Newborn Screening Service from January 1989 to December 1998 to ascertain infants identified by newborn screening with CF. We also reviewed the CF clinic lists of the two tertiary referral paediatric facilities in Victoria to determine if any children born in the years 1989-1998 had been diagnosed outside the newborn period.

Results: From 1989-1998 650 070 babies were screened for CF, 221 were diagnosed with CF (incidence 1/2942, 95% CI 1/3333, 1/2631), including 30 footseats detected antenatally. Of the 191 CF babies: 136 were detected by screening, 35 had meconium ileus (MI), 11 were siblings of older children with CF and 9 babies were missed by screening. The total number of babies detected early (screening, MI, siblings) was 182 which represents 95.3% of the screened cohort. Of the 9 babies missed by screening, 4 did not have an elevated neonatal IRT, 1 had a repeat IRT at 4-6 weeks which was not elevated (1989-1990), 3 did not have a ASCT/FS508 mutation (1991-1998) and 1 had a negative sweat test (CI 36 mmol/L). 7 of the 9 (77%) missed babies were diagnosed within 4 months of birth.

Conclusion: Newborn screening for CF in Victoria has proven effective in detecting most babies with CF in the newborn period. Despite this a sweat test should be requested when clinical features suggest the diagnosis of CF, even if the child has been screened.

SODIUM ABSORPTION ACROSS THE HUMAN AIRWAY IS DECREASED BY ELEVATED SURFACE CHLORIDE
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We have previously demonstrated that the human airway responds to addition of hypertonic saline to the airway surface liquid (ASL) with a decrease in potential difference (PD). This response was rapid, reversible and blocked by amiloride pretreatment, suggesting that the additional saline decreased Na+ absorption. To further investigate this response, we have separated the responses to increased Na+, increased Cl− and increased osmorality.

Methods: The effect of topical application of various hypertonic solutions on the nasal PD was measured in 8 normal volunteers (Eur Respir J 1994; 7: 2050-2056). Addition of (500 mM) sodium gluconate, (500 mM) N-methyl-D-glucamine (NMDG)-Cl and (1 M) mannitol to the diluent (Krebs HEPES) were tested on separate days.

Results: Addition of NMDG-Cl decreased PD from a mean (SEM) of -15.3 (1.9) to -4.0 (1.0) mV, similar to the response to saline -13.7 (1.7) to -5.1 (1.3) mV. In contrast, addition of mannitol or sodium gluconate resulted in small increases (more negative) in PD of 1.4 (0.8) and 2.7 (0.9) mV respectively (both p<0.05 vs saline).

Discussion: This suggests that the response to hypertonic saline is mediated by the altered Cl− ion concentration, not changes in osmorality nor Na+ ions. As the response to saline is blocked by amiloride pre-treatment, we hypothesise that the airway epithelium can respond to an increase in the ASL Cl− concentration by reflexly decreasing Na+ absorption.

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AIRWAY GENE TRANSFER IN-VIVO: IMPROVED VIRAL VECTOR TRANSDUCTION AND INCREASED PARTICLE DEPOSITION INTO AIRWAY EPITHELIUM WITH SIMULTANEOUS LPC TREATMENT.

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A primary limitation to effective airway gene therapy for cystic fibrosis (CF) lung disease is poor gene transfer efficiency. LPC (lyso-phosphatidylcholine) pretreatment substantially improves adenoviral gene transfer into mouse nasal airway in-vivo. This study assessed the efficacy of coformulations of LPC with vector, and began examination of mechanisms underlying the improvements in gene transfer efficiency. Methods: Reporter gene (AdLaC2) transfer in nasal airways was examined in standard sections after 2 days (XGal processing). A surrogate vector particle - 100nm dia fluorescent beads - was used to estimate vector particle deposition (semi-quantitative scale) onto a defined portion of ciliated nasal septum 30 mins after particle instillation.

Results: Vector coformulated with 0.01% LPC produced enhanced gene transfer (255.8 (82 SEM) transduced cells, n=5) similar to that observed after pretreatment with LPC (280.3 (34 cells, n=8; p=0.08, t-test). Various control-group instillations (no LPC / irrelevant vector / no vector) produced little gene transfer (range 0-50 cells). Compared to coformulation with PBS, LPC coformulation significantly increased fluorescent particle deposition onto epithelial cell surfaces (p<0.03, Mann-Whitney). Discussion: Preservation of enhanced in-vivo gene transfer when using coformulations of LPC and viral vector indicates LPC does not diminish vector viability, nor does it substantially degrade gene transfer enhancement in-vivo. Increased deposition of LPC-coformulated particles suggests one mechanism is improved vector particle delivery to cells, and we speculate this may be due to solubilisation of airway fluid/mucus, altered receptor access, and direct effects of LPC on other cell functions. Our findings suggest deposition and retention of particles onto respiratory cell surfaces can be modulated by exogenous LPC. Supported by USA CF Foundation & WCH Research Foundation

Key words: Gene transfer, adenovirus, nasal airway, particle deposition.

SPUTUM CONTENT OF IRON AND FERRITIN DURING ACUTE EXACERBATIONS IN PATIENTS WITH CYSTIC FIBROSIS.

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Introduction: Colonization of the cystic fibrosis (CF) airway by Pseudomonas aeruginosa (PA) stimulates the migration into the airway of activated polymorphonuclear neutrophils (PMN) which generate proteases and reactive oxygen species (ROS) which cause cell damage and ultimately lung destruction. Hypothesis: Iron may be part of the patho-immunological processes in CF because of its ability to both facilitate PA replication and catalyse the formation of toxic hydroxyl radicles. Methods: We determined the levels of total iron and ferritin within sputum from 21 CF patients admitted to our institution with an infective exacerbation of their bronchiectasis. We also assessed the sputum concentration of albumin as a marker of vascular leakage. Results: Sputum total iron and ferritin concentrations exceeded those found in normal serum (Table) and significantly correlated with sputum albumin levels (r=0.5, n=6, p<0.05, respectively). There were significant negative correlations between sputum total iron, ferritin and albumin concentrations and FEV1 (r=0.5, n=6, r=0.5, respectively, p<0.05) and FVC (r=0.8, n=6, r=0.8, p<0.05).

|                | Iron (μmol/L) | Ferritin (ng/mL) | Micro-albumin (mg/L) |
|----------------|--------------|------------------|----------------------|
| Plasma (NR)    | (13-32)      | (15-300)         | N/A                  |
| CF sputum      | 66           | 3801             | 633                  |
| (13-220)       | (525-23,560) | (168-2060)       |                      |

NR - normal range, data are expressed as median and (ranges).

Discussion: The increased extracellular concentrations of total iron and ferritin in CF sputum demonstrated in this study may facilitate PA colonisation and promote ROS generation thus perpetuating airway damage. Increased sputum albumin concentrations may represent a micro-vascular leak syndrome which contributes to the presence of iron and ferritin within the airway although their very high levels suggest that local production or release of tissue stores may be primarily responsible.

AMINOGLYCOSIDES IN CYSTIC FIBROSIS: A DESCRIPTIVE STUDY OF CURRENT PRACTICE IN AUSTRALIA

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Objective- To determine the diversity of clinical practice with respect to aminoglycosides in Cystic Fibrosis Units within Australia.

Method- In April 1999, a questionnaire was sent to 30 Cystic Fibrosis Units across Australia on the use of Aminoglycosides. Information was collected about drug selection, dosing, monitoring and toxicity with the intravenous and nebulised routes of administration.

Results- Completed surveys were received from 26 of the 30 units (response rate =86%) (100% of units with > 40 patients). There was a wide range of responses received to every question, suggesting that practices vary considerably throughout Australia. Tobramycin was the drug of choice in all but two centres where there was equivalent use of Gentamicin and Tobramycin. The survey demonstrated a trend in recent years to reduce the number of doses per day with 54% of centres prescribing daily doses for inpatients. Methods of intravenous infusion varied widely, depending on dose, the setting (home or hospital) and venous access device. There was considerable variation in the protocols used for serum level monitoring. Forty percent of centres had computer programs to assist in dose adjustments. In the setting of nebulised antibiotics, Tobramycin was prescribed more often than Colistin; although again there was a wide range of practices evident.

Conclusion- The prescribing, dosing, and monitoring of aminoglycosides in Cystic Fibrosis across Australia varies greatly. This may be due to a lack of definitive evidence as to the optimum use of these drugs.

Key words: aminoglycosides, cystic fibrosis, survey, diversity.

AIRWAY RESPONSIVENESS (AR) TO MANNITOL & 4.5% NaCl AEROSOLS IN SUBJECTS WITH CYSTIC FIBROSIS (CF)

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Mannitol dry aerosol challenge is used to assess airway responsiveness (AR) in asthmatics. It has not been used to assess AR in CF. Aim: To measure and compare AR to mannitol & 4.5% NaCl in CF subjects. Methods: 12 CF subjects (5F/19-33yr), inhaled 4.5%NaCl, generated by DeVilbiss™ ultra-neb, for 0.5, 1.2, 4.8, 8.8 & 16ml min or part thereof, and on a separate day inhaled mannitol(1) from capsules, 4.9ml in 0.5, 10, 20, 40, 60, 10, 160, 160mg doses via a Dinkihar™ or Inhalator™. FEV1 was measured 1min after each dose and salbutamol inhaled after challenge. 8 subjects repeated mannitol(2) challenge. Analysis: Mean FEV1(%,predicted)(SEM) was measured before challenge (Pre), during challenge (Lowest), and final challenge(Final) after salbutamol (postBD). The cumulative dose of salmine(mg) & mannitol(mg) was calculated at the lowest and final FEV1. Significance within and between challenges was tested using repeated ANOVA (p<0.05) and t-test with Bonferroni adjustment(p<0.01). Results: The airway response to 4.5%NaCl was different to mannitol(p=0.028; n=12). Transient AR occurred during 4.5% NaCl challenge. Lowest FEV1(Final FEV1; Dose lowest<Dose final) compared to sustained AR during mannitol challenge (Lowest FEV1=Final FEV1; Dose lowest=Dose final). The mannitol airway response was repeatable (p=0.736; n=6).

|                | Pre | Lowest | Final | Post BD | Dose lowest | Dose final |
|----------------|-----|--------|-------|---------|-------------|------------|
| 4.5%NaCl n=12  | 71±4.3 | 60±4.16 | 66±5.1 | 77±4.4 | 11±3 | 27±3 | 18±4 | 27±3 | 18±4 |
| Mannitol(n=12) | 71±4.6 | 62±3.9 | 63±4.0 | 70±3.9 | 495±50 | 575±30 | 575±30 | 575±30 |

# Lowest vs lowest p<0.001; Lowest vs final p=0.007; *Final vs post BD p=0.01; Lowest vs final p=0.001

Conclusion: Airway challenges of mannitol dry powder may be better than wet aerosol of 4.5%NaCl because it sustains an osmotic gradient longer.

Key words: Mannitol, Cystic fibrosis, airway hyperresponsiveness

Nominations for awards: Nil

(1) Supported by The Prince Charles Hospital Foundation
β-ADRENERGIC AGONISTS DO NOT IMPROVE EXERCISE CAPACITY IN CYSTIC FIBROSIS

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β-Adrenergic agonists are widely prescribed in patients with cystic fibrosis (CF). The physiologic rationale for their use includes a high incidence of acute bronchodilator reversibility (up to 85% of patients), improved mucus quality and transport potential. However, there is a paucity of data assessing functional or clinically relevant outcomes, and β-agonists may induce adverse effects.

RESULTS: In this single-center study, 38 unselected patients (24 females) aged 5-17 were studied. Baseline (mean ± SD) FEV1 was 115 ± 15% of predicted and body mass index was 19.5 ± 2.6 kg/m². Twenty-two of these patients (59%) had a significant improvement in FEV1, whereas 16 (41%) had no change or deterioration of FEV1. The mean (± SD) change in FEV1 was 17.3 (± 16.3) ml/min.

CONCLUSIONS: In this group of adult cystic fibrosis patients, inhaled β-adrenergic agonists did not result in improved exercise capacity, despite a significant bronchodilatation effect. These preliminary results do not provide support for the widespread use of β-Adrenergic agonists in adults with CF.

Key words: cystic fibrosis, bronchodilator, β-adrenergic agonists, exercise.

CLINICAL OUTCOME IN PATIENTS WITH CYSTIC FIBROSIS COLONISED WITH BURKHOLDERIA CEPACIA WITH REFERENCE TO SPECIFIC GENOMOVARs.

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The presence of colonisation with Burkholderia cepacia (B. cepacia) complex in patients with cystic fibrosis (CF) has been reported to be associated with adverse outcomes. Alims: To determine the etiologic survival, morbidity and post-transplantation prognosis with patients with CF colonised with B. cepacia, with reference to the specific genomovar and strain. To evaluate the effectiveness of the centre's segregation policy.

Methods: Retrospective review of spirometric, epidemiological and microbiological data on all patients whose primary CF care was obtained from an adult CF centre and who had a diagnosis of CF-colonised with B. cepacia colonised subject three age and gender matched case control subjects were randomly allocated. Phenotype and genomovar typing, random amplified polymorphic DNA (RAPD) strain type and B. cepacia epidemiic strain marker (BCESM) analyses were performed. The influence of transplantation on transplant-free survival was estimated by Cox's proportional hazards regression using the entire clinic population. Results: Fifteen patients were colonised with B. cepacia of which 6 (15%) had died in CF-related death. The mean (± SD) age of death was 30.9 ± 3 years.

Baseline (mean ± SD) FEV1 was 71 ± 15.3% of predicted and body mass index 21.8 ± 2.5. Lung function at the completion of exercise in the salbutamol arm 1185.2 ± 280.7 kpm vs 1209 ± 272.4, p=0.2). There was a significant bronchodilation effect. These preliminary results do not provide support for the widespread use of β-Adrenergic agonists in adults with CF.

Key words: cystic fibrosis, bronchodilator, β-adrenergic agonists, exercise.

THE INFLUENCE OF ENTERAL NUTRITION ON FEV1 AND BODY MASS INDEX (BMI) IN ADVANCED CYSTIC FIBROSIS

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Retrospective reviews of outcome in the management of adult cystic fibrosis have attempted to link nutritional status with respiratory function. Interventional studies have not yet demonstrated a causal link between improved nutritional indices and lung function. We reviewed the association between FEV1 and BMI in 330 patients with CF over 20 years. In addition we examined intervention with PEG feeding on BMI and lung function in n=32 adult CF patients with advanced disease between 1990 and 1999. Medical histories were reviewed to assess pancreatic status, height, genotype and CF related co-morbidities. Weight and FEV1, history from 400 days prior to gastrostomy insertion were reviewed. Data analysis from the year preceding PEG compared with the first year after commencing PEG, showed an improvement in change in percent predicted FEV1, and body mass index (BMI), p<0.001. The rate of decline of FEV1, one year prior to commencement of PEG feeding was 5.69% pred/year, and one year after was 0.34% pred/year. Mean BMI improved from 18.2 kg/m², to 19.2 kg/m² (p<0.001). The median weight gain was 5.9kg. PEG feeding significantly reduced the rate of fall of FEV1, in those with baseline BMI < 18 (p<0.002) and FEV1 <30 predicted (p<0.001). PEG feeding has been successful in improving BMI and FEV1, without causing significant adverse effects.

This study was supported by Solvay Pharmaceuticals and The Victorian Dept. of Human Services.

AZITHROMYCIN (AZM) REDUCES TNF-α RELEASE FROM LIPOPOLYSACCHARIDE (LPS)-STIMULATED MONONUCLEAR CELLS (PBMC) IN CYSTIC FIBROSIS (CF).

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Use of erythromycin (ERY) for treatment of diffuse pan-bronchiolitis (DPB) follows convincing clinical trials and in vitro evidence of immunomodulatory properties of macrolide antibiotics. We examined at low dose forer periods. CF shares many similarities with DPB. AZM is a macrolide antibiotic better tolerated than ERY and is a candidate for long-term oral therapy in CF. We examined the effect of AZM on TNF-α production by LPS-stimulated PBMC collected from 10 healthy individuals. The presence of AZM was associated with a 20% decrease in TNF-α production, compared with 49/173 (28.3%) of those colonised with B cepacia compared with 49/173 (28.3%) of the clinic population had either been transplanted or died. Cepacia status had a significant adverse effect on survival with a hazard ratio of 2.16 (95% CI 1.0 to 4.5, p=0.03). When those colonised with B cepacia were stratified according to genomovor and strain type: genomovor II was associated with 1/2 (50%) death, genomovor III RPAD 40, 3/3 (100%) deaths, genomovor III RPAD 10, 1/5 (20%) death. The remaining 5 subjects were found to be genomovor III with heterogeneous strains of which 1/5 (20%) died and two had lung transplantation and survived. Based on genomovor and strain types there has been no hospital transmission of B cepacia. Discussion. Colonisation with B cepacia had a significant adverse effect on survival within this study population. Genomovor and strain typing has been used to determine that segregation policy in place has been effective in preventing cross-colonisation.

There were trends towards lower pulmonary function and the data suggest prognostics are not uniform amongst specific genomovars and strains.

Supported by the NH&MRC and CHATA. Nomination for awards: Nil.

Key words: Cystic Fibrosis, B cepacia, survival

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Supported by the NH&MRC and CHATA. Nomination for awards: Nil.

Key words: Cystic Fibrosis, B cepacia, survival
NEBULISED HEPARIN IN CYSTIC FIBROSIS
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Heparin is a glycosaminoglycan found naturally in mast cells and is rapidly inactivated by macrophages in the circulation. As an immunomodulatory agent, heparin reduces the acute cutaneous reaction to allergens and inhibits bronchospasm in asthma. We studied the effect of this potentially useful therapy on pulmonary inflammation in CF.

Methods: 4 adult CF patients (2 male, mean age 23 (18-25)) chronically colonised by Pseudomonas aeruginosa with stable disease and no history of past severe, or recent haemoptysis inhaled heparin 1000 units/kg/day as a single nebulised dose for 10 days. Lung function and sputum samples were assessed at baseline and after the first dose, then again on Day 5 and 10 of therapy. APTT levels were performed on Day 5 and 10. IL-8 in sputum supernatant was measured by ELISA. T-tests compared FEV1, FVC and IL-8 levels in sputum.

Results: One patient had mild haemoptysis on Day 7 and ceased treatment. APTT remained within the normal range in all patients. There was no significant change in FEV1 or FVC (p% predicted) between baseline and all subsequent measurements (p>0.2). IL-8 levels in sputum were extremely high (maximum 200ng/ml). There was wide intra-individual variation in IL-8 levels detected in sputum samples. No significant difference in IL-8 levels was demonstrated during or after heparin therapy (p>0.18).

Conclusion: in this pilot group, short-term (10 days) nebulsed heparin therapy was well tolerated but was not associated with any detectable improvement in lung function or reduction in IL-8 in sputum.

Key words: cystic fibrosis, heparin, IL-8

ENDOBRONCHIAL TECHNIQUES IN MALIGNANT MAIN AIRWAY OBSTRUCTION
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Introduction: A variety of bronchoscopic techniques is available at our institution for the palliation of inoperable locally advanced airway malignancy or to improve survival in lung carcinoma in situ. This study is a review of the use of Nd:YAG laser ablation and airway stents in such patients. It aims to establish their efficacy at our institution compared to other previously reported series. Method: We retrospectively reviewed the records of 36 patients treated for progressive airway malignancy (26 primary lung) with Nd:YAG laser ablation (n=34) and/or stent insertion (n=16). 33 patients had advanced inoperable tumours and 3 had lung carcinoma in situ. Results: Successful palliation was achieved following 93% of Nd:YAG laser ablations and 81% of stent insertions. At 6 months symptomatic benefit was maintained in 45% post stent and 29% post laser. For all procedures, patients with primary bronchogenic carcinoma achieved a shorter duration of benefit. In this group radiotherapy post procedure was effective with 47% maintaining local control at 4 months compared with 26% without adjuvant radiotherapy. 24 patients died during follow up, 13 from progressive airway obstruction, 8 from generalised disease and 2 from immediate procedure related complication. In patients with lung cancer, the presence of stage 4 disease pre procedure adversely affected survival. Kaplan-Meier survival curves will be presented for censoring. Conclusion: Nd:YAG laser therapy and airway stents are both effective, safe procedures for the palliation of symptomatic malignant airway obstruction as previously reported in larger patient series. Adjuvant radiotherapy was demonstrated to be beneficial. Selection of appropriate lung cancer patients should favour those without distant metastases. There is probably also a survival benefit although a prospective, randomised clinical study would be required to further evaluate this.

Key words: Nd:YAG laser, airway stent, malignancy

LUNG CANCER AND ASBESTOS EXPOSURE IN VICTORIA - PRELIMINARY RESULTS
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Background: Lung cancer is a common malignancy in Australia. Whilst cigarette smoking is regarded as being the causative factor in most patients it is also true that most are not subjected to a detailed comprehensive occupational history. Aim: The aim of this study is to determine the incidence of asbestos in patients presenting with lung cancer. Method: All patients presenting with histologically proven lung cancer to the Depts of Respiratory Medicine, Cardio-Thoracic Surgery and General Medicine at St Vincent's Hospital were identified at presentation. Detailed occupational and smoking histories were taken. Demographic data (age, sex, ethnic background) was recorded. Matched control patients without lung cancer but suffering from other respiratory conditions were similarly interviewed. The data collected were stored and analysed using the Microsoft Access Database. Results: The results of the first 24 matched pairs enrolled in this study are presented. There were 4 female and 20 male pairs with a mean age 58.9yrs (range 52-69yrs) and 69.5yrs (range 53-83yrs) respectively. Mean smoking history was respectively 55.8 and 57.9 pk yrs in the controls and lung cancer patients. Seven lung cancer patients and 10 controls had had asbestos exposure (no significant difference). Conclusions: The results of the analysis of the first 24 patient pairs enrolled in this study indicate that there is no excess exposure to asbestos in lung cancer patients compared with controls.

THE IMPACT OF PET SCANNING ON SURGERY FOR LUNG CANCER
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Positron emission tomography (PET) has been available since 1992. While it was initially introduced for evaluation of cardiac and neurological disorders it has since been found to be most useful in the detection and evaluation of cancer. A review of its efficacy in lung cancer using F-18 fluoro-deoxyglucose (FDG) as a marker has shown it to be of particular value in the following situations:

1. Evaluation of N0 disease. An analysis of 70 patients with N0 non small cell lung cancer (NSCLC) showed PET scanning was more reliable than CT scanning and in particular a negative PET scan was highly specific.
2. Evaluation of adrenal masses in patients with lung cancer. A study of 10 patients showed a 90% accuracy for PET scanning.
3. Evaluation of response to Neo-adjuvant chemotherapy for lung cancer. A study of 20 patients has shown that generally the PET changes are more dramatic than the CT changes.
4. Evaluation of non-calci¢ed lung nodules. In Australia 60% of such nodules are malignant. Even wedge resection can be hazardous in patients with poor pulmonary function or significant co-morbidity and in these patients "cold" nodules can be safely watched.
5. Whole body PET scans in patients with secondary lesions in the lung has confirmed whether or not the primary lesion is well controlled and has been able to show other occult metastases.
6. PET has proven the most useful modality when local recurrence is suspected but chest X-ray and CT are difficult to interpret because of fibrosis.

We conclude that the routine use of PET scanning in patients with lung cancer has reduced the need for mediastinoscopy and needling of adrenal masses and gives confidence in decision making when dealing with solitary non-calci¢ed nodules and secondary tumours in the lung. It shows promise in the evaluation of the response to Neo-adjuvant chemotherapy and is the investigation of choice when local recurrence is suspected but unproven.

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PET Scanning, Lung Cancer, Surgery
CHARACTERISTICS OF PATIENTS WITH LUNG CANCER UNDER THE AGE OF 45

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Introduction: Lung cancer represents 12% of all cancers registered in New Zealand and 20% of all cancer deaths. The incidence of lung cancer, like other cancers, parallels the rate of cigarette smoking and is increasing. Smoking rates among teenagers are increasing raising concerns that this may result in increased rates of lung cancer in young people. The aims of this study was to determine the characteristics of young (<45yr) patients with lung cancer.

Methods: A case control study was undertaken. Cases were patients aged <45 diagnosed with primary lung cancer at Green Lane Hospital between 1993 and 1998. Controls were chosen by matching for the date of the diagnostic procedure. Clinical and pathological data were obtained retrospectively from clinical notes.

Results: 48 patients (<45yrs) were diagnosed as having lung cancer. These were matched with 123 control subjects (<45yrs). The mean age was 38 compared to 67 in the control group (p<0.01). There were 67% females versus 32% in the control group. Adenocarcinoma was the predominant type (48% v 27%) whereas squamous cell carcinoma was less common (17% v 35% (p<0.001). The majority of cases were current or ex-smokers (80%) compared with 95% of control. Mean survival overall was 11.1 versus 8.5 months (p=0.1). There was no difference in tumour stage, family history or ethnicity between the two groups.

Conclusion: These data suggest young (<45 yrs) patients with lung cancer are predominately female and adenocarcinoma is the most common histological diagnosis. Smoking is the likely aetiology but other factors (genetic) may contribute. The data may also suggest that young women may be more susceptible to the carcinogenic effects of cigarette smoke.

PRE-OPERATIVE PREDICTORS OF COMPLICATIONS POST LUNG CANCER (CA) RESECTION: LESSONS FROM LUNG VOLUME REDUCTION SURGERY (LVRS).

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The best pre-operative predictor of postoperative complications following lung resection remains unclear. Results from LVRS suggest that patients with severe emphysema can safely undergo thoracic resection of 'target' areas of lung with poor perfusion suggesting that even patients with severe emphysema and lung CA may be operable. We have elected to perform CA resection on patients with severe emphysema (FEV1 < 35% predicted), who would previously have been deemed inoperable, where it could be combined with unilateral LVRS. Between February and October 1999, surgery was performed on 5 patients with lung CA, an FEV1 < 35% predicted and appropriate 'target' areas of poor perfusion. Pre-operative and perioperative data are shown.

| FEV1* | DLCO* | VO2 max* | operation | Implant days |
|-------|-------|----------|-----------|-------------|
| 1 27 31 54 | (R) upper lobectomy | 24 |
| 2 25 40 51 | Wedge resection | 21 |
| 3 29 35 49 | (R) upper lobectomy | 17 |
| 4 32 30 60 | (R) upper + middle lobectomy | 36 |
| 5 23 37 47 | Wedge resection | 27 |

* % predicted.

Median (range) improvement in FEV1 was 24% (-3, 46; p = 0.23). There have been no deaths and none of the patients has required long-term oxygen. Two patients had prolonged (> 21 days) air leak and two required postoperative intravenous antibiotics. There were no episodes of reintubation and all patients were discharged from the intensive care unit within 48 hours. We conclude that the applicability of previously established risk factors for lung resection may need to be reassessed.

ABERRANT GENE PROMOTER METHYLATION IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Aberrant methylation of CpG islands in the promoter region of genes is a tumour acquired mechanism for inactivating the function of tumour suppressor genes. Aim: To determine the frequency of gene promoter methylation of the following genes: p16, C6-methylguanine-DNA-N-methyltransferase (MGMT), death-associated protein kinase (DAPK), E-cadherin (ECAD), and glutathione S-transferase P1 (GSTP1). Methods: DNA was obtained from 107 resected NSCLC and corresponding normal lung tissue. After bisulphite modification, unique PCR primers allowed the detection of methylated DNA sequences from unmethylated sequences. Results: Aberrant promoter methylation was identified in 25% for p16, 18% for ECAD, 19% for DAPK, 6% for GSTP1, and 20% for MGMT, whereas it was not seen (or only at very weak levels in the corresponding normal tissues). At least one of these five genes were aberrantly methylated in 62% of resected NSCLC. As expected, aberrant methylation of p16 corresponded with p16 down-regulation, as detected immunohistochemically. Correlations for various aberrant methylation changes include other genetic changes, disease stage and survival. Conclusions: This study confirms that a large proportion of NSCLCs are characterised by aberrant promoter methylation in the five genes tested. As other genes are known to be aberrantly methylated in other human cancers, it is likely that more genes will be identified to be aberrantly methylated in lung cancer. If so, not only will methylation studies contribute to knowledge of the pathogenesis of lung cancer, but may also provide an early detection strategy as others have found that aberrant methylation can also be detected in the peripheral blood of lung cancer patients.

Supported by:

Key words: lung cancer, molecular, promoter methylation, tumour suppressor genes

A COMBINED DIAGNOSTIC AND PLEURODESIS ROLE OF MEDICAL THORACOSCOPY USING FROZEN SECTION

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Background and Aims: Medical thoracoscopy has high diagnostic efficacy in pleural effusions and the potential to perform pleurodesis in the same procedure, thereby reducing the number of patient interventions. Because pleurodesis should be proceeded by tissue diagnosis, we investigated the role of frozen section at the time of thoracoscopy to determine if this could allow more combined procedures.

Methods: Prospective evaluation of 11 patients with undiagnosed symptomatic pleural effusions. All underwent medical thoracoscopy under local anaesthesia and conscious sedation in the bronchoscopy suite. Biopsies for frozen section and conventional histology were submitted at thoracoscopy. In addition, closed pleural biopsies (CPB) were taken through the entrance port before proceeding to compare diagnostic sensitivity.

Results: 11 patients had final diagnoses of 1) 6 benign and 2) 5 malignant (4 mesothelioma and 1 pleural synovial sarcoma). Frozen section concurred with the final histopathological diagnosis in 10/11 subjects, with 1 mesothelioma associated with extensive adipose tissue not detected. The diagnostic sensitivity for malignancy at thoracoscopy was 100%; the 6 benign cases have shown no evidence of disease progression or recurrence (mean follow up 4 months). In 7/11 subjects CPB results were consistent with thoracoscopic biopsies, with a sensitivity of only 40% for malignancy. One benign case along with all malignancies were pleurodesed with good radiological outcome. One patient with mesothelioma has a chronic pleurocutaneous fistula at the intercostal catheter site undergoing slow resolution. The patient with mesothelioma and negative frozen section was pleurodesed at a second thoracoscopy three weeks later. Conclusions: Medical thoracoscopy is the preferred intervention in pleural effusions in which the aetiology remains undetermined after simple thoracentesis. Frozen section analysis during the procedure facilitates the possibility of doing combined procedures.
AUDIT OF CLOSED PLEURAL BIOPSY LEADING TO AN ALGORITHM FOR THE MANAGEMENT OF PLEURAL EFFUSIONS USING MEDICAL THORACOSCOPY

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Background: An efficient diagnostic approach to exudative pleural effusions after an initial negative thoracentesis remains controversial. We conducted a retrospective review of patient records at the Princess Alexandra Hospital from 1994-99: 104 subjects who had undergone closed pleural biopsy (CPB) with thoracentesis for pleural effusion. Aims: 1) audit CPB with respect to diagnostic sensitivity and procedural aspects 2) consider the role of CPB in the diagnosis and management of pleural effusion. Results: Of 104 patients, 51 had final diagnoses of malignancy, 44 benign and 9 no final diagnosis. Adequate pleur was sampled in 82/104 subjects (79%). Only 30/51 (59%) malignancies were detected from the combined procedure of cytology pleural fluid and CPB with 19 requiring thoroscopic or open pleural biopsy (CPB) and 2 bronchoscopy. Sensitivity of CPB/Cytology for mesothelioma was 37% and the negative predictive value of a nonspecific biopsy 59%. In 39% of procedures, no sedation or analgesia was administered and 32% of biopsies specimens were not sent for microscopy. The sensitivity of taking 1 CPB was 0%, 2-4 51% and taking multiple biopsies 57%. Increasing volume of pleural fluid sent for cytological examination correlated with improved diagnostic sensitivity for malignancy. The complication rate was 16%. Conclusions: Procedural – The sensitivity of a single pleural biopsy is low and not improved beyond 2-4 percutaneous samples. There is a greater need for analgesia and sedation during CPB along with a need to send specimens for microscopy and culture. Pleural fluid sent for cytology should be of at least 100 ml volume for improved diagnostic sensitivity. Diagnostic Role – Our reported sensitivity of CPB is similar to previous published studies. Nonspecific biopsy results are common and pose a significant limitation to this technique given the low negative predictive value for malignancy. At our institution this has led to an algorithm including medical thoracoscopy in a combined diagnostic and pleurodesis role.

TRANSFORMING GROWTH FACTOR (TGF)β1 PRODUCES MORE EFFECTIVE AND FASTER PLEURODESIS THAN TALC

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TGFβ1 is a unique cytokine with potent pro-fibrotic and anti-inflammatory properties that make it an attractive agent for pleurodesis. We hypothesised that TGFβ1 can produce pleural fibrosis effectively, quickly and without causing excessive pleural inflammation. Aims: To compare the 1) degree and 2) speed of pleurodesis and 3) histologic changes after intrapleural instillation of TGFβ1 and talc. Methods: 18 rabbits were given either TGFβ1 (1.7μg) or talc slurry (400mg/kg) via a chest tube. 3 rabbits from each group were sacrificed at Days 1, 4 and 7. Pleurodesis was graded macroscopically from 1 (none) to 8 (>50% hemithorax). Histologically, pleural inflammation and fibrosis were graded from 1 to 8 (>50% hemithorax). Inflammation was determined by the presence of significant granulocytes, macrophages and lymphocytes.

Conclusions: TGFβ1 produced pleurodesis more effectively and faster than talc. TGFβ1 induced more collagen deposition and fibrosis without causing more inflammation.

OUTCOME AFTER SURGICAL RESSECTION OF NON-SMALL CELL LUNG CANCER (NSCLC) IN THE ELDERLY. B H Lam*, C Kennedy, L Truong, B G McCaughan, P N Hendel, M J Peters. Concord Repatriation General Hospital, Royal Prince Alfred Hospital and Strathfield Private Hospital, NSW.

Surgical resection offers the only realistic prospect of long-term survival in NSCLC. In NSW, half of all NSCLC is diagnosed in patients over 70. The presence of significant co-morbidity and previously reported high operative risks may dissuade clinicians from considering surgery in older patients. Methods We reviewed data collected prospectively on tumour staging, surgery performed and outcome in patients from CRGH and RPH (1985-98) and SPH (1989-98). All hospitals have in common an 'aggressive' approach to surgery. Mortality included death from any cause and is not age-corrected. Results Data were available on 455 patients. The table summarises results presented by operation and stage. In 18 cases resection was impossible. 30 day mortality was 4.2% (n=19). Common causes of death were cardiac (n=4) or respiratory complications (7) and CVA (5). Mortality after lobectomy fell from 7.1% for 1985-93 to 2.9% for 1994-1998 and was higher with right, 7.5%, than left-sided lobectomy, 1.6% (p<0.02). Conclusions Surgery is the treatment of choice for many elderly patients with NSCLC. Operative risks have fallen and are now lower than frequently reported. Operative risks are highest and outcomes are poor after right pneumonectomy. In this older group, there is no difference in survival between lobectomy and wedge resection.

Key words: Bronchogenic carcinoma, surgery, elderly, survival

GROWTH FACTOR INDUCED EXPRESSION OF METALLOPROTEINASE 2 IN CELLS CULTURED FROM PATIENTS WITH PLEURAL MESOTHELIOMA

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Mesothelioma develops in people exposed to asbestos and is characterised by a spread throughout the pleural space with tissue infiltration. In contrast to other lung carcinomas showing distant organ metastases early in the clinical course mesothelioma develops as a locally very aggressive tumour. Tumour proliferation is influenced by the composition of the extracellular matrix (ECM). ECM is regulated by de novo production, degradation by matrix metalloproteinases (MMP) and the action of the respective inhibitors. Furthermore different growth factors contribute to malignant cell proliferation. To investigate the role of MMPs in tumour progression in mesothelioma we analysed the expression of metalloproteinases. We have shown that the expression of metalloproteinases is upregulated in mesothelioma cells. In conclusion, we have shown that the expression of metalloproteinases is upregulated in mesothelioma cells.

Conclusions: TGFβ1 produces pleurodesis more effectively and faster than talc. TGFβ1 induced more collagen deposition and fibrosis without causing more inflammation.
CT-GUIDED FINE NEEDLE ASPIRATION BIOPSY OF INTRATHORACIC MASSES

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Background: CT has been established as the most accurate method for guiding fine needle aspiration (FNA) biopsies of intrathoracic masses, thereby allowing for cytological delineation of malignant from nonmalignant lesions. In January 1997, a database was established at a tertiary referral hospital specializing in cardiothoracic disorders to assess procedural outcomes and to quantify individual risk. Method: During a 2.5-year period (01.01.1997 – 30.06.1999), 315 FNA biopsies were performed on 312 patients (202 males, 110 females). Biopsies were performed with 3-5 ms of 1-5 mm lignocaine injected into skin. A Greene 19g-biopsy needle was used under CT guidance and samples aspirated via a finer gauge needle passed through the outer needle. Data were recorded at the time of patient referral and procedure and were followed up. Results: The mean age of patients was 65±12.4 yrs (range 19.1 - 89.7 yrs). Forty-nine (16%) patients were aspirin/NSAIDs; 11 (3.5%) on anticoagulants. Diagnostic material was obtained in 72.7% of samples. Lung cancer represented 201 samples (96% NSCLC, 4% SCLC). Other malignancy was diagnosed in 22 (7%) cases. Cellular atypia was noted in 17 (5%) cases. Benign lesions were diagnosed in 6 (2%) cases. Non-specific features characterized 71 (22.5%) samples. Eleven aspirates proved false-ve and 4 false+ve for malignancy. The only complications recorded were pneumothorax in 40% of cases (17 requiring ICC) and haemoptysis in 3 cases. The mean % predicted values for FEV1, VC and KCO did not correlate significantly with risk of pneumothorax. Conclusions: CT-guided FNA biopsy continues to be a reliable method of diagnosing intrathoracic lesions, there being reducing the need for diagnostic thoracotomy. Diagnostic accuracy is high in lung cancer, though negative results do not preclude malignancy. Benign cytology may be of use in a clinical context but is rarely useful in establishing a diagnosis. Pneumothorax, though a frequent complication, is significant in a relatively small number of patients.

Acknowledgments: Dr. G. Gillan

Key words: lung cancer diagnosis; fine-needle aspiration biopsy; pneumothorax

CARCINOMA OF THE BRONCHUS AND HIV INFECTION

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It is well established that lymphomas and cutaneous malignancies, such as Kaposis sarcoma and squamous cell carcinoma, are a common sequela of human immunodeficiency virus (HIV) infection. Carcinoma of the bronchus is less clearly associated with HIV. A review was therefore undertaken of HIV positive patients who presented with a diagnosis of carcinoma of the bronchus, and compared with a group of control patients who were not in a risk group for HIV. Methods: Case notes of all patients coded as both HIV+ve and lung cancer between the period from 1/1/96 to 31/12/98 were reviewed at 2 hospitals which are local centres for HIV care. For each case, 10 controls were matched for sex and compared for age, smoking, histopathology, and survival time. Results: Five patients who were HIV +ve were identified with biopsy proved primary lung cancer. All were male smokers. Median CD4 count was 180, range 120-500,10^6/L. Histopathology: large cell; squamous cell; & 1 adenocarcinoma. Survival time was brief, median 3-6 months, but all received palliative radiotherapy; 2 also required steroids and one required a pulmonary artery stent. Lung cancer was diagnosed at a median age of 49 yrs (range 37-53 yrs), and 2-9 yrs after diagnosis of HIV. Compared to the control group there was a significantly earlier median age of presentation; controls: 71yrs (42-81yrs, p<0.0001 chi squared). Conclusion: Bronchial carcinoma occurs at an earlier age in those with HIV infection, and has a poor prognosis.

Key words: HIV, lung cancer

A CLINICO-PATHOLOGICAL REVIEW OF PRIMARY PULMONARY NON-HODGKINS LYMPHOMA

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Objectives: To evaluate the clinical, radiological and pathological profile of disease in patients with primary pulmonary non-Hodgkins lymphoma in non-immunocompromised patients. Methods: A retrospective review of patients with histologically proven disease, between 1973 and 1999. 22 patients had confirmed lymphoma without extrathoracic involvement. Records were available for 15 patients. Pathology and radiology were reviewed by independent specialists. Two patients with primary pulmonary Hodgkins disease were not included.

Results: Low grade (LG) lymphomas were found in 6 male and 3 female patients (median age 70 years) who presented with cough (67%), dyspnoea (33%), weight loss (22%), B symptoms (11%) and haemoptysis (11%). Mean ESR at presentation 40.3. Imaging demonstrated localised nodules / opacities (89%), adenopathy (22%), pleural effusion (11%) and diffuse infiltrates (11%) without cavitation. Bronchoscopy revealed mucosal involvement in 22%. Monoclonal gammopathy (lgM and lgH) involved the marrow in 22% of patients. Treatment included surgery alone (22%), chemotherapy (44%), and supportive (22%). Survival (1 year) was 75%, and at 3 years 71%. High grade (HG) lymphomas occurred in 7 male and 2 female patients (median age 44 years). There was a higher incidence of weight loss (89%) and B symptoms (56%). Mean ESR at presentation 67.6. Hypercalcaemia was common (67%). The major radiological pattern was nodules (27%) with cavitation in 33%. Additional patterns included plural effusions (33%), diffuse infiltrates (33%) and adenopathy (11%). Mucosal abnormalities on bronchoscopy included extrinsic compression (33%), and a polypoid mass (11%). No marrow abnormalities were detected. Treatment included surgery (11%), adjuvant chemotherapy (22%), or chemotherapy alone (44%). One year survival was 25%.

Conclusions: Patients with HG lymphomas were younger and more symptomatic on presentation. Both groups had predominant nodular patterns on imaging. Poorer outcome was associated with HG tumours, weight loss and B symptoms, elevated ESR and hypercalcaemia, but not serum LDH. LG tumours were more responsive to combined chemotherapy (alone or adjuvant) with better survival outcomes.

Key words: Non-Hodgkins lymphoma, primary lung malignancy, chemotherapy

ADENOVIRAL MEDIATED GENE TRANSFER OF ACHAETA-SCUTE HOMOLOG-1 INDUCES APOPTOSIS IN NON-SMALL-CELL LUNG CANCER (NSCLC)

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Introduction. The achaete-scute complex of basic helix-loop-helix transcription factors determines neural cell fate in Drosophila development. A mammalian achaete-scute homolog (HASH1) is essential for neuroendocrine (NE) cell differentiation in the developing lung. A human ortholog (hASH1) is highly expressed in small cell lung cancer (SCLC) and has been implicated in the pathogenesis of the malignant NE phenotype. Though these findings suggest a role for hASH1 in commitment to NE cell fate in airway development and repair, the effects of hASH1 on cell growth and differentiation in non-NE airway epithelial cells are unknown. Aim. Using a replication deficient adenovirus strategy, we studied the effects of hASH1-overexpression in two classic HASH1 positive SCLC lines (NCI-H209, DMS-1-53), two variant SCLC HASH1 negative lines (NCI-H82, NCI-H417) and two HASH1 negative NSCLC lines (A549, 1775). Methods. Cells were infected with an adenovirus containing hASH1, or control viruses expressing either a hASH1 mutant deficient in the basic DNA binding domain, or beta-galactosidase. Viral dose was normalized for the expression of a green fluorescent protein reporter by FACs analysis. Cells were examined for changes in morphology, growth and nuclear condensation by Hoechst staining. Results. Both control viruses had no effect in all 6 cell lines. Infection with the hASH1 adenovirus induced growth arrest and apoptosis in both NSCLC lines, but induced no change in growth or morphology in the classic and variant NSCLC lines. Conclusion. These data suggest that hASH1 specifically induces apoptosis in NSCLC. This effect is likely to be transcriptionally mediated given the lack of apoptosis induced by the hASH1 mutant lacking DNA binding capability. This unexpected finding suggests an importance to the induction of a NE differentiation program in NSCLC, and implicates specific anti-apoptotic mechanisms in SCLC necessary for the expression of the NE phenotype.
A CASE OF GOOD RESPONSE TO ROXITHROMYCIN FOR DIFFUSE PANBRONCHIOLITIS

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Diffuse panbronchiolitis is a chronic progressive pan-inflammatory condition affecting the respiratory bronchioles. It is most commonly seen in Japanese people and rarely reported outside the Far East. The condition has a poor prognosis due to the inefficiency of corticosteroids although erythromycin has been shown to be effective. Case: We report a case in a Chinese-born man who presented with symptomatic airway obstruction and nodular infiltrate on radiological investigation. Diagnosis was subsequently made on open lung biopsy and he was treated with roxithromycin 300mg daily. Clinically and radiologically he has had a good response after three months therapy. His lung function has improved with FEV1 of 1.2 (pre-diagnosis) to 2.5L, and FVC of 2.7 to 3.7L, with less air-trapping but unchanged indices of diffusion. Conclusion: Roxithromycin has been used successfully in this patient. It should be considered as an alternative therapy to erythromycin. Once daily administration and better tolerance may improve patient compliance.

Key words: diffuse panbronchiolitis, roxithromycin

ASTHMA IN NEW ZEALAND SAWMILL WORKERS

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Exposure to both hard- and softwood dust has been shown to be associated with occupational asthma, chronic airflow obstruction, and respiratory symptoms. We conducted a cross sectional questionnaire study among 772 New Zealand sawmill workers (processing pinus radiata) focussing on respiratory symptoms. Preliminary results showed that asthma prevalence (current asthma medication, or shortness of breath or asthma attack(s) in past 12 months) in sawmill workers with moderate to high exposure to wood dust (based on job title) was significantly higher (19%; n=623) compared to non- or low wood-dust-exposed workers (12%; n=147) (OR=1.8; p<0.05). Non-exposed workers included office workers (n=52), saw doctors (n=27) and various other job titles with an expected low exposure to wood dust (n=68). Twenty two percent of the moderate to high exposure workers reported wheezing, shortness of breath or chest tightness in relation to certain work tasks compared to only 8% among the low or non-exposed workers (OR=3; p<0.001). Also cough and cough with phlegm were reported more frequently (OR=1.8 and 1.7; p<0.05) by the moderate to high exposure workers (34% and 28% versus 22% and 18%, respectively). Significant differences in smoking habits (but not in age and duration of employment) were found between both exposure groups. After adjusting for smoking, odds ratios for asthma and asthma symptoms in relation to work remained the same, whereas odds ratios for cough and cough with phlegm were only marginally decreased (OR=1.7 for both symptoms; p<0.05). In conclusion, preliminary results indicated that exposure to pine wood dust is associated with asthma and other airway symptoms.

Supported by the Health Research Council of New Zealand.

Key words: Occupation, epidemiology, respiratory symptoms, sawmill workers

THE INVESTIGATION OF CRYPTOGENIC FIBROSING ALVEOLITIS (CFA): RESULTS OF THE CFA PRACTICE SURVEY

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CFA is the most common cause of interstitial lung disease. Previous surveys of pulmonary physicians have shown little consistency in the diagnostic procedures used for, or the methods for monitoring progress in, CFA. The development of further diagnostic tools for CFA such as HRCT chest and DTPA scanning are likely to have had an impact on the evaluation of CFA. This prompted us to evaluate the investigation of CFA in Australia and New Zealand. Methods: A questionnaire was designed to explore the patterns of investigation and treatment of CFA using an example case of fibrotic CFA. This was distributed to all identified respiratory physicians in Australia and New Zealand. Results: 168 responses to the questionnaire have been received. When investigating a case of probable CFA, > 90% of respondents would routinely perform CXR, HRCT chest, spirometry and DLCO, while < 10% would routinely perform open lung biopsy (OLB), gallium scan, DTPA scan or measured VO2(max). The investigations considered most important in making a diagnosis of CFA were HRCT chest, DLO and OLB. The investigations considered most useful for monitoring progress of CFA were DLCO, spirometry and static lung volumes. In the example case of fibrotic CFA, 55% of respondents would recommend a biopsy, with 61% of these recommending a thorascopic or open biopsy. Conclusions: HRCT chest is now considered to be a routine part of the investigation of CFA, while the use of routine open biopsy has declined. Although <10% of physicians indicated they routinely perform OLB, 55% indicated they would perform it in a hypothetical case of fibrotic CFA, suggesting a discrepancy between perceived and actual practice.

Key words: Interstitial lung disease, investigation, lung biopsy, questionnaire.

EXHALED NITRIC OXIDE IN INFANTS AND DOMESTIC FORMALDEHYDE EXPOSURE.

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Formaldehyde is an ubiquitous indoor air pollutant. We have previously reported an association between residential formaldehyde concentrations and exhaled nitric oxide levels (eNO) in healthy children. We are currently investigating if a similar association can be demonstrated in infants. Methods: Formaldehyde was monitored in homes using passive sampling devices that were placed in the living room and child's bedroom for at least 3 days. The infants (n=20) made one visit to the Respiratory Medicine Department at Princess Margaret Hospital where they underwent a lung function test using the raised volume-rapid thoracic compression technique. Exhaled air was collected in gas sampling bags during tidal breathing and eNO was measured from the bags using a nitric oxide analyser (Seivers NOA280). Results: There was no effect of formaldehyde levels on lung function, however a significant correlation was found between eNO levels and indoor formaldehyde concentrations (r=0.48, p<0.05). Conclusions: These are preliminary data and the number of subjects is small, however this supports our previous findings that exposure to formaldehyde at levels typically encountered in the home may induce an inflammatory response in the Airways of children.

Supported by the NH&MRC

Key words: Formaldehyde, exhaled nitric oxide, infants

Nominations for awards: nil
MANAGEMENT OF CRYPTOGENIC FIBROSING ALVEOLITIS (CFA) IN AUSTRALIA AND NEW ZEALAND: TREATMENT PATTERNS

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Evidence supporting the use of drugs in the treatment of CFA is limited with no placebo controlled trials being performed. More recently, HRCT has helped stratify patients into those with a poorer prognosis and poorer response to treatment (honeycombing on HRCT vs ground glass changes). However as the prognosis is poor, many physicians feel a need to treat patients with CFA.

Methods: Using a postal questionnaire, respiratory physicians in Australia and New Zealand were asked about treatment of CFA using an example case of fibrotic CFA. The patient was a 65yo man with moderate symptoms for 6 months, exercise limitation to 100m, moderately impaired lung function (50% predicted) and honeycombong on HRCT. Results: 168 responses to the questionnaire have been received. In regard to the sample case, 74% of respondents would recommend treatment following the results of initial investigations, while a further 23% would start treatment if there were a decline in symptoms or lung function. Only 3% would never commence treatment, the reasons being fibrosis on HRCT and lack of evidence for effectiveness of treatment. Of the 163 who would consider treatment, the majority (76%) would use Prednisolone/Prednisone (Pred) alone as initial therapy, 15% Pred/Cyclophosphamide and 8% Pred/Azathioprine. In addition, 3% would use methylprednisolone in the initial phase. If the patient deteriorated, the most common alternatives (>25% of respondents) considered were azathioprine, cyclophosphamide, cyclosporin and colchicine. Conclusions: A pro-active approach to treatment of a hypothetical case of fibrotic CFA is demonstrated in Australia and New Zealand. This may reflect the lack of good evidence supporting or refuting the role of therapy in CFA and a poor prognosis in this disease.

Key words: Cryptogenic fibrosing alveolitis, drug therapy, questionnaire.

MALIGNANT MESOTHELIOMA IN AUSTRALIA (1945-2000)

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Between 1945 and 1980, 658 (535 male, 123 female) cases of malignant mesothelioma were identified in Australia and the condition was regarded as rare. Since 1981 Australia has maintained a complete national register for cases of malignant mesothelioma. This is a specific disease register with histologically confirmed notifications accepted from clinicians and medical records administrators. Cross checks using patient identified data are regularly carried out with all State cancer registries in Australia. Incidence has increased rapidly and is still increasing in both males and females. In 1999 the extrapolated annual incidence rate was 6.6 per 100,000 (male >20/year) (1982-85: 2.7) and 1.6 per 100,000 (female >20/year) (1982-85: 0.325). Therefore, incidence rates are similar to bladder cancer in males and uterine cancer in females. As at 3 December 1999, there were 5806 cases in Australia, almost all of them fatal. Pleural:peritoneal ratio was found to be 18:1 (male), 6:1 (female). Positive asbestos exposure history was obtained in 85% of cases. Mean latency from first exposure was 37 years. Common exposure histories were: repair and maintenance of asbestos materials (13%), shipbuilding (3%), asbestos cement production (4%), railways (3%), power stations (3%), boilermaking (3%), Wittenoom (5%), wharf labour (2%), paracoccidental, hobby, environmental (4%), carpenter (4%), builder (5%), navy (3%), plumber (2%), brake linings (2%), and multiple (12%). The pattern of exposure is shifting away from the older traditional industries towards product, domestic and environmental exposure. The incidence is still increasing and assuming peak amphibole exposure occurred about 1965 and peak chrysotile about 1975, peak incidence is not expected until about 2010. These incidence rates are the highest national rates in the world. The estimated number of cases still to occur in Australia is about 10,000 by 2020.

Key words: Mesotheliomas, incidence, Australia, exposures

CORRECTING FOR HETEROGENEITY USING THE ILO CLASSIFICATION DOES NOT IMPROVE RADIOLOGICAL-PHYSIOTHERAPEUTICAL CORRELATIONS

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The International Labour Organisation classification of radiographs for the pneumoconioses is a validated, economical and clinically & epidemiologically extremely useful tool in assessing for the presence and progression of asbestosis (Hill et al. 1992). The correlation between the ILO classification and functional parameters is however modest. The most densely concentrated zone determines the profusion score without regard for heterogeneity among the 6 radiographic zones thus it may not accurately represent the true disease burden. AIM: To examine the correlations between ILO score for small-opacity profusion and parameters of functional impairment (%predicted FVC, %predicted DLCO and %predicted VO2max) with and without a correction for profusion heterogeneity. METHOD: Two scorers (GBM & AW) independently classified CXRs from 52 patients with asbestosis assigning profusion scores for each separate zone individually. The sum of the six zones’ scores was averaged to provide a “corrected for heterogeneity” ILO score per radiograph. Each radiograph was also scored by conventional ILO criteria. The “corrected” and conventional profusion scores were then tested for correlation against ventilatory function, gas exchange and exercise test results for these 52 subjects. RESULTS:

| R² | ILO profusion | "Corrected" ILO | p* |
|----|---------------|-----------------|----|
| %pred FVC | 0.207 | 0.233 | >0.4 |
| %pred DLCO | 0.412 | 0.437 | >0.4 |
| %pred VO2max | 0.079 | 0.027 | >0.4 |

*Using Fisher's transformation

CONCLUSION: Averaging of profusion scores for the 6 zones on the plain CXR does not improve the modest correlation between radiographs and functional parameters in patients with asbestosis. KEYWORDS: asbestosis, radiology Hill et al, Chest Radiographs in subjects with asbestos-related abnormalities: comparison between ILO categorisations and clinical reading. Am J Ind Med 1992;21(6):855-61.

AMIODARONE LUNG TOXICITY: A CASE SERIES

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Background: Amiodarone toxicity is an unusual cause of diffuse parenchymal lung disease. Case studies: A series of four cases is presented, for which causation was either proven on biopsy or strongly suggested by clinical features. The clinical, radiological and histologic features are described in detail, and for three patients, serial respiratory function testing is reported. In all cases, a mixed alveolar and interstitial infiltrate was present. One case had severe hepatitis, and was also notable for the presence of marked peripheral blood eosinophilia. This patient developed pulmonary fibrosis and still required domiciliary oxygen five months after cessation of amiodarone. The remaining patients had complete resolution of their pulmonary infiltrates, however two had reduced carbon monoxide transfer documented at the end of the follow up period. Three patients were treated with corticosteroids. In the remaining case, corticosteroid therapy was contra-indicated by low grade pulmonary infection and poorly controlled diabetes. This patient, nevertheless, had an excellent outcome. Comment: Amiodarone pulmonary toxicity is a rare event and needs to be considered in all patients treated with this drug. A review of the literature is presented, with recommendations for screening.
ENDOTOXIN AND (1,3)-GLUCAN EXPOSURE IN NEW ZEALAND SAWMILL WORKERS

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Background: Sawmill workers have been shown to have an increased risk of developing occupational asthma and other respiratory symptoms. Exposure to both wood dust and airborne microorganisms, and particularly fungal spores, has been suggested as playing a role in the development of respiratory symptoms among these workers. Few studies, however, have measured microbial exposure levels in sawmills. Methods: The preliminary study reported here assessed airborne levels of wood dust, bacterial endotoxin and (1,3)-glucan in 37 personal exposure samples taken in two New Zealand sawmills. Results: The wood dust levels measured were generally low (GM 0.7, range: 0.1-5.8 mg/m3), with approximately 80% of the samples being below 1 mg/m3 and only one exceeding 5 mg/m3. Endotoxin levels, however, were clearly elevated above background levels (GM 68.5, range: 7-588 EU/m3) with 50% of all measured exposures exceeding 50 EU/m3 which is a recently recommended Dutch occupational exposure standard. The (1,3)-glucan levels were comparable with levels measured in similar industries, however no quantitative dose-response relationships have been described. Dust levels were only weakly correlated with endotoxin and (1,3)-glucan levels. Conclusions: Endotoxin exposures in sawmill workers are at levels sufficient to potentially contribute to the development of respiratory symptoms. Moreover, measurement of dust exposure is a poor proxy for (1,3)-glucan and endotoxin exposure in sawmill workers.

Supported by the Health Research Council of New Zealand. Key words: sawmill, wood dust, endotoxin, (1,3)-glucan, asthma

LUNG FUNCTION CHANGES IN ASBESTOS EXPOSED WORKERS WITH PLEURAL ABNORMALITIES

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Background: As asbestos exposure has declined, interest has increasingly focused on the clinical relevance of the so-called “markers of asbestos exposure”, namely pleural plaques and pleural thickening. The New Zealand Occupational Safety and Health Service maintains National Asbestos Registers, with over 800 cases on a Disease Register and over 14,000 individuals on an Exposure Register. The database includes a work history, estimated exposure index, ILO categorisation of radiographs, lung function data and basic demographic details. Methods: Cases from the Disease Register with pleural changes and with lung function measured to ATS standards, ILD reading of 01 or less, and with smoking and occupational data available, were selected for study. Our analysis of lung function compared actual with predicted values, and evaluated the effect of asbestos exposure and smoking habit. Results: Overall the group (n=185) showed a significant loss of FEV1 (p<0.01), and FVC (-0.02% predicted, CI -29.27 to -9.6, p<0.001) and FVC (-0.02% predicted, CI -10.88 to -6.12, p<0.001). FEF 25-75 was also reduced (-18.43% predicted, CI -26.44 to -10.42, p<0.001), where this was measured. Stratification by smoking habit showed a similar loss in FEV1, and FVC in the never-smokers (n=62). Stratification by exposure showed a clear dose response relationship in the group taken as a whole, which was maintained in never-smokers. Conclusions: Whilst preliminary, these results demonstrate an adverse effect on lung function in workers with pleural changes or thickening. These effects are independent of smoking habit, and show a clear dose response.

Presented on behalf of the National Asbestos Medical Advisory Panel. Key words: asbestos, pleural plaques, pulmonary function

INHALED FINE CARBON PARTICLES ARE NOT ACUTELY BRONCHOCONstrictive.

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Due to the possible association between ambient air degradation and exacerbations of asthma, we have explored the response to the inhalation of fine carbon particles. Methods: The subjects were 8 patients (4 males) with stable asthma (mean age 40.6 yrs) receiving regular inhaled corticosteroid therapy supplemented with occasional use of inhaled 8-agonists. Their initial FEV1 was 84% of predicted. Therapy was ceased at least eight hours prior to the study. All were atopic with positive skin reactions to at least three common allergens and with bronchial hyper-reactivity to lyophilised total eye grass pollen extract (mean PDPD= 3.78 mg). Suspensions of carbon black particles in air were produced from a nebulizer-large particle trap device, the output of which produced 70% of the particles between 2.5 and 7 microns. The dust concentration was determined using a TSI Dustrak™ laser dust monitor. Single inhalations (RV to TLC) of particle suspensions of increasing concentrations, followed by breath-holding for 10 seconds were carried out and FEV1 measured at 3, 10 and 20 minutes after inhalation and peak flow measurements were charted by the subjects on two occasions over the next 4-6 hours. Most subjects received four concentrations. Results: No subjects showed any symptoms or statistically significant falls in FEV1 following particle inhalation at concentrations up to 55 mg/m3 (equivalent to a total retained dose of approximately 100 µg). Late reactions did not occur. Conclusions: The lack of an acute bronchoconstrictive response to the inhaled dust is surprising and may have been due to the protection afforded by inhaled corticosteroid therapy or the total dose of particles delivered may be too small to elicit reactions which might be evident on more chronic exposure.

Supported by the Commonwealth Employees Medical Research Fund. Key words: Diesel fumes; air pollution; asthma

IDIOPATHIC PULMONARY FIBROSIS – A REVIEW

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BACKGROUND: No Australian data are currently published correlating the clinical course of idiopathic fibrosing alveolitis (IPF) with histological subtype and radiological features. A review of the medical records, histology and chest radiographs of 70 cases of biopsy proven idiopathic pulmonary fibrosis were undertaken at The Prince Charles Hospital, a tertiary referral hospital for cardiothoracic disorders, from 1975 onwards. RESULTS: The median age of patients presenting with IPF was 62 years (mean 60.8+/-12.3 yrs); 76% were male and all were Caucasian. Eleven (16%) patients were current smokers at time of diagnosis (mean 36.6+/-11.7 pk/ys) and 34 (48.5%) former smokers (mean 40.8 +/-27 pk/ys). Of histological subtype, 51 (73%) patients had a diagnosis of UIP, 5 (7%) of DIP, 13 (18.5%) of NSIP and one of AIP. Seven patients had dual pathologies. Dyspnoea was the primary presenting symptom in 64 (91%) of patients with a median duration of symptoms of 12 months. Three patients had a family history of IPF. Open lung biopsy alone was undertaken in 32 patients, transbronchial biopsy alone in 18, and both procedures in 17. Chest radiograph was normal in 3% of cases, revealed fine nodular markings as a feature in 55% of cases, ground glass opacities in 13%, ill-defined, patchy infiltrates in 20% and honeycombing in 27%. No significant difference was found among pathological subtypes in clinical presentation or tests of respiratory function. Steroids alone were first-line treatment in 28 (40%) patients and no treatment was undertaken in 17 (24%) patients. Fifteen patients received combination cytotoxic and steroid; 10 underwent transplant assessment and one underwent lung transplantation. Median survival in patients with UIP from date of diagnosis was 17 months (range 1 - 192 months). CONCLUSION: Clinical features alone do not allow for distinction among histological subtypes of IPF. Steroids with or without a cytotoxic agent remain initial treatment options with decision to treat subject to a number of considerations. This study represents an important starting point to the prospective evaluation of IPF in Australia. Key words: idiopathic pulmonary fibrosis
RESPIRATORY SYMPTOMS AND LUNG FUNCTION CHANGE IN WELDERS: HOW DO THEY COME TO WORKPLACE EXPOSURES?

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The possibility was investigated that work related respiratory symptoms and acute falls in FEV1 seen in current welders relate to measured workplace exposures to total fume and metals. Methods: Changes in pulmonary function and reported respiratory symptoms were recorded in 75 welders (and non-welders) in four work sites in New Zealand. Personal breathing zone levels of total fume and various metals were also determined. Results: Work related respiratory symptoms were reported by 21.3% of all workers and related significantly only to personal breathing zone nickel exposure; (odds ratio (OR) and 95% confidence interval (CI) of the high exposure group in relation to a low exposure group) OR 7.0, CI 1.3-36.6. There were non significant associations (odds ratio>2.5) seen with total fume exposure, exposure index of greater than 10 years and age between 25 and 40 years. A fall in FEV1 of at least 5% after 15 minutes of work was significantly associated with aluminium exposure alone; OR 5.8 CI 1.7-20.6. Conclusions: Current MIG and TIG welding, and particularly respectively nickel and aluminium exposure are associated with work related respiratory symptoms and a fall in FEV1 of at least 5% after 15 minutes of work.

Supported by the Health Research Council of New Zealand.

Key words: Occupation, epidemiology, respiratory symptoms, welders.

Posters – Population Health

EXPERIENCE OF TROCAR-FREE THORACOSTOMY TUBE PLACEMENT BY NASAL SPECULUM TECHNIQUE AT THE Sir CHARLES GAIRDNER HOSPITAL

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Tube thoracostomy is commonly performed using a trocar, which provides rigidity and assists placement of the catheter tip into the desired position. Following the fatal impaling of a patient's myocardium in 1997, our hospital adopted a new technique for inserting and directing a trocar-free ICC by nasal speculum.

AIM: To examine the indications for, problems with, and patient characteristics of those requiring thoracostomy tube placement in the department over the last two years since the change in technique. METHODS: 32 patients who required ICC placement in clinical management were recorded on a database for analysis. RESULTS: 13 patients (41%) had pneumothorax and 21 (66%) had pleural effusions (2 had both indications). Nine (28%) were performed emergently. The most frequent problems noted were significant pleural fluid leakage (19/21) and increased analgesia (r2=0.028) or BMI (r2=0.155). Time taken for the procedure correlated with number of problems per patient (r2=0.385) with the average insertion is safe but appears to create possibility of greater than 1 unit of pleural fluid in the pleural space. CONCLUSION: In keeping with international literature, there is evidence in Christchurch of a relationship between paediatric levels and admissions with cardiac and respiratory illnesses. The size of the effect is in keeping with overseas data with the greatest impact seen on the respiratory system.

Particulate Air Pollution and Hospital Admissions in Christchurch

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Aims: Winter air pollution in Christchurch is dominated by particulate from solid fuel domestic heating. The aim of the study was to explore the relationship between particulate air pollution and admissions to hospital with cardiorespiratory illnesses.

Methods: Air pollution data (PM10) were obtained from the Canterbury Regional Council monitoring station in the central city. The New Zealand Health Information Service provided data on admissions to the Princess Margaret and Christchurch Hospitals for the period June 1988 through December 1998 for both adults and children with cardiac and respiratory disorders. The relationship between PM10 and admissions was explored using a time series analysis approach controlling for weather variables. Missing data were interpolated from carbon monoxide values for the same time period, which showed a close relationship with PM10.

Results: There was a significant association between PM10 levels and cardiorespiratory admissions. For children and adults combined there was a 2.52% increase in respiratory admissions for each interquartile rise in PM10 (interquartile value 14.8 mcg/m3). In adults there was a 1.26% rise in cardiac admissions for each interquartile rise in PM10. There was no relationship between PM10 and admissions for appendicitis, the control condition selected.

Conclusions: In keeping with international literature, there is evidence in Christchurch of a relationship between particulate levels and admissions with cardiac and respiratory illnesses. The size of the effect is in keeping with overseas data with the greatest impact seen on the respiratory system.

Compliance in the Childhood Asthma Prevention Study (CAPS)

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Introduction: CAPS is a randomised controlled trial to evaluate the effectiveness of dietary modification and house dust mite allergen reduction as methods for the primary prevention of asthma. The results of the study will be compromised if compliance with either of the interventions is poor.

Methods: The dietary intervention consists of supplying margarine and oils and addition of a supplement to the child's food each day. Compliance is assessed by parents self rating and nurse rating of margarine, oil and supplement use. The house dust mite intervention consists of washing the child's bedding every 3 months in an acaricide wash; covering the child's mattress with an allergen impermeable mattress encasing and removing sheepskins and soft toys. Compliance was assessed by completion of a dairy diary and by nurse observations of the presence of the impermeable mattress cover on the bed. As an objective measure, dust was collected from the child's bed and assayed for Der p 1.

Results: At one year, 83% of households in the active house dust mite allergen reduction group (n=117) had completed the acaricide wash and 81% of children's beds had allergen impermeable mattress covers fitted. In children's beds, 58% in the active group had allergen levels below 10μg/g compared with only 29% in the control group (p<0.001).

Conclusion: Compliance with the use of margarines and oils was high (94-96%) and there was good agreement between self-rating and nurse rating. Compliance with supplements, laundry routines and mattress covers was lower and will need to be improved. The finding that almost twice as many children's beds in the active group had allergen levels below 10μg/g, is encouraging.
PULMONARY THROMBOEMBOLISM AND FAT EMBOLISM ARE BOTH COMMON EARLY AFTER JOINT REPLACEMENT SURGERY M Peters, L Morgan, W Bruce, H van der Wall. Departments of Thoracic Medicine, Orthopaedic Surgery and Nuclear Medicine, Concord Hospital, NSW

Introduction. Respiratory complications are common after arthroplasty with pulmonary thromboembolic disease (PTE) and fat embolism being the most serious. It is generally thought and taught that the high risk period for PTE is 7-10 days after surgery. As fat embolism from bone marrow should contain reticulo-endothelial cells, we hypothesised that these cells would take up colloid in the lung. We conducted a scintigraphic study designed to assess the occurrence of both diseases. Methods. Patients with previous PTE were excluded. Within 48 hours of surgery, tomographic lung studies were acquired after 99m Tc MAAP injection. Pre and post-operative blood gases (ABG) and relevant chest radiography/CT were obtained. ABGs were analysed as the difference in alveolar-arterial oxygen gradients, pre and post-operatively (ΔAa). Results Forty patients were studied (16F, 24M) with a mean age of 71 yr (Range: 36-88 yr). Of these, 16 were hip and 24 knee replacements. Either focal or diffuse uptake was present. Lung uptake of 99m Tc Colloid was present in 35% of cases (7/16 hips and 7/24 knees). Either focal or diffuse uptake was present. Diffuse uptake was associated with mottling in the lung perfusion studies. PTE was detected in 25 of 38 (66%) evaluable patients. There was no significant difference in the incidence or number of segments affected, between hip and knee arthroplasties. ΔAa was significantly higher in patients with scan evidence either of PTE (p<0.05) or fat embolism (p<0.05). All patients recovered well and were free of respiratory symptoms at 6 months. Conclusion PTE immediately after arthroplasty is common and PTE should not be discounted as a clinical diagnosis in the early post-operative period. Prospective studies are needed to establish its nature and whether intervention is of benefit. We have developed a simple test that appears able to demonstrate fat embolism to the lungs and that this is common after joint replacement surgery.

Key words Joint replacement, complications, pulmonary embolism, fat embolism, nuclear imaging

GENDER, ASTHMA AND THE IMAGE

Rhonda Hawley, Department of Clinical Nursing, University of Sydney, 2006

The purpose of this descriptive study of the print media was to quantify the nature of the community health message and to gain an insight into how media stories on asthma are constructed. Method: Print media articles on any aspect of asthma were obtained from two media agencies, the Sydney Morning Herald and Associated Consolidated Press for the 40 month period from January 1995 to April 1998. This included daily metropolitan newspapers and non-daily print magazines available in Sydney. Content analysis was then undertaken on the news articles (n=160). The news articles were coded according to which newspaper or magazine published the article, controversial issues relating to asthma (where opposing views were given), type of message (information or action orientated), spokesperson, main themes and images created. Results: The vast majority of messages gave information (81%), both sides of controversial issues were reported and each side received approximately the same coverage. The most frequently quoted spokesperson was from the medical profession (50%), however when sports personalities were quoted (5.6%) they received more coverage and space. One of the main themes which emerged, was asthma across the life span; however, the images that accompanied this theme revealed a story which indicated that asthma was gendered and that this image was consistent from childhood through to early adulthood. Conclusion: Within the limits of this study the media provided an important forum for discussion and interpretation of health messages on asthma. This study also found that when a story was accompanied by a picture the image created was one that reinforced typical feminine and masculine stereotypes in Western society.

THE ASTHMA MANAGEMENT PROFILE QUESTIONNAIRE (AMQP): A TOOL TO ASSESS PATIENT ATTITUDES TO ASTHMA, ADHERENCE AND SELF-MANAGEMENT

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A questionnaire (AMQP) was developed as part of The Alfred inpatient Asthma Education Program (IAEP). The IAEP was developed to enable inpatients with asthma to receive an individualised education program that included consideration of health beliefs to promote positive health behaviour change and improve self-management. Aim: To develop the AMQP as an instrument to assist the educator to explore and address attitudes to asthma with the patient, in addition to assessing the educational needs of the person. Method: A 31-item questionnaire was devised in six sections: Health Beliefs, Causes of Asthma, Medications, Devices/Techniques, Monitoring Asthma and Action Plan based on two previously published questionnaires. This was administered to 30 people admitted to Ward 5D at The Alfred with asthma over a two-month period. The responses to the questionnaire were summarised and nursing staff was asked to provide format evaluation on the AMQP. Results: 19 (69%) patients held health beliefs that were consistent with positive health behaviour change. 20 (67%) understood what happens in the airways when they have symptoms. 12 (40%) reported they were smokers. 14 (47%) people were unsure about the role of their medications. 27 (90%) had been prescribed an aerosol steroid and of these 17 (58%) used a spacer. 19 (70%) reported forgetting to take their preventer and 7 (37%) forgot more than 6 times per week. 20 (67%) had a peak flow meter. Administration time was 10-15 mins. All the nurse educators were positive about the length of time involved and the information collected. Conclusion: The Asthma Management Profile Questionnaire provided useful information to educators about patient health beliefs and asthma management. This allowed the information delivered to be tailored to meet the specific needs of the patient in the context of their health beliefs.

CASE DISCUSSION: THE IMPORTANCE OF PRESERVING AUTONOMY IN THE DYING PERSON WITH CYSTIC FIBROSIS – THE NURSE’S ROLE.

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Background: Lung transplantation may allow prolongation and improved quality of life in end stage cystic fibrosis. It may, however, hamper the treating team’s ability to offer a consistent approach to palliative care. Objective: To describe a case that illustrates the contribution of the distinctive nursing ethic to a morally just outcome in the management of the terminal event in an adult with cystic fibrosis. Case discussion: A 59-year-old male with severe lung disease and substantially reduced quality of life was receiving inpatient treatment. The primary aim of medical management was the preservation of life to transplantation, including aggressive anti-microbial, nutritional and non-invasive ventilatory support. The patient’s condition deteriorated prompting an honest and open discussion of treatment options with the patient. The goal of treatment was then changed (as a direct result of the intervention of the nurse and consistent with the expressed wishes of the patient) to ensure that suffering was minimized and dignity preserved. In the context of the caring relationship that exists between nurse and patient, the role of advocate was vital to ensuring that the wishes of the patient were reflected in the treatment goals. Conclusion: In the terminal phase, if possible, the patient should be given the opportunity to make an autonomous decision when to continue aggressive medical treatment or not. This should occur at a stage when the patient can make an informed choice about how and when they wish to die. The nurse has a pivotal role in this process.
RECRUITMENT IN THE CHILDHOOD ASTHMA PREVENTION STUDY (CAPS)
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CAPS is a multicentre randomised controlled trial designed to determine whether certain interventions may reduce the incidence of asthma in children.
AIM: the aim of this sub-study is to determine the main reasons for not participating in those subjects who were eligible to participate in CAPS.
METHODS: Pregnant women whose unborn children were at high risk of developing asthma were identified using a short questionnaire at the antenatal clinics of 5 hospitals in western and south-western Sydney. Subjects were excluded if they had a cat at home, lived over 30km from the centre of recruitment, if the baby was delivered before 36 weeks gestation, if the baby had neonatal complications or a low birth weight. Eligible subjects were sent printed information about the study and telephoned to determine whether they wanted to participate. Their reasons for not participating in the study were recorded on the questionnaire.
RESULTS: A total of 7375 women were screened and 1462 (20%) women were eligible for the study. A total of 917 women (66% of eligible population) declined to participate. The main reasons were: 42% were not interested or too busy to participate; 22% were ineligible for the study because they delivered early, were moving out of the area or for some other reason; 16% did not call back after three attempted contacts; 7% did not agree with the study intervention; 3% stated the study was too long; 2% cited medical reasons; 2% said family/marital problems were the main reasons they couldn’t participate; and 2% cited other reasons. A total of six hundred and eighteen pregnant women (42% of the eligible population) have been successfully recruited into the study. CONCLUSIONS: Complexity and length of the study and amount of time available for the participants were the major factors involved in deciding not to participate in this research study. Recording the reasons for not participating in studies enabled us to have a better understanding of why people chose not to participate. This may have a bearing on the way a research project is presented to the general population and the way in which recruitment into research studies is planned.

THE INCIDENCE OF SLEEP DISORDERED BREATHING IN QUADRUARIGES 3 MONTHS AFTER INJURY
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There are approximately 1600 spinal cord injured (SCI) persons cord injured in Victoria (900 quadriplegics), with most having a nearly normal life expectancy. In cross-sectional studies the prevalence of sleep disordered breathing (SDB) in quadriplegics is 2 to 5 times higher than in the general population (McEvoy, 1995; Short, 1992). The reasons for this increased prevalence are unknown. Aims: The aim of this study was to investigate the evolution of SDB in the first year following acute cervical SCI. Methods: Assessments will commence as soon as possible post injury (>48 hrs) and comprised serial polysomnography (CompumedicsTM PSG, Abbotsford, Australia) and respiratory function testing (flow-volume loops, MIPs & MEPs). Assessments were performed immediately post injury, at 2 weeks, 1, 3, 6 and 12 months. Evidence of undiagnosed SDB that may have existed prior to the SCI was quantified using the Masiin et al (Sleep 1955) multivariate apnoea prediction equation (MAP). Results: Subject recruitment began in December 1998 and will continue for 1 year. As of 30th September 1999, 67 patients had been admitted to the VSCS, 42 quadriplegics. Ten were excluded because they were older than 70, 2 because of an associated head injury and 3 declined to participate. Three have been ventilator dependent since admission, leaving 24 in the trial. Twelve subjects (11 men, average age 35, range 18-65 years) have been studied at 3 months. All had a restrictive ventilatory deficit (average VC 45%, range 14 - 84%) and 10 of the subjects have SDB (RDl > 5), despite only 2 having a pre injury MAP likelihood of > 0.5, i.e. chance of pre-existing SDB of 75% (CI 70-80%).
Conclusion: The incidence of SDB 3 months following cervical SCI is 83%, significantly higher than previously reported.
Supported by: Physiotherapy Research Foundation-009/96 & NHMRC-997544
Key words quadriplegia, sleep apnoea
Nomination for awards: None

SURFACE TENSION OF UPPER AIRWAY MUCOUS SURFACE LIQUID
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Surface tension (ST) properties are recognised as playing an important role in the maintenance of alveolar and small airway patency. In recent years, there has been interest in the role surface forces may play in the control of upper airway patency. This concept is particularly relevant to the control of pharyngeal patency during sleep in the obstructive sleep apnea syndrome (OSAS). While the ST of saliva samples obtained from the oral cavity have been studied extensively there is little information describing the surface forces associated with oropharyngeal laringeal liquid. There are a number of approaches to the measurement of ST, however, many require relatively large samples of the liquid under study. We have now developed an approach which utilises small (microlitre) sample volumes. Methods: ST was quantified using the "pull-off" force technique in which ST is measured as the force required to separate two curved silica discs bridged by the liquid sample. After calibration with liquids of known ST, we measured the ST of 0.2uL samples of upper airway surface liquid (UASL) obtained (using 0.5uM ID polyethylene tubing attached to a 1uL syringe) from ten adult subjects (4 females, 6 males) and from three sites within the upper airway. Results: There was no significant difference (P=0.5, ANOVA) between the ST values of UASL samples obtained from the tongue [61.6(10.1) dynes/cm] at the oral surface of the soft palate [56.1(10.1) dynes/cm] and the posterior pharyngeal wall [58.7(6.7) dynes/cm]. These values are similar to published values for the ST of saliva (~57 dynes/cm). Conclusion: We conclude that the "pull-off" force technique is suitable for measuring the ST of small samples of liquid obtained from the respiratory tract and that the ST of UASL from the oropharyngeal wall (site of collapse in OSAS) is equivalent to that of saliva.
1 Christensen H.K., J. Collaid Interface Sci., 121(1):170-8, 1988
Supported by: The Garnett Passe & Rodney Williams Memorial Foundation and the NH&MRC
Key words: oropharyngeal wall collapse, upper airway patency, saliva, surface tension.
Nomination for Awards: John Read Prize

CPAP IMPROVES CARDIAC FUNCTION IN PATIENTS WITH CENTRAL SLEEP APNEA AND CARDIOMYOPATHY.
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Introduction: Two groups in Toronto have shown improvement in cardiac function by non invasive means using nasal CPAP therapy. Their data however have not been reproduced elsewhere. Therefore the aim of this study was to assess the effects of nasal CPAP on cardiac function in patients with cardiomyopathy and central sleep apnea (CSA). Methods: 5 adult male subjects (age: 67.8±6.7 yrs, BMI: 25.9±7.6 kg/m2 (meansSD)) with cardiomyopathy and CSA (central apnea/hypopnea index >20/hour) were studied before and after three months of nasal CPAP therapy set at a level to control any coexistent upper airway obstruction. Cardiac function (cardiac index (CI), Pulmonary Artery Occlusion Pressure (PAOP), Systolic Vascular Resistance Index (SVRI) and Pulmonary Vascular Resistance Index (PVR)) was measured invasively by pulmonary artery catheter. Extravascular lung water (EVLW) was measured by double indicator dilution technique. CPAP compliance was measured objectively by measuring actual mask application time (Respironics AriaTM). In three subjects data were also collected after 12 months of CPAP treatment. Results: The mean CPAP compliance was 6.3±0.7 hours per night and the mean pressure was 15±2.5 cmH2O.

| Measurement | Baseline (n=5) | 3 months (n=5) | 12 months (n=3) |
|-------------|---------------|----------------|-----------------|
| CI           | 4.1±0.3 l/min/m² | 4.2±0.5 l/min/m² | 4.5±0.3 l/min/m² |
| PAOP         | 19.9±12.2 mmHg | 16.9±8.9 mmHg | 11.6±5.6 mmHg |
| SVRI         | 2980±1055 cm H2O | 2360±566 cm H2O | 2176±628 cm H2O |
| PVR          | 622±389 cm H2O | 384±230 cm H2O | 261±191 cm H2O |
| EVLW         | 10.6±2.1 kg | 10.8±5.4 kg | 7.1±3.8 kg |

Data are means±SD, * = p<0.1, ** = p<0.05, 1: subject died at 6 months after stopping CPAP. Conclusion: These preliminary results show by direct mapping trends towards significant improvement in cardiac function after three months CPAP treatment. The improvement appeared to continue over the following 9 months.

Acknowledgement: ALF, NANS, Peninsula Private Sleep Laboratory
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NASAL CPAP IMPROVES CENTRAL SLEEP APNEA AND UNMASKS OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH CARDIOMYOPATHY.

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Introduction: The potential interactions between central sleep apnea (CSA), obstructive sleep apnea (OSA) and cardiac dysfunction are not well defined. Therefore the aim of the study was to assess the effect of 3 months nasal CPAP therapy on sleep disordered breathing in patients with (CSA) due to cardiomypathy. Methods: 8 adult male subjects (age: 67.8±6.7 yrs, BMI: 25.9±7.5 kg/m2 (means±SD)) with severe cardiomypathy and CSA (central apnea/hypopnea index > 20/hour) were treated with nasal CPAP for 3 months after a CPAP pressure determination study. Three subjects continued CPAP for 12 months. Polysomnographic measurements were recorded after 3 and 12 months. A pulmonary artery catheter was used to measure Cardiac index (CI) invasively. All patients received standard medical therapy which was either unchanged or reduced during CPAP therapy. Results: Patients BMI did not change. The mean compliance was 6.3±0.7 hours per night and the mean pressure was 13±2.5 cmH2O.

EFFECT OF NECK POSITION, MANDIBULAR ADVANCEMENT AND MOUTH OPENING ON HYPOPHARYNGEAL DIMENSIONS

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Introduction: Pharyngeal narrowing predisposes to obstruction during sleep. Aim: To determine the effects of neck position (NP), mouth opening (MO) and mandibular advancement (MA) on hypopharyngeal dimensions (Hb and MA, lateral (L), cross-sectional area (XSA)). Methods: 5 healthy subjects (44±12 years, BMI: 25.9±7.5 kg/m2) were studied awake using a naso-pharyngoscope (tip in velopharynx) to visualize the hypopharynx. They were studied at 3 levels of MA (neutral, 5mm, maximum (7-10mm)), 3 levels of MO (teeth opposed, 10mm apart, 20mm apart) and 3 NP (neutral(0°), flexion(20°), extension(20°)). During tidal breathing, end-inspiratory images were stored digitally. AP and L dimensions were obtained from these images and expressed in units of epiglottic width to correct for magnification. XSA was calculated from AP and L. The separate effects of changes in NP, MO and MA on hypopharyngeal dimensions (AP, L, XSA) were determined relative to each baseline condition (neutral neck, teeth opposed, mandible neutral) (multiple regression).

Results: Neck Neutral Teeth Opposed Mandible Neutral

Coef AP L XSA AP L XSA AP L XSA

NP,° 0.469 0.669 1.16 ns ns ns 0.198 0.306 0.519

MO,mm ns ns ns ns 0.052 ns -0.404 -0.727 -2.227

MA,mm ns ns ns ns ns 1.129 1.119 2.632

a=p<0.05, b=p<0.01, c=p<0.005, d=p<0.001

Neck extension increased all dimensions. MO decreased lateral dimensions. MA increased all dimensions with this increase enhanced by neck flexion but diminished by neck flexion and MO. Conclusions: Pharyngeal dimensions can be increased by MA, mouth closure and neck extension. Their study may help determine optimal mandible position for MA therapy. Neck extension may be a useful additional treatment principle.

Key words: Airway dimensions, Mandibular advancement, Neck position
NASAL POWER DYNAMICS DURING EXERCISE
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Flow resistive work of nasal breathing (WONB) and nasal power (NP) values are known to be consistent, subject specific, predictors of the 'switching point' ventilation from nasal to oro-nasal breathing during exercise. Methods: To investigate the relationship between respiratory ventilation (Vt) within an individual subject, we studied 13 healthy, adult subjects (6 males, 7 females; age: 27.8(6.2) SD yrs); who performed a progressive, graded exercise task (30 to 140-230 watts in 2 minutes, 30 watt steps) on a cycle ergometer while breathing only via the nose. Tidal volume (Vt) was monitored using an integrated nasal airflow signal obtained with a nasal mask and pneumotachograph. Trans-nasal pressure was calculated as the difference between nasal mask pressure and oro-pharyngeal pressure (measured using a stoppered mouthpiece, with no flow in a patent oral pathway). Inspiratory WONB (joules per breath, mean of 5 steady-state breaths) was measured by planimetry from pressure-volume plots constructed from the trans-nasal pressure and flow data at each level of exercise. Inspiratory NP was calculated as inspiratory WONB x respiratory rate (i.e. joules/sec or watts) and increased progressively with exercise. The relationship between NP and V for each subject was mathematically fitted using the function NP=aVb (where a and b are constants, P< 0.91). The rate of change of NP with V was calculated as the first derivative of the fitted function (NPC) and the rate of change of NPC as the second derivative (NPCR). Results: There was considerable subject variation in these parameters such that at Vt=30 Vmin (i.e. within the published range for V at the 'switching point') NP, NPC and NPCR ranged from 1.02 to 2.68 watts, 0.01 to 0.02 watts 1-1 min and 0.0004 to 0.01 watts 1-1 min respectively. Moreover, each of these parameters was positively correlated with inspiratory nasal resistance (Rn at peak nasal airflow) measured at rest (Rn = 1.1-12.9 cm H2O/lit; R=0.77-0.96; P<0.002). Conclusions: Thus, a higher Rn at rest may lead to a relatively larger increase in NP; NPC and NPCR during exercise. We conclude that resting Rn influences NP dynamics at higher V and, thus, may be a subject specific determinant of the 'switching point' to oro-nasal breathing during exercise. Supported by: NH&MRC
Key words: Nasal power, oro-nasal airflow partitioning, nasal resistance
Nominations for Awards: Nil

BREATHING ROUTE LABILITY IN ASTHMATIC AND HEALTHY SUBJECTS
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Recently, we demonstrated for the first time that asthmatic patients spontaneously breathe exclusively via the nasal route when asymptomatic but switch to oro-nasal breathing during an acute exacerbation. We have now examined the sensitivity to external inspiratory nasal loading to switch the route of breathing as in asymptomatic asthmatic patients (6 females; age = 31.8(11.7) SD yrs; FEV1 = 83.4(2) % predicted) and healthy subjects (2 females, 2 males; age = 31.0(13.5) yrs; FEV1 = 101(14.8) % predicted). Methods: Subjects breathed via a dual compartment face mask with attached nasal and oral pneumotachographs. Starting with exclusive nasal breathing, subjects inspired via a one-way valve connected to a chamber in which a constant negative pressure (inspiratory load) was maintained. Progressively increasing external loads were applied until subjects spontaneously switched to oro-nasal breathing. The external load at which this occurred was termed the 'switching load'. Standard posterior rhinomanometry was subsequently employed for measuring nasal resistance at the 'switching load'. The total nasal resistive load (NRL) was calculated as the sum of the 'switching load' resistance and nasal resistance (at 0.4 1/sec inspiratory flow). Results: The 'switching load' for the healthy subjects was -5.5 (2.1) SEM cmH2O and tended to be lower for asthmatic patients (-3.5 (0.7) cmH2O), although this difference did not achieve significance (p=0.3, unpaired t-test). However, the NRL for healthy subjects was 6.0(2.0) cmH2O/sec and did not differ from that for the asthmatic patients (6.0(1.9) cmH2O/sec; p=0.9). Conclusion: The total NRL at which asthmatic patients switch to oro-nasal breathing is not different from that at which healthy subjects switch. Thus, asymptomatic asthmatic patients do not appear to demonstrate enhanced sensitivity to switching of breathing route in response to increased nasal loading.
Supported by: NH&MRC & Australian Postgraduate Award
Key words: inspiratory loading, upper airway, asthma, physiology
Nominations for Awards: NIL

TRANSPORT DRIVERS ARE SLEEPIER THAN WORKING ADULTS AND THEIR VEHICLE ACCIDENTS ARE RELATED TO DURATION OF SLEEP AND WORK
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Aim: To describe the characteristics and outcomes of patients treated with nocturnal bi-level positive airway pressure ventilation (BiPAP) at home for Obesity Hypoventilation Syndrome (OHS). Methods: A case-note review of all patients treated with home BiPAP. Results: 59 patients (37 male) with a primary diagnosis of OHS were treated between March 1993 and November 1999. The (SD) age was 45 (11). Most were either Maori (n=26) or Pacific Islanders (27). All were extremely obese with a mean BMI of 53 kg/m2 (range 37-80). 33 had been admitted acutely (16 to intensive care) with respiratory failure. Several others had had previous acute/ICU admissions. 39 patients also had obstructive sleep apnoea. 43 had right heart failure and 30 had biventricular failure. Other co-morbidity included: polythemia (n=20), asthma/COPD (22), hypertension (21) and non-insulin dependent diabetes (14). A striking feature was a history of cellulitis (13 patients) which often precipitated the index admission. The median duration of BiPAP therapy so far is 22 months (range 1-79). The mean (SD) weight loss since presentation is 7.7kg (19). Only 2 have lost sufficient weight to stop treatment. 7 patients have changed to CPAP. 5 have refused to continue treatment, 2 have been lost to follow-up and 2 are followed up elsewhere. 37 patients continue on BiPAP. Nocturnal ventilation in most patients remains sub-normal with mean morning arterial blood gases after BiPAP: pCO2 7.0 kPa, pO2 8.3 kPa, HCO3 29.8 mmol/l. Despite this the mortality is surprisingly low. Only 4 are known to have died, one died from renal failure and one from obesity-related cardiomyopathy. Two probably died from respiratory failure; one 8 months after refusing to continue BiPAP; the other was thought to be non-compliant. Conclusions:OHS in New Zealand is predominantly a disease of Maori and Pacific Islanders and is associated with important co-morbidity. This descriptive study suggests that nocturnal BiPAP ventilation may improve survival.
Key words: obesity-hypoventilation, non-invasive ventilation, BiPAP

A REVIEW OF HOME BIPAP FOR OBESITY-HYPOVENTILATION SYNDROME
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Aim: To describe the characteristics and outcomes of patients treated with nocturnal bi-level positive airway pressure ventilation (BiPAP) at home for Obesity Hypoventilation Syndrome (OHS). Methods: A case-note review of all patients treated with home BiPAP. Results: 59 patients (37 male) with a primary diagnosis of OHS were treated between March 1993 and November 1999. The (SD) age was 45 (11). Most were either Maori (n=26) or Pacific Islanders (27). All were extremely obese with a mean BMI of 53 kg/m2 (range 37-80). 33 had been admitted acutely (16 to intensive care) with respiratory failure. Several others had had previous acute/ICU admissions. 39 patients also had obstructive sleep apnoea. 43 had right heart failure and 30 had biventricular failure. Other co-morbidity included: polythemia (n=20), asthma/COPD (22), hypertension (21) and non-insulin dependent diabetes (14). A striking feature was a history of cellulitis (13 patients) which often precipitated the index admission. The median duration of BiPAP therapy so far is 22 months (range 1-79). The mean (SD) weight loss since presentation is 7.7kg (19). Only 2 have lost sufficient weight to stop treatment. 7 patients have changed to CPAP. 5 have refused to continue treatment, 2 have been lost to follow-up and 2 are followed up elsewhere. 37 patients continue on BiPAP. Nocturnal ventilation in most patients remains sub-normal with mean morning arterial blood gases after BiPAP: pCO2 7.0 kPa, pO2 8.3 kPa, HCO3 29.8 mmol/l. Despite this the mortality is surprisingly low. Only 4 are known to have died, one died from renal failure and one from obesity-related cardiomyopathy. Two probably died from respiratory failure; one 8 months after refusing to continue BiPAP; the other was thought to be non-compliant. Conclusions:OHS in New Zealand is predominantly a disease of Maori and Pacific Islanders and is associated with important co-morbidity. This descriptive study suggests that nocturnal BiPAP ventilation may improve survival.
Key words: obesity-hypoventilation, non-invasive ventilation, BiPAP
METHOD FOR VALIDATING MEASUREMENTS OF TLCO AND VA
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The carbon monoxide transfer factor (TLCO) and alveolar volume (VA) are routinely measured to assess the integrity of that part of the alveolar-capillary membrane accessible to inspired gas. However, these physiological measurements are complex and there is no method available for validating the TLCO results. Aim: To develop a method for producing a known value for TLCO and VA to validate TLCO testing systems. Method: A 3.00 litre calibration syringe, 9-way tap and two gravimetric gas mixtures (BOC) containing accurately known Ne and CO concentrations were used to simulate the TLCO manoeuvre. One gas mixture (“inspired gas”) contained 0.3000 ±0.0015% CO, and 0.4991 ±0.0025% Ne; the other mixture (“alveolar gas”) contained 0.1002 ±0.0005% CO and 0.3057 ±0.0018% Ne. Theoretical TLCO and VA values were computed (target values) based on a 3.00 litre inspired volume, standardised breath-holding time of ten seconds and the accuracy range of the gas mixtures. Theoretical values were compared to results measured using a computerised TLCO system (MedGraph1cs, Elite, MN, USA). Measured values of TLCO were standardised to a breath-hold time of ten seconds. Results: See table. The validation method has proved easy to apply and the TLCO and VA values obtained from the MedGraph1cs system were reproducible. VA was found to be accurately measured but TLCO was underestimated by 0.7 mL/min/mmHg. However, TLCO was within the target range when calculated using the measured inspired VC. This method can be easily adapted to other TLCO systems including those which use He or methane and can provide any physiological value for VA and TLCO. Conclusion: This TLCO validation method shows promise for confirming TLCO and VA measurements.

| Measured (n=6) | Target Absolute Range | Error From Target |
|---------------|----------------------|--------------------|
| VC (ATPD)     | 2.94 (0.015)         | 0.06               |
| VA (ATPD)     | 4.08 (0.04)          | 0.02               |
| TLCO          | 20.3 (0.19)          | 20.8 - 21.4  |

and the TLCO and VA values obtained from the MedGraph1cs system were reproducible. VA was found to be accurately measured but TLCO was underestimated by 0.7 mL/min/mmHg. However, TLCO was within the target range when calculated using the measured inspired VC. This method can be easily adapted to other TLCO systems including those which use He or methane and can provide any physiological value for VA and TLCO. Conclusion: This TLCO validation method shows promise for confirming TLCO and VA measurements.

A SLOW DECLINE IN UPPER AIRWAY DILATOR MUSCLE ACTIVITY EXISTS FOLLOWING A BRIEF HYPOXIC STIMULUS

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Following abrupt removal of a brief respiratory stimulus, there is a slow decline in ventilation back to resting levels known as ventilatory afterdischarge (VAD). VAD has been proposed to stabilise breathing patterns and has been shown to be reduced in patients with Obstructive Sleep Apnea (OSA). Theoretically, it would appear a slow decline in upper airway dilator muscle activity would be necessary to accompany the VAD, to prevent upper airway collapse during this time. The purpose of the current study is therefore to investigate if such an upper airway afterdischarge exists and to compare its decay to that of an inspiratory pump muscle. METHODS: Healthy volunteers (n=7 to date) were exposed to multiple 46 second periods of hypoxia (9% O2 in N2) abruptly terminated with one breath of 100% O2. Ventilatory, inspiratory diaphragmatic and genioglossal muscle responses were measured during and after this intervention. The half times of decay were calculated for each variable. RESULTS: The mean of 63 trials are reported. The half time of decay in minute ventilation, inspiratory activity and genioglossal activity were not significantly different at 9.1 (2.3 (SEM), 8.4 (2.4) and 9.3 (2.8) seconds respectively (p>0.05). CONCLUSIONS: Preliminary analysis of this study shows a slow decline in upper airway dilator muscle activity concurrent with the VAD, suggesting that upper airway afterdischarge exists in healthy volunteers. The time course of this decay appears to be of similar magnitude to that of VAD if the upper airway afterdischarge is proportionately less than VAD in any situation or in any patient group, then the upper airway would theoretically be more prone to collapse. Investigation of this phenomenon in OSA patients, during sleep and between men and women is therefore important.

Supported by the NHMRC
Key words: Genioglossus, Ventilatory Afterdischarge, Obstructive Sleep Apnea, Upper Airway function, Hypoxia.
Nominations for awards: Nil

RESISTIVE LOAD DETECTION AND MagnITUDE ESTIMATION DURING Submaximal steady-state Exercise in normal SUBJECTS

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Normal subjects can rate magnitudes of added resistive loads at rest and on exercise. Aim: To investigate if, during sub-maximal steady-state exercise normal subjects can estimate the magnitude of added inspiratory loads on the first or second breath after presentation and the effects of these loads on inspiratory flow. Methods: 12 normal subjects (6F: aged 20-21yr) were studied. Exercise levels of 33 and 66% of maximal ventilation (VE) were obtained from a maximal treadmill test (Balke protocol). At rest, at 33% and at 66% VE, resistors of A) 0, B) 0.5, C) 0.7, D) 1.3, E) 2.5 and F) 5.0 cmH2O·l.s-1 were each presented 10 times, for 2 breaths, in a random order. Subjects estimated the magnitude of the resistor using a digital 100 mm visual analogue scale (VAS). Data were compared at rest, 33% and 66% VE using ANOVA and are given as mean ± sem in the form (Rest: 33%: 66%).

| Load (cmH2O·l.s-1) | Baseline | Post Ventilin |
|---------------------|---------|--------------|
| 0                   | 1.00 ± 0.71 | 0.73 ± 0.52 |
| 0.5                 | 0.59 ± 0.42 | 0.59 ± 0.42 |
| 0.7                 | 0.48 ± 0.34 | 0.55 ± 0.39 |
| 1.3                 | 0.41 ± 0.29 | 0.40 ± 0.35 |
| 2.5                 | 0.35 ± 0.26 | 0.46 ± 0.34 |
| 5.0                 | 0.29 ± 0.21 | 0.42 ± 0.29 |
| 1.3                 | 1.19 ± 0.85 | 0.88 ± 0.62 |
| 2.5                 | 0.74 ± 0.52 | 0.55 ± 0.39 |

and 1.0 ± 0.4 l.s-1 were not significantly different. They were also not significantly different from baseline values. Conclusion: In these patients there is an improvement in the repeatability and precision of Rs, Z and X5 obtained using IOS after administration of Ventolin via spacer device.

Key words: Airways Resistance, Impulse Oscillometry

IMPULSIVE OCCILLOMTERY: REPEATABILITY OF INDICES OF RESISTANCE BEFORE AND AFTER VENTOLIN.

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Impulse oscillometry (IOS, Jaeger) is a rapid, non-invasive method of estimating airway resistance. Resistance (Rn), measured at frequencies from 5Hz to 35Hz, peripheral reactance (Xn) and the respiratory impedance (Zn) are obtained during tidal breathing. Aim: To determine the repeatability of the indices obtained using IOS in patients before and after Ventolin. Method: 23 patients (aged 41–81yrs) produced two technically acceptable estimates of the indices from IOS, spaced 2 mins apart, each estimate being recorded over 30s – 40s. Repeatability was reassessed 10 min after inhalation of 200µg of Ventolin via spacer using the one second forced expiratory volume (FEV1) obtained from a volume-time curve using a wedge-bellows spirometer (Vitagraph). Results: For each index, the coefficients of repeatability and precision were obtained (British Standards Institute, 1979). The results for baseline and post Ventolin are given in the table in the form (repeatability: precision), the units being kPa/l.s. Mean (± SD) baseline FEV1 was 1.6 ± 0.7l.s-1, FVC was 2.5 ± 1.0l, and FEV1/FVC was 65% (range 32% - 77%). After Ventolin, FEV1 was 1.91 ± 0.71l.s-1, FVC was 2.7 ± 0.8l, and FEV1/FVC was 68% (range 56% - 68%). From IOS, mean baseline tidal volumes were 0.30 ± 0.11 l and 0.89 ± 0.45l, and were not significantly different. After Ventolin, mean tidal volumes were 0.95 ± 0.30 l and 0.44 ± 0.18 and were not significantly different from baseline values. Conclusion: In these patients there is an improvement in the repeatability and precision of Rs, Z and X5 obtained using IOS after administration of Ventolin via spacer device.

Key words: Airways Resistance, Impulse Oscillometry
**ADAPTATION TO RESISTIVE LOADS DURING SUBMAXIMAL STEADY-STATE EXERCISE IN NORMAL SUBJECTS.**

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We have observed that inspiratory flow significantly decreases on the first breath after the presentation of a resistor. The number of breaths needed to adapt to the presence of a resistor at different workloads has not been studied. Aim: To investigate if, during sub-maximal steady-state exercise, inspiratory flow and pressure returns to pre-load values within 5 breaths of presentation. Methods: 6 normal subjects (3F: aged 21-22yr). An exercise level of 33% of maximal ventilation, obtained from a maximal treadmill test, was used and resisters of A) 0, B) 0.5, C) 0.7, D) 1.3, E) 2.5 and F) 5.0 cm H2O-l/s were each presented 10 times, for 5 breaths, in a random order. Inspiratory flow (l.s⁻¹) and mouth pressure (cmH2O) were recorded throughout. Results: There were no significant effects on flow or pressure with resistors A or B. For resistors C to F, inspiratory flow significantly decreased (p<0.01) on the first breath after presentation and had not returned to baseline after 5 breaths. Inspiratory pressure significantly increased (p<0.001) on the first breath after presentation and remained significantly greater than baseline after 5 breaths.

| Flow     | Pre | Post 1 | Post 2 | Post 3 | Post 4 | Post 5 |
|----------|-----|--------|--------|--------|--------|--------|
| Press 2.6 ± 0.4 | 5.3 ± 0.3 | 5.1 ± 0.2 | 4.8 ± 0.3 | 4.4 ± 0.3 | 3.9 ± 0.3 |

Data are shown for resistor D as mean±sem. Conclusion: In normal subjects, inspiratory resistors of 0.7 cmH2O-l/s and above significantly influence the inspiratory pressure and flow during steady-state exercise at 33% maximal ventilation. These changes indicate that adaptation, mainly through changes in inspiratory pressure occur in order to maintain an adequate tidal volume.

**Key words:** Perception, Exercise, Normal subjects

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**IMMUNE OSCILLOMETRY: RELATIONSHIP OF CENTRAL RESISTANCE, RESPIRATORY IMPEDANCE AND PERIPHERAL REACTANCE TO DYNAMIC LUNG VOLUMES.**

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Impulse oscillometry (IOS: Jaeger) is a rapid, non-invasive method of estimating central resistance (Rc), peripheral reactance (Xc) and respiratory impedance (Zr) at a frequency of 5Hz during tidal breathing. Aim: To determine if there is a relationship between Rc, Xc and Zr to the 1s forced expiratory volume (FEV1), forced vital capacity (FVC) and the FEV1/FVC ratio. Methods: 76 subjects (48M:28F aged 16 - 82yr (mean 53.3 yr) were studied. All measurements were made in the upright sitting position. Estimates of Rc, Xc and Zr were made during resting tidal breathing over a 30s recording period. Measurements of FEV1 and FVC were obtained using a wedge-bellows spirometer (Vitalograph, UK), with the highest value for each index obtained from three technically acceptable attempts being used. Relationships between each spirometric index and Rc, Xc and Zr from IOS were obtained using regression analysis. Results: Mean ± SD values of FEV1 were 1.9 ± 0.9 l, FVC were 2.95 ± 1.1 l. FEV1/FVC were 0.62 ± 0.13 l (range 28% to 78%). Rc were 0.54 ± 0.29 kPa.l/s.l, Xc were -0.25 ± 0.24 kPa.l/s.l and Zr were 0.59 ± 0.37 kPa.l/s². There were significant (p < 0.001) linear relationships between the spirometric indices and Rc, Xc, Zr = 2.80 ± 1.71 R² = 0.32; FVC = 3.93 - 1.61 R² = 0.22; FEV1/FVC = 74 - 22.6 R² = 0.25; Xc = 2.52 + 2.38 R² = 0.38; FVC = 3.67 - 2.71 R² = 0.31; FEV1/FVC = 70.5 + 26.6 R² = 0.26; and Zr = 2.61 - 1.50 R² = 0.37; FVC = 3.96 - 1.64 Zr = 0.27; FEV1/FVC = 75 - 17.9 Zr = 0.30. Conclusion: In these patients there are significant relationships between airway function assessed by conventional dynamic lung volume measurements and estimates of central resistance, peripheral reactance and respiratory impedance obtained from IOS.

**Key words:** Airways Resistance, Impulse Oscillometry

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**EXTRACORPOREAL MEMBRANE OXYGENATION: INDICATIONS, TRANSPORT, PREGNANCY.**

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Extracorporeal Membrane Oxygenation (ECMO) is a technique that when used appropriately, is often lifesaving. We describe the first recorded case of its use in pregnancy. Case: A 29 year old woman presented to a hospital with a 2 day history of dyspnoea, malaise and fevers. She was 25 weeks pregnant and had a past history of mild asthma. A chest X-ray showed bilateral consolidation, and she was admitted with a diagnosis of pneumonia and asthma. She deteriorated rapidly over the next day and had to be intubated. Despite full mechanical ventilation and paralysis her oxygen saturations were < 80%. It was felt that she should be transferred to a tertiary hospital for specialised obstetric care. To facilitate her transfer and improve her oxygenation it was decided that she should be commenced on ECMO. This was done and within 10 minutes her saturations had improved remarkably to 99%. She was transferred without incident. Her condition stabilised and she was weaned off ECMO after 3 days and extubated several days later. She went into spontaneous labour at 30 weeks gestation, 3 months later mother and baby are in good health with no residual problems. Discussion: ECMO has been used for almost 30 years. It has been used extensively in the treatment of respiratory failure in neonates, with survival rates of > 80%. In adults it has not had such a good reputation and until recently has been regarded as being fairly unsuccessful, with survival rates of < 10%. However, improved techniques and in particular better patient selection, have resulted in recent survival figures being reported as 60-70%. ECMO should be considered for young patients with acute reversible respiratory failure who have a 30% mortality risk with conventional treatment, as calculated by published compliance and vascular shunt measurements. Its use in this case saved two young lives. ECMO is also a way of guaranteeing oxygenation when transferring highly unstable hypocapnic patients. Several small studies have reported uniform success in transporting such patients. Portable machines are available that will fit inside an ambulance. There have been reports of ECMO in post partum patients but this is the first documented case of its use in pregnancy.

**Key words:** ECMO, pregnancy, respiratory failure, transport

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**HYPERTENSION IN OSAS: CHANGES IN THE FIRING PATTERN OF SINGLE MUSCLE VASOCONSTRICTOR NEURONES IN AWAKE PATIENTS.**

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Muscle sympathetic outflow is greatly elevated in awake patients suffering from the obstructive sleep apnoea syndrome (OSAS), with the increase in multi-unit burst activity being similar to that seen in congestive heart failure (CHF). To increase our understanding of the neural mechanisms of sympathoexcitation, single-unit activity of 12 muscle vasoconstrictor neurones (recorded via tungsten microelectrodes in the peroneal nerves of 6 OSAS patients) was compared with that of 16 neurones recorded in 8 CHF patients and 33 neurones recorded in 14 healthy controls (CTL). For both groups of patients the mean firing rates and firing probabilities were significantly higher than in the controls (Table). However, while the percentages of cardiac intervals in which neurones generated 1, 2, 3 or 4 spikes were statistically identical in CHF and CTL, the OSAS patients generated significantly fewer solitary spikes and more double spikes. These firing properties were identical to those generated by 9 neurones during acute increases in sympathetic drive (inspiratory-capacity apnoea) in 5 controls. We conclude that the sympathoexcitation associated with OSAS differs from that of CHF, perhaps due to an acute sympathetic drive related to the resting hypoxaemia in OSAS.

| CTL rest | CHF rest | OSAS rest | CTL apnoea |
|----------|----------|-----------|------------|
| frequency 0.40 Hz | 0.98 Hz* | 0.96 Hz | 1.04 Hz |
| firing prob. 30.8 % | 55.1 % | 51.8 % | 56.3 % |
| 1 spike 72.7 % | 70.6 % | 58.8 %* | 61.2 % |
| 2 spikes 18.4 % | 18.2 % | 27.3 %* | 26.7 % |
| 3 spikes 5.1 % | 7.3 % | 9.7 % | 9.5 % |
| 4 spikes 2.9 % | 3.0 % | 2.9 % | 1.7 % (*p<0.05) |
SURVEY OF VICTORIAN SLEEP LABORATORIES: EQUIPMENT, STAGING AND SCORING CRITERIA.

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Surveys of laboratories overseas have documented significant diversity in the working definitions used for reporting respiratory events in sleep studies. Aim: To assess sources of variability in the measurement of sleep disordered breathing (as defined by the Respiratory Disturbance Index) between different sleep laboratories throughout Victoria. Methods: A self-complete written questionnaire was constructed following literature review and interviews with staff at 3 separate sleep laboratories. The survey was sent to all laboratories listed in Victoria by the Australasian Sleep Association in 1999. The first part of the survey related to the type of equipment used to record sleep & other variables during overnight polysomnography and the second part to the definitions and methods used for the reporting of the results. Results: The response rate was 94% (17 out of 18 laboratories returned the surveys). Overall there was reasonable consistency between laboratories with respect to the type of variables measured during overnight polysomnography & the methods used to measure them. Some differences are described. In relation to the methods used for scoring sleep study results the greatest inconsistencies were noted in the definition of hypopneas. Variability was also noted in the scoring of apnoeas, & arousals. Conclusions: Several sources of variability in the methods used to measure & define sleep-disordered breathing are described. The extent to which these variations may affect the comparability of reported results between different laboratories requires further research. Supported by: Victorian Department of Human Services for the CPAP Service Development Project.

Key words: Survey, sleep disordered breathing, sleep laboratories

OUTCOMES OF THE VICTORIAN CPAP PILOT PROGRAM PATIENT FOCUS GROUPS.

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The Victorian CPAP Pilot Program was developed to provide CPAP Services to eligible participants with sleep disordered breathing. As part of the evaluation of that program patient focus groups were conducted at institutions involved in service delivery. Aim: To examine patient perceptions of the CPAP Pilot Program with an emphasis on service delivery, outcome, side effects, reasons for presentation & barriers to compliance. The purpose was to inform the development of a patient satisfaction survey & validate the researchers' understanding of the research agenda from the viewpoint of patients. Methods: Focus groups were conducted by an independent observer at 4 institutions involving a total of 24 patients. Both compliant & non-compliant patients attended. The procedure for the conduct of focus groups followed standard recommendations. Taped discussions were transcribed verbatim and the text was submitted to independent thematic analysis. Results: Most participants were happy with the delivery of the program & its outcomes. The main area of concern to participants was the lack of technical support related to the use of equipment particularly masks, & costs related to consumables. Several triggering factors for entry to the program were identified and include; a bad driving experience, chronic tiredness & family pressure to attend. Conclusions: The results have been used to develop a survey that will assess patient satisfaction quantitatively. Further research may help to establish whether additional technical support improves long-term adherence & examine the relationship between triggering factors for presentation, outcome & compliance. Supported by: Victorian DHS for the CPAP Service Development Project.

Key words: CPAP focus groups, sleep disordered breathing

EFFECTS OF LONG-TERM NOCTURNAL NON-INVASIVE VENTILATION (NIV) ON GAS EXCHANGE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND HYPERCAPNIA.

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It is postulated that long-term nocturnal non-invasive ventilation (NIV) reverses hypercapnic respiratory failure due to obesity hyperventilation or chronic ventilatory abnormalities largely by increasing alveolar ventilation. The effects of long-term NIV in patients with hypercapnia due to chronic obstructive pulmonary disease (COPD) remain unclear. We have performed detailed gas exchange studies on four patients with COPD and hypercapnic hypoventilatory failure, at baseline and following three months of NIV plus oxygen. All patients had severe COPD with an FEV1 0.58(0.20 L (SD), (216 predicted), FVC 1.89(0.48 L (56(5%) predicted) and RV 22(415% and chronic respiratory failure with PaCO2 61(9 mmHg and PaO2/FIO2 348(114. At baseline, the MIGET measure of perfusion to low V/Q units (log SD Q) was abnormal at 0.83(0.15 (normal <0.6) and the MIGET measure of ventilation to high V/Q units (log SD V) was abnormal at 0.76(0.31. There was minimal shunt (0.8(0.3%) and alveolar ventilation was 4.1(1.8 L/min (dead space of 56(5%). After three months of NIV plus oxygen, PaCO2 fell by >6mmHg in three patients and rose by 5 mmHg in one patient with a mean PaCO2 of 54(5 mmHg (p=0.1, paired t-test). Alveolar ventilation fell in all patients to a mean 3.7(1.8 L/min (p=0.03, paired t-test), with no change in dead space or PaO2/FIO2 and no significant change in log SD Q or log SD V. These findings show that improvements in PaCO2 occur with NIV despite falls in daytime alveolar ventilation. In the absence of significant changes in intrapulmonary gas exchange this suggests that the fall in PaCO2 may be due to a reduction in CO2 production, possibly due to reduced respiratory muscle work. Supported by the NH&MRC.

Key words: COPD, MIGET, hypercapnia, non-invasive ventilation

Nominations for Awards: TSANZ/ALF John Reid Prize Phystiological Research

Supported by an Otago Research Grant

MANDIBULAR ADVANCEMENT SPLINT IMPROVES INDICES OF OBSTRUCTIVE SLEEP APNEA AND SNORING BUT SIDE EFFECTS COMMON.

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OBJECTIVE: To assess the efficacy of a Mandibular Advancement Splint (MAS) in the treatment of Obstructive Sleep Apnoea Syndrome (OSAS).

DESIGN: Randomized double blind crossover study.

METHODS: 18 OSAS patients, consecutively treated with a MAS, were randomised to sleep a half night with and a half night without the MAS. A paired student t test was used to compare polysomnographic indices of sleep-disordered breathing and sound (Rion — integrating sound meter). Snorers were scored when inspiratory noise was greater than five dB above background. A questionnaire was used to assess symptoms and side effects. RESULTS: 18 patients (17 male and 1 female) with a mean ± SD age of 47.2 ± 9.0 years, Body Mass Index of 32.1 ± 4.9 kg/m2 and an Initial Respiratory Disturbance Index (RDI) of 32.7 ± 24.5 hour were studied. Total sleep time, sleep efficiency, % REM sleep and % sleep spent supine were similar (p>0.05) with and without the MAS. The use of the MAS significantly reduced mean RDI from 22.8 ± 20.8 to 17.4 ± 21.7 hour (p = 0.047), Arousal index from 25 ± 17 to 19 ± 15 hour (p = 0.02), average snoring intensity from 2.7 ± 1.8 to 0.9 ± 2.7 dB (p = 0.02). Treatment over 9.3 ± 9.9 (±9.0) weeks with the MAS was associated with a small improvement in daytime somnolence (mean Epworth Sleepiness Score 12.0 ± 4.9 c.f. 9.9 ± 3.1, p = 0.07) and significant side effects. 15 patients (83%) reported difficulty using the MAS and 38% use the device for less than 3 nights a week. CONCLUSION: The use of the MAS resulted in a small but statistically significant reduction in indices of OSAS. A significant number of patients had difficulty tolerating the device with 38% falling to achieve satisfactory compliance.

Supported by an Otago Research Grant

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MEASUREMENTS OF SMALL AIRWAYS NARROWING IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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OSA has been thought to selectively involve the pharynx or upper airway, however several recent studies suggest that OSA may be associated with intrapulmonary airways dysfunction. If proven this would shed new light on the possible pathogenesis of airways disease and suggest a new approach to management. Aim: To investigate the presence of small airways narrowing in patients with documented OSA. Methods: Consecutive patients referred to the respiratory laboratory at RGH with a diagnosis of possible OSA underwent full respiratory function testing (RFT) and impulse oscillometry (IOS) the morning after their polysomnography (PSG). Results: 40 patients were studied with RFT, IOS and PSG (33 males). The mean age was 55 years (range 22-75) and body mass index (BMI) was 35 (range 25-50). 10 (25%) patients had a history of prior or current respiratory disease (6 asthma, 4 COPD) and 28 (70%) had a history of prior or current smoking. The mean RDI of the total group was 41 (range 2-112), 16 (40%) patients had severe OSA (RDI>40). PSG excluded the diagnosis of OSA in only 3 patients (RDI<5). Significant associations with the severity of OSA (based on RDI and minimum SaO2) were seen with BMI (p<0.01) but not with age, history of respiratory disease or smoking. Measurements of small airway narrowing by IOS and flow volume curves were not significantly associated with severity of OSA based on RDI. Conclusions: Our preliminary RFT and IOS data failed to confirm the observations by other groups of abnormalities in the small airways in patients with OSA. Larger studies including larger numbers of normal (non-OSA) patients are required to further investigate this area and provide conclusive findings.

Key words: Obstructive sleep apnea, small airways, oscillometry.

UTILITY OF AWAKE IMPULSE OSCILLOMETRY IN DETECTING AIRWAY NARROWING IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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The "gold standard" investigation for obstructive sleep apnea (OSA) is polysomnography (PSG) which is costly and time-consuming for patients and health care staff. History and examination show poor predictive values for PSG-proven OSA and thus other investigations (cephalometry and CT scanning) have been examined for their ability to detect upper airway narrowing and consequently select those patients likely to have OSA and warranting PSG. Aim: To investigate the utility of IOS measurements in assessing upper airway resistance in awake patients with OSA. Methods: Consecutive patients referred to the respiratory laboratory at RGH with a diagnosis of possible OSA underwent full respiratory function testing (RFT) and impulse oscillometry (IOS). IOS recorded "central" and "peripheral" resistance. The former is thought to mainly reflect upper airway resistance. Results: 40 patients were studied with RFT, IOS and PSG (33 males). The mean age was 55 years (range 22-75) and body mass index (BMI) was 35 (range 25-50). PSG excluded the diagnosis of OSA in only 3 patients (RDI<5/hr of sleep). The mean RDI of the total group was 41 (range 2-112), 16 (40%) patients had severe OSA (RDI>40). There was no significant association of upper airway resistance as measured by IOS (sitting or supine) with the severity of OSA as measured by RDI. However, the small numbers of normal (non-OSA) patients prevented a meaningful comparison of upper airway resistance (as measured by IOS) between normals and OSA patients. Conclusions: Although current data do not show an association between upper airway resistance and severity of OSA our work to date provides a preliminary profile of resistance measures (by IOS) in patients with OSA.

Key words: Upper airways resistance, obstructive sleep apnea, oscillometry.

EXAMINING THE ASSUMPTIONS IN A METHOD FOR MEASURING THE VOLUME DISPLACED BY DIAPHRAGM MOTION (ΔVdi)

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Departments of Respiratory and Pulmonary Physiology, Sir Charles Gairdner Hospital (SCGH), Western Australia and 1Physiology, University of Western Australia. We have proposed a method for measuring ΔVdi from the change in subphrenic volume (Singh et al JRCM 1999;160:1507-15). The subphrenum was defined by the diaphragm dome, diaphragm-apposed rib cage and a horizontal plane at the inferior insertion of the diaphragm. Subphrenic volume was calculated by dividing it into multiple 1 cm horizontal slices, the cross-sectional (CS) areas of which were determined from a geometric model of each slice and measurements from PA and lateral CXRs, and was corrected for spiral volume. In this study, we examined in healthy (N) and hypertrophied (H) subjects 1) the accuracy of several geometric models used to calculate lower rib cage CS area and 2) the internal consistency of the proposed method for measuring ΔVdi. The former was studied near TLC using chest CTs in 25 N and 22 H subjects by comparing lower rib cage CS area measured by planimetry against that calculated from the mid sagittal and coronal axes of the lower rib cage using several models: ellipse, rectangle, 1/2 the way between an ellipse and a rectangle, circle, 1/2 the way between an ellipse and a rectangle, and a rectangle bounded by two semicircles. The internal consistency of ΔVdi was examined in 10 N and 9 H subjects by comparing it with the difference between change in lung volume (ΔVl) measured by the method of Pierce et al. (Thorax 1979;34:726-34) and the change in lung volume attributable to lateral expansion of the rib cage (ΔVrc) measured radiographically for breaths from RV to FRC, FRC + 1/2 inspiratory capacity and TLC. We found that in both groups, lower rib cage CS area measured by planimetry was most closely predicted by modelling the rib cage as 1/2 the way between an ellipse and a rectangle (r² = 0.96, difference [mean ± SD] 1.3 ± 4.2%), and there was a close relationship between ΔVdi and ΔVl-ΔVrc (r² = 0.97, difference 94 ± 148 ml). We conclude that in healthy and hyperinflated subjects, lower rib cage CS shape is close to 1/2 of the way between an ellipse and a rectangle, and the proposed method for measuring ΔVdi is internally consistent.

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INFLUENCE OF EXPIRATORY FLOW ON ANATOMICAL DEAD SPACE MEASUREMENTS

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Background. The anatomical dead space (VD) represents the luminal volume of the conducting airways not involved in gas exchange. Its measurement, using a single-breath nitrogen washout technique, is influenced by initial lung volume and the pause between inspiration and expiration of the test gas. It is unclear whether the flow rate of the expired gas influences VD. Aim. To measure the VD at varying expiratory flow rates on different days in normal subjects and determine whether a suitable range could be found that would provide consistent VD values.

Methods. 2 male subjects were recruited, aged 42 (TD) and 29 (PW). They had no history of respiratory disease. A modified Fowler's method utilised a single-breath nitrogen wash out after oxygen inhalation to measure VD. Subjects exhaled to FRC then inhaled 1L of 100% oxygen from a reservoir bag at about 0.5L/sec. After an inspiratory pause of less than 1 second the expired volume and nitrogen concentration were simultaneously recorded. The VD was taken as the volume that coincided with the arithmetic mean of the phase II slope of the nitrogen washout curve. The procedure was repeated at varying expiratory flow rates on 4 different days. Results. Subject TD had 63 readings taken with an expiratory flow varying from 253ml/sec to 1278ml/sec. VD ranged from 188-372ml. PW had 52 readings with flow varying from 264-1231ml/sec. VD ranged from 191-596ml. VD did correlate with expiratory flow in both subjects (R² 0.82 for TD, R² 0.90 for PW). VD values between flows of 350-700ml/sec were relatively consistent. Over the 4 days TD averaged 253ml (range of averages 249-262), coefficient of variation 9.9%. PW averaged 242ml (233-250), coefficient of variation 8.8%. Conclusion. Expiratory flow rates do alter VD and need to be controlled. The lower VD at slow flow rates probably results from increased time for mixing at the interface. The larger VD at higher flows is probably non-artifactual. Using the arithmetic mean for VD calculation may introduce error. The consistent VD value at intermediate flow rates enables comparison of VD at different lung volumes.

Key words. Anatomical dead space, single breath nitrogen test Supported by the RMH Research Foundation.
SPIROMETRY IS LESS DEMANDING FOR PATIENTS AND MORE REPRODUCIBLE USING FEV<sub>1</sub> INSTEAD OF FVC

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Spirometry can be a physically demanding manoeuvre for patients with severe respiratory disease because of the long exhalation time required to meet standardised testing criteria. Aims: To determine if the forced expiratory volume in 6 seconds (FEV<sub>6</sub>) could serve as an acceptable alternative to FVC in the diagnosis of airway obstruction and lung restriction. We also compared the reproducibility of FVC and FEV<sub>6</sub>. Methods: We analysed data from consecutive patients referred to our laboratory for spirometry. FEV<sub>1</sub>/FVC was compared with FEV<sub>6</sub>/FEV<sub>6</sub> and FEV<sub>6</sub> with FVC. Results: Compared to FEV<sub>1</sub>/FVC using FEV<sub>6</sub>/FEV<sub>6</sub> the sensitivity for obstruction was 94.6% and for restriction 92.8% The intra-subject coefficient of variation was 3.4 for FEV<sub>6</sub> and 4.5% for FVC. Conclusions: FEV<sub>6</sub> is a good spirometric predictor of a restrictive pattern.

Key words: Spirometry, reproducibility, obstruction, restriction.

Nomination for Awards: Nil.

A STUDY OF THE EFFECTIVENESS OF LOCAL ANGEL (LOCAL ANAESTHETIC GEL) IN THE REDUCTION OF PAIN DURING ARTERIAL PUNCTURES

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Background: Needle punctures have been shown to cause considerable pain and discomfort. Topical use of local anaesthetics has been shown to reduce the pain associated with venous punctures, especially in children. No data are yet available concerning the use of local anaesthetic with arterial punctures.

Aims: To evaluate the effectiveness of local anaesthetic gel, containing amethocaine 4% (Local AnGel), in the reduction of pain during arterial punctures.

Methods: A placebo controlled, double blinded study was employed. Gel was applied for 30 minutes prior to the procedure. Pain was rated by a visual analogue scale and a short questionnaire. The scale was from 0 (no pain) to 100 mm (most severe pain). Follow-up by telephone was used to determine side effects. Heart rate was monitored with a pulse oximeter.

Results: Preliminary results: 32 subjects were evaluated, 19M and 13F; mean (sd) age 67.3 (12.8). 16 received placebo and 16 Local AnGel. Mean pain scores were 16.2 (13.8) and 17.9 (25) respectively (p = 0.8). The mean (sd) heart rates before arterial puncture were 88 (11.5) with placebo and 85 (13.2) with AnGel (p = 0.5), and after the puncture were 89(13.4) and 84(13.6) respectively (p=0.4). Twelve subjects in each group said that they would prefer to have gel applied next time they had an arterial puncture. Two subjects in the placebo group reported slight lingering sensation at the site of the puncture after the procedure.

Conclusion: Local AnGel is not effective in the reduction of pain during arterial puncture when applied for 30 minutes prior to the procedure. This is an important finding suggesting widespread use of local anaesthetic in this setting is not justified.

Key words: arterial puncture; local anaesthetic.

A COMPARISON OF VENTILATORY MODES OF NONINVASIVE POSITIVE PRESSURE VENTILATION IN ACUTE HYPERCAPNIC RESPIRATORY FAILURE IN CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

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Aim: The role of noninvasive positive pressure ventilation (NIPPV) in patients with chronic obstructive airways disease (COAD) presenting in acute hypercapnic respiratory failure (AHRF) is now well established. However, no studies have compared different ventilatory modes in this group. The aims of this study were to compare the efficacy of NIPPV in spontaneous (S) and spontaneous/timed (S/T) modes in AHRF complicating COAD, in the respiratory ward setting. Methods: Thirteen subjects presenting with COAD and AHRF, considered unsuitable for mechanical ventilation, were recruited into a double blinded trial with NIPPV via a full face mask randomised to either S or S/T mode on a bi-level airway pressure device (Respironics BiPAP STD). Arterial blood gases (ABGs), respiratory rate (RR), Borg dyspnoea score (BDS) and pulse oximetry were measured at 0, 1, 6, 24, and 48 hours on NIPPV. Results: Baseline indices at time of randomisation were (mean ± SD) age 76.6±3.7 and 72.6±6.3 years, FEV<sub>1</sub> 0.45±0.13 and 0.63±0.19 l, RR 32.3±15.1 and 28.0±5.7 bpm, BOS 9.0±2.8 and 7.3±2.2, pH 7.30±0.04 and 7.27±0.06, and pCO<sub>2</sub> 70.3±11.5 and 75.2±15.1 mmHg, in the S and S/T groups respectively. There were no significant differences in indices between ventilatory modes at any time point. All indices improved significantly from baseline to 1 hour (p<0.05) when groups were combined. There were no NIPPV induced complications.

Conclusions: In a highly selected group of elderly subjects with COAD and AHRF, NIPPV significantly improved ABGs, RR and dyspnoea within 1 hour using either S or S/T modes. No significant difference between ventilatory modes was demonstrated which may reflect the small numbers, and recruitment is ongoing. NIPPV was effectively managed in a respiratory ward setting.

Key words: Noninvasive positive pressure ventilation, acute hypercapnic respiratory failure, BiPAP

VALIDATION OF A SLEEP APNOEA SYMPTOM QUESTIONNAIRE

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Barnes et al. have assessed nasal CPAP in patients with mild obstructive sleep apnoea (OSA) and found that a sleep apnoea symptom questionnaire (SASQ) was the only test that showed a significant improvement with CPAP. Aim: To validate the SASQ with the following aims: (I) To establish the feasibility of answering the questionnaire. (II) To establish that SASQ scores are low in normal people. (III) To determine the difference in the scores between normal subjects and patients with OSA. (IV) To determine the correlation between the SASQ and ESS, RDI, arousal index (AI) and Miaslin score (MAP). (V) To test the consistency of answering the questionnaire over time. (VI) To determine the difference in scores before and after treatment with CPAP in patients with OSA.

Methods: The normal group was medical students, who completed the SASQ, ESS and MAP twice. The patient group was patients referred for a sleep study. They completed the questionnaires on 3 occasions, twice before and once after treatment with CPAP. The SASQ consisted of 14 items with responses given on a visual analogue scale 0 to 100 mm. Lower scores meant fewer symptoms.

Results: N = 70 students (29 females) and 106 patients (24 females). (I) 94% students and 86% patients successfully completed the SASQ. (II) The responses of the students were in the lower third of the range of possible scores. (III) Mean (sd) SASQ scores of patients with RDI < 5 and RDI ≥ 5: 53.9 (22.4) and 69.0 (22.0) (p<0.004). (IV) Correlation between SASQ and ESS r = 0.64, MAP r = 0.65, RDI r = 0.14, and AI r = 0.23 (V) Consistency of answering the SASQ: r = 0.93 (V) SASQ scores before and after CPAP were 70.7 (15.4) and 38.9 (24.1) (p<0.001).

Conclusions: The SASQ was able to be completed by patients, produced low scores in normal people, had different scores between people with and without OSA, and had poor correlation with RDI and AI, but good correlation with ESS and MAP. It was answered reliably and was responsive when OSA was treated. Key words: sleep apnoea, questionnaire.
AN INVITRO ASSESSMENT OF NONINVASIVE BILEVEL POSITIVE PRESSURE VENTILATORS.
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BACKGROUND: Noninvasive positive pressure ventilation (NIPPV) can effectively treat patients with acute respiratory failure. However, the performance of the NIPPV ventilators at high respiratory rates has not been described. AIM: To examine and compare the performance of NIPPV ventilators across a range of respiratory rates. METHOD: A spontaneously breathing respiratory model was built and connected, in turn, to 4 different ventilators capable of providing NIPPV. They are designated ventilator A, B, C, D. Each device was set up in a spontaneous mode to deliver, when triggered, an inspiratory pressure of 10 cmH2O and an expiratory pressure of 5 cmH2O. The respiratory model breathed at respiratory rates between 10 and 50 breaths per minute. The respiratory model was similar to a normal thorax, having a compliance of 100 ml/cmH2O and a resistance of 2.4 cmH2O.sec.L-1, but different in that the inspiratory to expiratory rate was fixed at a ratio of 1:1 and that both phases of respiration were active. RESULTS: Table 1. Average inspiratory and expiratory pressures.

| Resp. rate | 10 | 20 | 30 | 40 | 50 |
|-----------|----|----|----|----|----|
| A: Insp.  | 14 | 13.4 | 12.7 | 11.9 | 10.3 |
| Exp.      | 9.7 | 9.8 | 9.9 | 10.3 | 11.8 |
| B: Insp.  | 8.9 | 8.3 | 8.3 | 7.4 | 6.2 |
| Exp.      | 6.2 | 6.3 | 6.6 | 7.1 | 7.8 |
| C: Insp.  | 10.1 | 9.1 | 7.6 | 6.3 | 4.7 |
| Exp.      | 5.8 | 6.1 | 6.7 | 7.4 | 8.4 |
| D: Insp.  | 8.4 | 8.1 | 6.8 | 5.2 | 3 |
| Exp.      | 4.6 | 5.6 | 6.4 | 7.5 | 9 |

CONCLUSION: As the respiratory rate increased beyond 30 breaths/min, the devices failed to deliver effective level ventilation.

Key words: Noninvasive ventilation, ventilator performance, respiratory model.

BRONCHOSCOPY IN FEBRILE NEUTROPENIC PATIENTS WITH PULMONARY INFILTRATES.
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We undertook a retrospective review of 35 (20 men, 15 women) consecutive neutropenic patients with pulmonary infiltrates who failed to respond to conventional neutropenic antibiotic protocol. These patients were referred for bronchoscopy with washings, brushings, lavages and bronchial biopsies obtained. The age range was 17-77 years, with the commonest cause for neutropenia being chemotherapy. The mean duration of neutropenia and antibiotic therapy was 14 days (2-40 days) and 11 days (1-40 days) respectively. The yield from all types of specimens was low. The extent of the radiological involvement did not influence the yield. The commonest results obtained were growth of bacteria and fungi which were difficult to interpret without a histological correlation. The procedure overall impacted on the management of 8 patients. It was useful in excluding an infective cause and allowing rationalization of antimicrobial therapy in non critically ill patients but was disappointing in aiding the management of the critically ill when mortality remained high. However, the procedure was safe with a low complication rate despite the presence of hypoxaemia and thrombocytopenia. Open lung biopsy provided a diagnosis of pneumocystis in 2 cases when bronchoscopy was negative. In conclusion, bronchoscopy in this setting proved to be disappointing even with lavage specimens in identifying an infective cause. Perhaps in conjunction with the routine use of transtracheal biopsies, we can improve the yield of this procedure and render it a useful diagnostic tool in the management of these patients without the elevated risk of complications which often accompanies other invasive pulmonary procedures.

Key words: Neutropenia, bronchoscopy, pulmonary infiltrates.

A PROTOCOL FOR THE MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA IS COST-EFFECTIVE
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In July 1998 a district hospital (DH) implemented a protocol for the treatment of community acquired pneumonia (CAP) in order to eliminate empirical use of third generation cephalosporins (TGC). This study assesses its efficacy and cost-effectiveness by comparing patient outcomes with those of patients treated at an urban teaching hospital (UH) where standard therapy for CAP involves the use of TGC. Methods: A retrospective review of patients with coded records admitted to the DH and UH with CAP between January 1999 and June 1999 was performed. Rate of compliance with the protocol by emergency department (ED) staff at the DH was assessed. The age, sex, severity, smoking history, underlying lung disease, initial treatment, culture results, duration of fever and intravenous (IV) therapy and length of stay (LOS) were compared and an estimate of cost effectiveness of the protocol made. Results: Of the 86 patients with CAP at the DH 52 (60%) received treatment as per protocol. Twenty-four patients (28%) received empirical treatment with TGC despite the protocol. Of the 62 initially treated with penicillin or ampicillin, 8 (13%) were later treated with TGC because of failure to improve. Protocol adherence was significantly less likely in patients allergic to penicillin (RR 0.33; 95% CI 0.16 to 0.76). At the UH 93% (67/72) of patients with CAP received empirical treatment with TGC. Patients at the DH were older (63.0 vs 56.6 years; p=0.04) and on more regular medications (4.0 vs 2.6, p=0.002). The vital signs, white cell counts, creatinine levels, prevalence of underlying lung disease, intercurrent illness, smoking history and rate of clinically relevant culture results were similar in the two groups. There was no significant difference in time to defervescence (p=0.4) or LOS (p=0.62). Mean duration of IV therapy did not differ significantly (4.2 days DH vs 4.9 days UH; p=0.14). Ampicillin treatment for one day costs $4.40 ($1.10x4) and ceftaxime $19.38. Therefore, the DH saves an average of $77.73 for every patient treated as per protocol. Conclusion: One year after implementation, a protocol for the treatment of CAP is proving efficacious and cost-effective. Compliance with the protocol by ED staff is good but could be improved by continuing education.

Key words: Pneumonia, third generation cephalosporins, cost-effectiveness.

TUBERCULOSIS UNDERTAKING CLINIC - A 27 MONTH EXPERIENCE
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Background: Subjects migrating to Australia as permanent residents or entering Australia as students are required to have a health screen provided by the Department of Immigration and Multicultural Affairs. Those found to have abnormal chest X-rays (CXR) which are not due to active TB, sign a Tuberculosis Undertaking (TBU) and are reviewed when in Australia. Aim: To review the experience of a TBU clinic and outcomes of referral from the TBU clinic for isoniazid preventive therapy (IPT). Methods: Prospective analysis of CXR and Mantoux test results and retrospective analysis of TBU clinic patients referred for IPT. Results: Between November 1995 and February 1999, 2395 subjects were referred to the TBU Clinic of whom 1919 (80%) attended in person and 206 (8%) had X-ray only review. The most common countries of birth were China (20%), Vietnam (12%), India (5%) and Philippines (5%). Assessment was: inactive TB (39%), possibly active TB (1.6%), non-TB (12%), or normal (47%). Twenty-eight percent of TBU subjects were referred to a consultant, 13% to a general practitioner, and 58% were discharged without follow-up. Mantoux (10 TU) was 215 mm in 106 of 272 (39%) subjects aged <35 years who had an abnormal CXR or were from a high risk country. Of 126 people referred for IPT, 9 (7%) did not attend their appointment at Western Hospital TB clinic and 13 (10%) were referred to other clinics. Of the 104 who were followed at Western Hospital, IPT was offered to 75 (75%). Of these, 9 (12%) refused IPT, 20 (26%) started but failed to complete IPT and 48 (63%) completed six months IPT. Conclusions: Of subjects referred on a TBU, 47% had no significant pulmonary abnormality on expert review. Forty-three percent of TBU subjects referred for IPT and managed at Western Hospital completed 6 months therapy.

Support: Department of Human Services, Victoria.

Key words: tuberculosis, migrants, isoniazid preventive therapy.

Nominations for awards: nil.
FACTORS INFLUENCING PRESCRIPTION OF ISONIAZID CHEMO-PREVENTIVE THERAPY
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Background: Physicians vary widely in their use of isoniazid (INH) chemopreventive therapy in subjects with a positive Mantoux reaction. In this study a questionnaire was used to ascertain the reasons physicians prescribed or withheld INH in two groups of subjects. Method: 18 physicians seeing 181 health care workers detected by hospital staff screening, and 103 migrants in a migrant screening clinic, all with Mantoux=15mm, filled a questionnaire for each patient detailing their reasons for or against use of INH.

Results: 79 of the 181 health care workers were <35yrs mean Mantoux size 20mm; (range 15-58), 10 were recommended INH, 5 agreed to take it. Of the 69 not offered INH physicians recorded the following reasons: known past positive Mantoux 6, reactivation unlikely 11, Mantoux likely to be due to past BCG 46, others 6. Among 103 migrants (mean age 30.7yrs, range 16-71), mean Mantoux size 20.7, (range 15-50), 76 were offered INH, 67 accepted. Of the 27 not offered INH physician reasons were as follows: previous adequate treatment 7, reactivation unlikely 14, Mantoux likely to be due to prior BCG 2, others 4.

Conclusions: Prescription of INH chemopreventive therapy is highly context sensitive and not driven by size of Mantoux alone. Simple prescription algorithms are unlikely to be of use. Physicians more often ascribed Mantoux positivity to prior BCG vaccination in health care workers of many ethnic backgrounds than they did in migrants who had also had high rates of prior BCG.

Key words: isoniazid, tuberculosis, chemopreventive therapy

SUCCESSFUL OUTCOME FOR NON-HIV MULTIDRUG RESISTANT TUBERCULOSIS (MDR TB) TREATED WITH DIRECTLY OBSERVED THERAPY (DOT).

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Aim: To review the experience in non-HIV MDR TB individual.

Methods: Five consecutive patients with positive sputum smears & MDR cultures are presented.

| Patient (Pt) | Sex/Age (years) | Country of birth | Time in Australia | Chest radiograph |
|--------------|-----------------|------------------|-------------------|-----------------|
| 1            | F 36            | Philippines      | 5 years           | RU & RLL cavities |
| 2            | M 28            | Korea            | 6 months          | LUL cavity |
| 3            | M 34            | Korea            | 2 years           | RUL, RMZ & LUL infiltrate |
| 4            | M 48            | U.K.             | 35 years          | Bilateral cavities |
| 5            | M 14            | China            | 2 years           | LUL infiltrate |

All patients were given DOT with 5 to 8 drugs, chosen from: ethambutol, pyrazinamide, ciprofloxacin, amikacin, capreomycin, cefotaxime, cycloserine, para-aminosalicylic acid, amoxycillin/clavulanate, interferon γ. Two patients came to surgery for cavities: Pt 1 – right upper lobectomy, Pt 4 – right upper & middle & left upper lobectomies. Results: Duration of follow up from 0 (current treatment) to 6 years. Patients 1, 2 & 3 completed treatment & remain smear & culture negative with improved chest radiographs. Patients 4 & 5 are still on therapy. Pt 4 had most of the disease removed and became smear negative 14 weeks into treatment. Pt 5 is now smear negative with marginal radiographic improvement.

Conclusion: A successful outcome in these 5 patients has been achieved. Two patients still continuing treatment show signs of recovery. Aggressive treatment with at least 5 drugs combined with surgery in cavitory disease gives promise of cure in this difficult, life-threatening disease.

Key words: tuberculosis, multidrug resistant, non-HIV, DOT.

PULMONARY MANIFESTATIONS OF MALARIA
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Severe pulmonary disease is an infrequent complication of malaria. Clinical manifestations of milder disease however occur in up to 18% of patients with Plasmodium falciparum infection with a reduction in FEFR on the third to fourth day of symptoms1. Method: prospective study of 10 subjects returning from malaria endemic regions who were hospitalised with blood smear confirmed malaria. Lung function testing was performed daily for 1-5 days, and at 1 week post discharge. Lung function testing included spirometry, single breath CO diffusion (DLCO SB), body plethysmograph lung volumes, and airway resistance. CXRs were performed on day 1 & 3 and 1 week after discharge, 99mTc-DTPA ventilation scans on day 1, 3, 5 and 99mTc-sulphur-colloid scans on day 1, 2 and 3 Results: 3/10 subjects had cough on the day of presentation. Cough was more common in subjects with P vivax (3/4) compared with those subjects with P falciparum (0/6) (Fisher's exact, p=0.01) This difference persisted until at least day 4 post-presentation. Predicted FEV1, had a mean increase of 4.5% (1.9(SEM)) from day 1 to day 5. Conclusion: Mild pulmonary involvement is common in patients with malaria. Increased investigation of respiratory physiology in this condition may facilitate a greater understanding of what is a multisystem disease. Supported by: Flinders University Northern Territory Clinical School

Key words: Malaria, respiratory physiology, nuclear medicine

Nominations for Awards: nil

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IN VITRO EFFECTS OF STREPTOKINASE AND DEOXYPURINOCHELASE ON VISCOSITY OF HUMAN SURGICAL AND EMPYEMA PUS

Graham Simpson, David Roomes, Mal Heron

Purified streptokinase is now frequently used intra-pleurally to treat empyema thoracis replacing the older preparation (Varidase™) which contains streptococcal DNase as well as streptokinase. Our clinical impression was that the purified preparation was less effective than Varidase. To investigate whether DNase was contributing to easier drainage of pus we have measured pus viscosity using a simple viscometer. Pus from three soft issue abscesses drained surgically and from six patients with empyema thoracis was studied. Pus samples were incubated with normal saline (as control) and with streptokinase, Varidase, human recombinant DNase (Pulmozyme™) and a mixture of streptokinase and Pulmozyme.

Purified streptokinase had little effect on pus viscosity with mean reduction of 11.1% in surgical specimens and 1.7% in empyema samples. Varidase reduced viscosity by a mean of 52.8% in surgical samples and 94.8% in empyema samples and human recombinant DNase reduced viscosity by a mean of 32.8% in surgical samples and 93.4% in empyema samples. Adding streptokinase to DNase did not reduce viscosity further. Final viscosities in all samples treated with DNase were similar whatever the starting viscosity.

DNase thus significantly reduces pus viscosity whereas streptokinase has little effect and may work simply by breaking down loculations in empyema thoracis. Combining streptokinase with DNase may be of clinical benefit in empyemas where pus viscosity is high.
SUCCESSFUL TREATMENT OF EMPYEMA THORACIS WITH HUMAN RECOMBINANT DNA

Graham Simpson and Ben Reeves

Treatment of empyema thoracis with fibrinolytic enzymes if simple tube drainage fails is increasing in popularity. Recent work 1,2 suggests that streptokinase may break down fibrinous loculations in empyemas but has no effect on pus viscosity whereas DNase does reduce pus viscosity and may facilitate drainage.

An 82 year old lady presented with pneumococcal pneumonia and subsequently developed an empyema. Treatment with intravenous antibiotics and intercostal tube drainage for five days failed to improve the empyema and a second intercostal drain was inserted. Streptokinase in standard doses (250,000U daily for 3 days) was instilled into the pleural cavity but the empyema persisted. The patient refused surgical intervention. She was treated with intrapleural human recombinant DNase 5mg daily for 3 days. This resulted in drainage of further 700ml of pus with clinical and radiological Improvement.

We believe this is the first use of human recombinant DNase in treating empyema thoracis in man.

References:
1) Simpson G., Roomes D. Thrombolytics and pleural empyema. Medical Journal of Australia. 1998. 168, 144
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SPUTUM INDUCTION IN A HETEROGENEOUS POPULATION.

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BACKGROUND: Inhaled hypertonic saline via an ultrasonic nebuliser can be effectively used to induce coughing and sputum production for the diagnosis of diseases of the lower respiratory tract. However the place of this technique in populations with ready access to fibre-optic bronchoscopy (FOB) remains controversial. AIM: To compare sputum induction with FOB in the assessment of patients with lower respiratory tract diseases. METHOD: Induced sputum samples (20mls of 6% saline given as continuous nebuliser) were taken from 16 consecutive patients referred to the primary investigator with one or more of the following two indications for FOB: (a) haemoptysis for investigation (in patients age >40yo, a smoking history and an abnormal CXR) and/or (b) possible TB (with a significant clinical risk of TB and normal sputum smears). All induced sputum procedures were well tolerated with no adverse effects seen. All patients proceeded on the same day to FOB. The type of specimen taken at FOB was at the discretion of the bronchoscopist. Specimens from both investigations were sent to the same laboratory and were analysed with cytology and microscopy and culture, including AFB. RESULTS: Adequate induced sputum specimens were obtained in 11 of the 16 patients. The FOB included general washings (n=15), brushings (n=10), lavage (n=5), biopsy (n=5). In total 8 patients received definitive diagnoses. 5 malignancies (2 small cell, 2 adenocarcinomas and 1 squamous cell lung cancer), MTB was diagnosed in two patients and an atypical TB was diagnosed in one patient. 7 of these 8 patients with diagnoses had adequate induced sputum specimens. Bronchoscopy diagnosed all 8 cases while the induced sputum technique diagnosed only 2 of the malignancies also seen on bronchoscopy (odds ratio in favour of bronchoscopy = 7:1). CONCLUSION: In our small, heterogeneous group of patients, sputum induction did not provide additional diagnoses to FOB.

Key words: Fibre-optic bronchoscopy, sputum induction.

TRANS-THORACIC NEEDLE ASPIRATION IN COMMUNITY-ACQUIRED PNEUMONIA.

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In New Zealand and Australia trans-thoracic needle aspiration (TNA) is not a commonly used method of obtaining diagnostic material in community-acquired pneumonia (CAP). Conventional culture techniques usually require more than 24hrs to yield a microbiological diagnosis. Molecular techniques have recently been shown to increase the diagnostic yield by 30% to 44%. Pneumothorax is the most common complication and has been reported in up to 30% of procedures. There is variation in the use of radiological guidance for TNA. Methods: Prospective study of all patients admitted to our hospital with CAP. TNA was performed on patients in whom there were no contraindications and from whom informed consent was obtained. For TNA to proceed certain chest ultrasound features were required. The complication rate of TNA and the patient's perceptions of the procedure were recorded. Results: 84 patients have been enrolled to date. 18 patients were asked to undergo TNA, 13 patients consented, 3 did not meet the ultrasound requirement, 10 patients had TNA. There were no pneumothoraces, 4 patients experienced pain during the procedure, and 1 patient would not have had a repeat procedure. Conclusions: TNA is not associated with an unacceptable complication rate and patients find it an acceptable procedure. TNA in combination with molecular techniques may improve the accuracy and reduce the time to microbiological diagnosis.

Supported by Respiratory Research Services, Waikato Hospital

Key words: pneumonia, trans-thoracic needle aspiration, complications.

* Refer to page A16 for