INTRODUCTION OF A CLOSE OBSERVATION UNIT ON A THORACIC MEDICINE WARD—REVIEW OF OUTCOMES IN THE FIRST TWELVE MONTHS

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Patient care delivered by ‘Nursing Specials’ (one on one nursing care) is a costly venture and, in today’s fiscal climate, is not sustainable. However, there is still the need to continue to provide safe, quality patient care, to unwell patients requiring close monitoring in the ward setting. The Thoracic Programme at The Prince Charles Hospital provides care for a range of patients with complex co-morbidities including Hypercapnic Respiratory Failure, Motor Neurone Disease, Muscular Dystrophy, and Respiratory Induced Delirium. These patients require one on one nursing when unwell in the ward environment.

History: From July 2011 to January 2012, nursing specials in the Thoracic Programme accounted for an expenditure of almost $310,000, equating to 9,684 nursing hours, or an FTE of 4.90 nurses.

Aim: To develop an alternative and cost effective model of care to Nursing Specials that would provide safe and effective nursing care to a cohort of patients with severe respiratory problems.

Method: A section of a thoracic ward was redeveloped to create a dedicated, purpose built six bed ‘Close Observation Unit’ (COU), with the aim of providing multi-disciplinary care to a cohort of higher acuity patients. Specific admission criteria were developed to ensure admission of appropriate patients. The existing one to one nursing model was adapted changing to 3 nurses for 6 patients.

Results: From April to September 2013, 298 patients were admitted to the Close Observation Unit, dramatically reducing the number of patients being ‘specially’ across the Thoracic Programme. Our experience over the first six months of care provision and patient outcomes on the COU will be presented.

Conclusion: Caring for high acuity patients in a close observation setting facilitates safe care that is more cost effective than conventional Nurse Specials and also provides the opportunity for up-skilling of nursing teams involved in the care of unwell patients with severe respiratory illnesses. Data collection is ongoing.

THE EFFECTS OF HEATED HUMIDIFICATION IN PATIENTS ON NONINVASIVE VENTILATION (NIV) FOR ACUTE VENTILATORY FAILURE

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Background: During NIV patient airways experience high pressures and flows of dry gas. This, combined with an already compromised airway commonly causes drying of the upper airway mucosa and may lead to loss of comfort, dry mouth, nose and throat and nasal congestion.

Objective: To determine whether heated humidification (HH) improves patient comfort and alleviates the side effects of NIV in acute ventilatory failure.

Method: Patients with type II respiratory failure caused by an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) or obesity hypventilation syndrome (OHS) requiring NIV were randomized to an open-label, parallel study to receive a 4 h ‘washout’ period of NIV, followed by 8 h of NIV with either heated humidification (HH) or without heated humidification (No HH). Patient comfort (visual analogue scale), facial skin temperatures inside and outside of the mask were measured and a NIV side effects questionnaire was completed.

Results: 33 patients were recruited onto the study and data was obtained for 31, 15 in the HH group and 16 in the No HH group. There was no significant difference in the change in comfort scores, from the end of the washout NIV to 8 h of treatment NIV, between HH and No HH groups. However, at 4 h of treatment HH was significantly less comfortable (p = 0.01).

For facial skin temperatures, the difference between body temperature and chin temperature was significantly lower in the HH group compared to the No HH group (mean difference of 3.2°C for HH and 5.4°C for No HH; p = 0.03), indicating that the facial skin temperatures within the mask were higher with HH.

Conclusion: Using HH during NIV increases facial skin temperatures within the mask which had a varying effect on patient comfort.
HOME OXYGEN THERAPY ASSESSMENT FOR COPD PATIENTS DISCHARGED FROM HOSPITAL: RESPIRATORY NP MODEL OF CARE—A PILOT STUDY

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Introduction: Worldwide it is common practice to discharge patients from hospital with chronic obstructive pulmonary disease (COPD) with home oxygen therapy. Patients traditionally have been assessed for short term oxygen therapy (STOT) according to the guidelines for the provision of long term oxygen therapy (LTOT). Assessment of STOT prior to discharge for all COPD patients is empirical in ensuring safe patient discharge, improving quality of life and reducing representation to hospital.

Aim: To determine if patients discharged with COPD were assessed for STOT prior to discharge from hospital and if there has been a change in practice since the introduction of the Chronic Respiratory Disease Nurse Practitioner Model of Care (CRD NP MOC).

Methods: A retrospective uncontrolled comparison clinical audit pilot study of patients discharged with a diagnosis of COPD were assessed pre and post the introduction of the CRD NP MOC. Data collected included assessment of hypoxia and arterial blood gas analysis within 48 hours prior to discharge; readmission rates within 28 days in patients not assessed for STOT and patients discharged with STOT were examined.

Results: There was an increase in the number of arterial blood gas analysis for STOT assessment from 2009 to 2011 and patients discharged with STOT. There was also a reduction in readmission of patients within 28 days of discharge after the introduction of the CRD NP MOC.

Conclusion: Since the introduction of the CRD NP MOC there has been an increase in the number of COPD patients being assessed for STOT and a reduction in hospital readmissions within 28 days of discharge therefore resulting in improved patient outcomes. A recommendation would be for further research into this area.

ANTIOXIDANT-BASED THERAPY FOR THE SUPPRESSION OF EARLY-LIFE INFECTION-INDUCED SEVERE ASTHMA

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Introduction: Clinical and our experimental data suggest that early-life Chlamydia lung infections result in alterations in immunity and lung structure and function, which drive the development of severe asthma in later-life. Oxidative stress plays an important role in the pathophysiology of asthma and has been shown to result in similar changes in the lungs to those induced by early-life infection. We propose that the deleterious effects of an early-life Chlamydia infection may be attributable to infection-induced oxidative stress and that antioxidant-based therapy may protect against Chlamydia-induced severe asthma in later-life.

Aim: To determine the effects of antioxidant treatment in preventing the deleterious effects of early-life Chlamydia lung infection on lung disease in later-life.

Methods: Neonatal mice were infected with Chlamydia and treated with vitamin E, lycopene, vitamin E and lycopene combined or placebo during infection (d0-20). Mice were then subjected to ovalbumin-induced allergic airways disease (AAD) in later-life (d45-61). The effects of treatment on Chlamydia replication and inflammation during early-life infection (d10) and on features of infection-induced severe AAD in later life (d61) were assessed.

Results: We show that antioxidant therapy suppresses infection-induced inflammation in the lung during Chlamydia infection. Surprisingly, we show that whilst vitamin E suppresses, lycopene exacerbates, Chlamydia replication in the lung during infection. These differential effects are associated with contrasting expression profiles for pro-inflammatory and oxidative stress-induced genes. Importantly, despite having opposite effects on Chlamydia replication, vitamin E and lycopene administration during infection protects against Chlamydia-induced severe AAD in later-life, with significant reductions in airway hyperresponsiveness and airways mucus secreting cell numbers observed in infected, antioxidant-treated mice, compared to placebo-treated controls.

Conclusion: These findings suggest that antioxidant therapy protects against the detrimental effects of infection-induced oxidative stress in early-life and may be a therapeutic option for preventing early-life infection-induced severe asthma and lung disease in later-life.
OXIDATIVE STRESS IMPAIRS MITOCHONDRIAL FUNCTION AND LEADS TO DEFICIENT ANTIVIRAL RESPONSES IN PRIMARY BRONCHIAL EPITHELIAL CELLS

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Aim: Oxidative stress characterizes asthma exacerbations. Mitochondria are important in managing reactive oxidant species (ROS). ROS also damages the mitochondria. The mitochondria are also crucial in early antiviral responses to rhinovirus (RV) infection. Our aim was to assess how ROS may affect mitochondrial function and antiviral responses in pBECs to RV infection.

Methods: pBECs from healthy non-smokers were infected with Rhinovirus (RV1B) at an MOI of 1 and were then treated with 1% cigarette smoke extract (CSE) and 0.2 mM H2O2, CXL10, CXL8, interferon (IFN)-λ, cytochrome c and 8-isoprostane were measured by ELISA. ATP levels were measured by bioluminescence. Mitochondrial transcription factors (mTFA, mTB1 and mTB2) were measured by PCR. MAVS cleavage, MDAS, IRFS and NFκB expression were measured by western blotting. Viral replication was measured by TCID50.

Results: Infection with RV led to an increase in CXL8 and an antiviral response with increased CXL10, IFN-λ and RV replication. There was no increase in lipid peroxidation (8-isoprostane) or loss of mitochondrial integrity (release of cytochrome-C). Treatment with CSE and H2O2 resulted in ROS-induced mitochondrial damage; with increased expression of mitochondrial transcription factors (mTFS), release of cytochrome-C, ATP and 8-isoprostane. Treatment with CSE/H2O2 followed by RV infection further increased mTFS expression and cytochrome-C release. There was reduced phosphorylation of IRF3 and a marked reduction in CXL10 and IFN-λ, release, but an increase in NFκB expression and CXL8. In the case of CSE, there was an increase in RV replication. CSE/H2O2 had no effect on MDA-5 expression or cleavage of MAVS.

Conclusion: Exposure to ROS impairs mitochondrial function of pBECs and results in impaired antiviral responses to RV. This may be an important mechanism that increases susceptibility to RV in those with chronic airways disease.

VITAMIN D DEFICIENCY ALTERS LUNG STRUCTURE AND FUNCTION IN MICE

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Introduction: Vitamin D deficiency is associated with increased markers of asthma severity however the causal link has yet to be established.

Aim: We aimed to determine if vitamin D deficiency causes airway hyperresponsiveness (AHR) by altering airway smooth muscle (ASM) mass and if the timing of vitamin D deficiency impacts the response. We also investigated if vitamin D deficiency exacerbates asthma outcomes in a chronic asthma model.

Methods: A mouse model of vitamin D deficiency was developed by raising BALB/c mice on vitamin D-deficient or -replete diets. To study the effects of the timing of vitamin D deficiency, vitamin D-deficient and -replete pups were cross-fostered at birth. To establish a chronic asthma model, mice were intranasally inoculated with house dust mite (HDM) or saline 5 days a week for 5 weeks. AHR was assessed using a ScIREQ flexiVent system. Bronchoalveolar lavage fluid was collected to assess cellular inflammation and cytokine levels. Lungs were inflation-fixed and 5-μm-thick transverse sections from the left lung were stained with Masson’s Trichrome for ASM measurements. Lung structure was assessed in right lung sections using stereological methods.

Results: Vitamin D-deficient female mice had higher airway resistance at the maximal dose of methacholine and had significantly more ASM in large airways. Male mice which were vitamin D-replete in utero had lower airway resistance compared to whole-life vitamin D-deficient males. HDM-treated vitamin D-deficient females had increased baseline airway resistance and ASM. Transforming growth factor (TGF-β) levels were reduced in vitamin D-deficient mice.

Conclusions: Vitamin D deficiency caused increased ASM, AHR and altered lung structure in vitamin D-deficient adult female mice. Unexpectedly vitamin D deficiency protected against impairments in baseline lung function and ASM increases following chronic HDM exposure. The effects of vitamin D deficiency on TGF-β levels may contribute to the altered lung function and structure observed.

REDUCED TLR7 EXPRESSION MAY UNDERPIN IMPAIRED RESPONSE TO VIRAL INFECTION IN ASTHMA

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Introduction: Some asthmatics display impaired type 1 IFN responses and exaggerated inflammatory responses upon Rhinovirus (RV) infection, however, the molecular basis for these observations remain obscure despite intensive research. Recently, impaired production of antiviral molecules and IFN-induced cytokines have been described in asthmatics when peripheral blood mononuclear cells (PBMC) were stimulated with the TLR7 agonist imiquimod but not in response to the TLR3 agonist poly I : C (Roponen et al. ERJ 2009). Interestingly, some asthmatics display variations in their TLR7 genotype that may be related to impaired TLR7 function.

Aim: To identify the molecular basis for the aberrant response to RV observed in asthmatics.

Method: Bronchial biopsies were taken from well characterized asthmatics and healthy controls. Expression of key pattern recognition receptors including TLR3 and 7 were enumerated using qPCR. WT and TLR7-/- BALB/c mouse models of RV18 induced exacerbation of house dust mite driven allergic airways disease were employed to determine the relevance of TLR7 signalling in antiviral responses and inflammation.

Results: Expression of TLR7 was found to be significantly reduced in bronchial biopsies from eosinophilic but not neutrophilic asthmatics. TLR7-/- mice were found to have a deficient response to RV1B infection with reduced levels of type I and III interferons and elevated viral titre at 24 hr post infection when compared to wild type controls. Treatment with type I or type III interferons limited RV1B replication as well as impaired both neutrophilic and eosinophilic inflammation.

Conclusion: Our study suggests deficient TLR7 function as a crucial mechanism underpinning impaired IFN responses to RV1B in allergic airways inflammation. Restoration of IFN not only reduced viral replication but also impaired RV1B-induced inflammation. These studies may indicate that augmentation of TLR7-regulated effector functions could be exploited as a novel therapeutic approach for the treatment of virus-induced asthma exacerbation in asthmatics with deficient IFN responses and/or eosinophilic inflammation.

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ABERRANT SPLICING OF HISTONE MODIFICATION GENES AFFECTS ASTHMA PATHOGENESIS AND SEVERITY

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Aim: Alternative splicing represents a mechanism for increasing the diversity of proteins. However, an imbalance in splicing variant expression can lead to disease development or impact on severity. Dendritic cells (DC) function is affected in asthmatic patients. This influences the immune response in asthmatics and their respond to stimuli. The purpose of this research was to assess the overall gene expression and alternative splicing events in immature Monocyte-derived DC (imMoDC) in healthy subjects and mild and severe asthmatics.

Methods: Exon array analysis was performed using total RNA isolated from imMoDC of mild and severe asthmatics and healthy controls. RT PCR was used to confirm the existence of newly identified splice variants.

Results: The 10 genes found to have the most significant splice variants associated with Asthma and Asthma phenotypes had functional roles in a variety of disease and cellular mechanisms such as histone modifications, dendritic cell differentiation, development of dendrites, NFkB and p53 pathways, GPCR signalling and cell cycle progression. Two genes SETD7 and KDM6A associated with histone methylation marks known to have a co-localized, bivalent priming effect on gene expression of a subset of genes including central immune genes. We identified novel splice variants of these genes. Splicing events were confirmed, and found to cause a loss of functional 5′UTR predicted miRNA binding sites. Furthermore, expression of these splice variants may influence asthma severity.

Conclusions: These differential splicing events between asthma phenotypes represent a novel regulatory chromatin model of epigenetic control of the immune system, offering exciting new insights into the interface of the epigenetic and genetic landscape of the disease. Understanding regulatory mechanisms underlying the methylation in asthma, this research has the potential to facilitate development of a new approach in the field of pharmacogenetics in asthma treatment.

MACROPHAGE ACTIVATION IS A DETERMINANT OF DEVELOPMENTAL EFFECTS OF IMMUNOMETABOLISM IN OBESE ASTHMA

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Aim: Obesity is characterized by infiltration of adipose tissue by activated macrophages and mast cells, which further expedite a proinflammatory microenvironment, systemic inflammation and negative clinical effects (immuno-metabolism). However, the interaction between these activated immune cells and obese asthma, across age and sex remains unexplained. The aim of this study was to determine if there is a developmental effect of immuno-metabolism in obese asthma.

Methods: Obese and non-obese asthmatic children and adults underwent clinical assessment including spirometry, asthma control questionnaire (ACQ) and body composition assessment by dual x-ray absorptiometry. Systemic inflammation was assessed by measuring plasma sCD163, tryptase, CRP and other adipo-cytokines. Associations between systemic inflammatory markers, body composition and clinical aspects of asthma were examined across age and sex.

Results: Obese asthmatic adults were characterized by significantly high CRP (p = <0.0001) and leptin (p = <0.0001), compared to non-obese adults and obese children. In contrast, obese asthmatic children were characterized by significantly high sCD163 in obese girls (p = <0.0001) and CRP in obese women (p = <0.001). Tryptase, a marker of mast cell activation, was not significantly different across age groups. A positive correlation between percentage of android fat and sCD163 was noted in obese girls (r = 0.7, p = 0.003) and obese women (r = 0.65, p = 0.003). In obese girls, sCD163 was inversely associated with FEV1% predicted (r = −0.55, p = 0.02) and positively associated with ACQ (r = 0.57, p = 0.02).

Conclusion: Obese children with asthma have evidence of macrophage activation, which may be sex-specific and contribute to worse asthma control and airflow limitation. A greater understanding of the mechanistic link between inflammation and clinical effects in obese asthmatics may enable us to develop age specific therapeutic options, thus reducing treatment related adverse effects, particularly in children.
ROUTinely COLlected CLINICAL and LABORATORY Data CAN RELiABLY PREDICT LONGER SURVIVAL in MALIGNANT PLEURAL MEsOTHELIOMA

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Aim: Selection and identification of appropriate patients with malignant pleural mesothelioma (MPM) for treatment remains a challenge. Conventional multivariate logistic regression often produces complex models with limited applicability for clinicians and with no account of the interaction between parameters.

Method: Using electronic database search we identified 274 cases of histologically or cytologically confirmed MPM over a 72-month period at a single site. Electronic laboratory, radiological and case note review was performed. Variables were collected from the time of diagnosis including demographics, symptoms, routine haematology and serum biochemistry. Regression Tree analysis using chi-squared Automatic Interaction Detection (CHAID) methodology was employed using 12 month survival as the dependent variable. Internal cross validation using 10 sample-folds was used to assess model accuracy.

Results: Median (IQR) age was 69.0 (62–76) years, male 237 (86.2%), histology: epithelioid 115 (41.8%), biphasic 36 (11.1%), sarcomatoid 32 (11.8%), not defined 91 (33.1%). Overall median survival was 13.01 months. From 21 variables, histology sub-type was the strongest predictive factor. The other statistically significant variables were performance status, serum Na (dichotomized above/below 140 mmol/L) and Hb (dichotomized above/below 123 g/L). Six risk groups were created by the model with 2 high risk, 1 medium risk and 3 low risk groups. Epithelioid histology and a normal haemoglobin (>123 g/L) conferred the lowest risk of mortality with 76% of patients with these characteristics surviving more than 12 months. The sensitivity of the model was 84.7%, specificity 69.8%, negative predictive value 0.91. Median and 12 month survival varied significantly across the six groups (Chi-square p < 0.0001; Log Rank test, p < 0.0001).

Conclusion: Survival greater than 12 months can be reliably predicted using routinely collected data from the time of diagnosis in a simple model. The model’s risk groups had significantly different survival characteristics.
12 MONTHS OF LOW DOSE CT SCAN SCREENING AN ASBESTOS EXPOSED POPULATION: RESULTS FROM THE WESTERN AUSTRALIA ASBESTOS REVIEW PROGRAM

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Aim: Asbestos mining (particularly in the Wittenoom region) and its widespread use in Western Australia has led to significant asbestos exposures to the local population. In 2012 the Asbestos Review Program (ARP) introduced low dose CT (LDCT) screening as an alternative to chest radiograph, with which the population has been previously screened.

Method: All subjects offered LDCT over a 12-month period were enrolled. Subjects with abnormal scans were further investigated by routine clinical pathways. The images were acquired using a helical acquisition in the prone position with no intravenous contrast. A significant nodule was defined as having a volume of at least 50 mm³ without benign type calcification, with semi-solid nodules also regarded as suspicious. Each scan was read by a specialist thoracic radiologist using commercially available viewing software (Siemens LungCare™).

Results: 892 of 1235 ARP participants underwent LDCT; median age was 70 years, 730 (81.8%) were male. 130 were ex-Wittenoom mine workers, 226 ex-Wittenoom residents, 536 other had occupational exposure. 68 were current smokers, 505 ex-smokers, 319 never smoked; 221/573 (38.6%) with a >30 pack/year smoking history. Significant nodules were reported in 79 (8.8%) subjects (64 with one nodule, 12 with two nodules and one with three). 77 participants had a 3-month interval CT (recall rate for nodules 8.6%). In all, 8 participants had further investigation for nodules: 6 subjects underwent CT-guided biopsy and two proceeded directly to excision. Lung cancer was diagnosed in 6 cases (4 stage 1a adenocarcinoma, 1 stage 2a squamous cell carcinoma, and 1 atypical carcinoid). All subjects underwent curative surgery; 2 where never smokers, 2 ex-smokers and 1 current smoker. One nodule was a benign intrapulmonary lymph node and 1 patient had a non-diagnostic needle biopsy and the nodule did not change on follow-up at 3 months. True positive rate was 7.59% and false positive 92.4%. There were no major complications from investigations or treatments. Mean effective radiation dose estimate was 1 mSv (range 0.6–2 mSv). Additionally, malignant pleural mesothelioma (MPM) was diagnosed in 4 other subjects.

Conclusion: The prevalence of lung cancer in an asbestos exposed, pre-screened, population was 0.67% and MPM 0.45%. LDCT screening in this setting is effective at identifying early stage lung cancer. Defining an asbestos-exposed at risk population and cost-effectiveness of the screening needs further assessment.

BARD1, AN ONCOGENIC DRIVER AND BIOMARKER OF LUNG CANCER

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Recently, overexpression of BRCA1 mRNA was strongly associated with poor survival in NSCLC patients. Furthermore, BRCA1 deficiency was correlated with resistance to poly(ADP-ribose) polymerase (PARP) inhibitors. However, the rationale for this correlation is poorly understood. We were interested in whether BARD1, a BRCA1 interacting and stabilizing protein and tumour suppressor in its own right, was also overexpressed in NSCLC and a marker of progression. We found that full length (FL) BARD1 was down-regulated in more than 100 samples tested, but deletion-bearing isoforms lacking the BRCA1 interaction domain were overexpressed. We had reported previously that such isoforms are antagonists of the tumour suppressor functions of BARD1 and BRCA1 and that BARD1 isoforms are oncogenic drivers in various cancers including NSCLC. In a study performed on more than 100 NSCLC cases all expressed BARD1 isoforms, but not FL BARD1, on the protein level. Cancer-associated isoforms of BARD1 are immunogenic and antibodies against could be detected in NSCLC patients. Analysis of more than 200 patients and controls permitted to define a highly sensitive (95%) and specific (93%) test for the detection of lung cancer based on autoimmun antibodies against isoforms of BARD1.

DETERMINANTS OF THE 6-MIN WALK DISTANCE IN INDIVIDUALS WITH LUNG CANCER

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Introduction: Non-small cell lung cancer (NSCLC) is associated with high disease burden and physical hardship. The 6 Min Walk Distance (6MWD) is the most commonly used measure of functional capacity in NSCLC, however limited information is available about its clinical determinants in this population.

Aims: To identify: 1) the relationship between 6MWD, demographic and disease-related factors and 2) the clinical profile of patients whose 6MWD declined over 6-months post-diagnosis.

Method: Fifty participants (32 male, mean ± SD age 68 ± 9 years) with stage I-III NSCLC completed the 6MWD at diagnosis prior to treatment and 6-months later. Minimal important decline in the 6MWD was set at 30 m. Additional measures included; Colinet Comorbidity Index, Eastern Cooperative Oncology Group Scale (function), dynamometry (strength) and questionnaires (physical activity, symptoms, mood and health-related quality of life (HRQoL)). Correlations and linear regression were used to identify relationships between variables.

Results: The mean ± SD 6MWD at baseline was 408 ± 106 m. There was a small positive relationship between the 6MWD and age (r = 0.35, p = 0.028). The 6MWD correlated positively with function (r = 0.60, p < 0.0005), strength (r = 0.61, p < 0.0005) and physical activity (r = 0.51, p = 0.001); and negatively with fatigue (r = 0.50, p = 0.002), dyspnoea (r = 0.54, p = 0.001), pain (r = 0.38, p = 0.021) and depression (r = 0.49, p = 0.003). The 6MWD declined significantly from baseline by a mean (95% confidence interval) of 78 m (5–148) p = 0.037. 62% of participants had a decline in 6MWD >30 m: these patients had greater comorbidities (p = 0.009); worse function (p = 0.030), pain (p = 0.006) and distress (p = 0.017); and lower physical activity levels (p = 0.024) at baseline compared to patients whose 6MWD declined <30 m over 6-months. Pain and comorbidities were independent predictors, explaining 17.2% of variance and together correctly classifying 76% of patients whose functional capacity declined.

Conclusion: The 6MWD is closely related to physical performance, comorbidities and symptoms in NSCLC.
AN AUDIT OF LUNG CANCER DIAGNOSIS AND TREATMENT WAITING TIMES AT THE GOLD COAST HOSPITAL

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Introduction/Aim: We aimed to assess waiting times for diagnosis and treatment of patients referred to the Lung Cancer Clinic at the Gold Coast Hospital. As there are no national guidelines on cancer waiting times, we adopted National Health Service (England) Cancer Plan standards, which prescribe waiting times of two weeks for first appointments, one month from decision-to-treat to treatment, and two months from referral to treatment.

Method: All new patients referred between December 2012 and May 2013 were included. The audit was conducted by case-note review. Data collected included demographic information and cancer type, completeness of referral (assessed against departmental guidelines which require chest radiograph, baseline blood tests and chest CT results), and waiting times for clinic appointments, diagnostic investigations, tissue diagnosis and first treatment.

Results: 31 new patients were seen, with males comprising 52% (16 patients). The median age was 71 years. 42% of referrals were complete. There were 27 cases (87%) of non-small cell lung cancer. The median time from referral to first appointment was 13 days. Median times to bronchoscopy, CT-guided fine-needle aspiration and PET scan were 3.14 and 7 days respectively. 17 cases (55%) received oncological therapy, 8 (26%) surgical and 5 (16%) conservative palliation. The median time to oncological treatment was 15 days compared to 36.5 days for surgery, and from referral to treatment, 62 days.

Conclusion: Referring doctors would benefit from education on making complete referrals. While the target for waiting time from referral to first appointment has been achieved, there are significant delays to surgical treatment. There is also a lack of capacity in Interventional Radiology compared to other investigation modalities. The median overall waiting time from referral to treatment meets the audit standard, but we have identified areas where further investment is necessary to make the patient pathway smoother and shorter.

OLIV SIG 1 – ORAL PRESENTATIONS

RITUXIMAB IN SEVERE, TREATMENT REFRACTORY CONNECTIVE TISSUE DISEASE ASSOCIATED INTERSTITIAL LUNG DISEASE

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Introduction: In patients with connective tissue disease associated interstitial lung disease (CTD-ILD) progressing despite conventional immunosuppression, rituximab, a B lymphocyte depleting monoclonal antibody, may offer an effective rescue therapy.

Methods: Retrospective assessment of patients with severe, progressive CTD-ILD treated with rituximab between 2007 and 2013. Change in pulmonary function tests (PFTs) compared to pre-rituximab levels, was assessed at six to twelve months post-treatment.

Results: Forty-two patients (twenty-four females) with a mean age of 50.9 ± 11.6 years and underlying CTD diagnoses of idiopathic inflammatory myopathy (n = 15), undifferentiated CTD (n = 11), systemic sclerosis (n = 10), mixed CTD (n = 2), rheumatoid arthritis (n = 2), systemic lupus erythematosus (n = 1) and Sjögren’s syndrome (n = 1) were treated with rituximab. All patients received conventional immunosuppression (including intravenous cyclophosphamide in 38 patients) prior to rituximab administration, and continued to deteriorate (defined as worsening respiratory symptoms, PFTs and/or CT imaging attributable to CTD-ILD). At the time of rituximab administration patients had severe physiologic impairment with a mean forced vital capacity (FVC) of 49.0% (± 15.5) and diffusing capacity of the lung for carbon monoxide (DLco) of 24.8% (± 8.1). In contrast with a mean decline in FVC of 16.1% (± 13.9) and DLco of 21.1% (± 16.0) in the six to twelve months prior to rituximab, analysis of paired pulmonary function data revealed an improvement in FVC of 15.2% (± 21.6; p < 0.01) and DLco of 14.6% (± 12.9; p < 0.01) in the six to twelve months following rituximab. During a median follow-up of 12.2 months (range 1 to 47 months), five patients died (progressive CTD-ILD in four patients, and pneumonia in one patient), and three patients developed serious infectious complications requiring hospitalization.

Conclusions: In severe CTD-ILD unresponsive to conventional immunosuppression, rituximab may represent an effective, potentially life-saving, therapeutic intervention.

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DYSREGULATED REPAIR AND EPITHELIAL INJURY IN SMALL AND LARGE AIRWAYS OF LUNG TRANSPLANT PATIENTS IS AMELIORATED BY AZITHROMCYIN

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Introduction: Dysregulated airway epithelial repair following injury is a suggested mechanism of post-transplant obliterator bronchiolitis (OB), but there is limited direct evidence of this or whether epithelial repair is a feasible treatment target.

Aims: To compare gene and cellular characteristics of injury and repair pre/post azithromycin in the small (SA) and large (LA) airway epithelium of transplant patients.

Methods: Primary airway epithelial cells (pAECs) were obtained from OB, non-OB and healthy control subjects. Initially, markers of injury and dysregulated repair were determined via qPCR. Proliferative capacity of SA and LA epithelial cells were determined via proliferation assays. Wound repair experiments (+/-) azithromycin (1 μg/ml) were performed and repair assessed.

Results: Gene expression of MMP7 post transplantation was downregulated (1.3 fold SA & LA), but was significantly upregulated in OB SA (2.8 fold) compared to control. There was significant upregulation in the expression of MMP3 (2.6 fold SA; 1.8 fold LA) and Integrin B6 (2.8 fold SA; 2.6 fold LA), and a significant downregulation in Integrin B8 (3.5 fold SA; 3.3 fold LA) in OB AEC compared to controls. Small AEC were observed to proliferate at a significantly higher rate than their large airway counterparts (p < 0.05). Despite a higher proliferative capacity SA were found to have a dysregulated repair process post injury. Addition of azithromycin significantly induced repair in these cells (2 fold; p < 0.05) however, complete repair was still not achieved.

Conclusion: Chronic airway epithelial injury and dysregulated repair appear evident in the airway of post-transplant patients. Azithromycin appears to partially mitigate this process and assist epithelial repair post injury.

Supported by: McCusker Foundation, NHMRC.

Keywords: airway epithelium, azithromycin, repair, transplantation, obliterator bronchiolitis.
UTILITY OF CARDIAC MAGNETIC RESONANCE IMAGING (CMR) IN THE DIAGNOSIS OF CARDIAC SARCOIDOSIS

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Introduction: The diagnosis of Cardiac Sarcoidosis (CS) remains controversial and often clinically challenging. Cardiac Magnetic Resonance Imaging (CMR) is an emerging modality for the diagnosis of CS. We compared CMR with the current guidelines for the diagnosis of CS.

Aim: To determine the utility of CMR in the diagnosis of CS and to evaluate the spectrum of CMR findings.

Methods: We retrospectively studied patients with pulmonary sarcoidosis who were referred for CMR to evaluate for CS. We reviewed electrocardiograms, echocardiograms and, where available, gallium and PET scans. The diagnostic accuracy of CMR for CS was determined using the 1993 Japanese Ministry of Health and Welfare guidelines and the modified 2006 guidelines as the reference standard.

Results: Thirty-eight patients (49±14 years; 53% Male) with pulmonary sarcoidosis underwent CMR for assessment of CS. Nine (24%) had CMR findings consistent with CS. All of these patients had late gadolinium enhancement and 78% with LGE had positive T2 weighted imaging. There was no significant difference in left ventricular volumes and function in patients with or without LGE.

Two patients with LGE fulfilled the 1993 diagnostic criteria for CS while only one fulfilled the 2006 guidelines. Three patients with LGE on CMR had ventricular tachycardia (33%). Only one patient with a normal CMR met the reference diagnostic criteria for CS.

There was an association with pulmonary stage and LGE on CMR in that CS was less common with stage I disease (11%) compared to stage III or IV (67%). However, LGE was seen across all stages.

Conclusion: CMR has a higher sensitivity and may have more optimal specificity for the diagnosis of CS compared to the current diagnostic criteria. Given cardiac involvement accounts for the majority of deaths from sarcoidosis, in particular the risk of arrhythmia and sudden cardiac death, we suggest a greater role for CMR in the diagnosis of CS.

PRIMARY LUNG FIBROBLASTS FROM PATIENTS WITH IPF SHOW INCREASED STIFFNESS WHICH MAY BE DUE TO DIFFERENTIAL PRODUCTION OF ECM PROTEINS

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Idiopathic pulmonary fibrosis (IPF) is a chronic and fatally progressive interstitial lung disease with no current treatment. Dysregulation of the lung fibroblast is an important driver of pulmonary fibrogenesis. Progression of fibrosis, driven by transforming growth factor-beta 1 (TGFβ1), leads to changes in extracellular matrix (ECM) composition and results in the loss of lung function.

The aim of this study was to investigate the relationship between the production of ECM proteins fibulin-1, peristin, tenasin-C and fibronectin, and the stiffness of the matrix of isolated pulmonary fibroblasts grown in culture under basal and TGFβ1-stimulated conditions.

Primary parenchymal fibroblasts derived from 5 patients with IPF and 4 subjects without lung disease were assessed for levels of mRNA by real-time quantitative PCR and for levels of cellular protein by western blot. Stiffness (Young’s modulus) of fibroblasts was measured using atomic force microscopy. Whole lung lysate from 4 patients with IPF and 4 subjects without lung disease was collected and protein levels were measured by western blot.

Fibroblasts derived from patients with IPF had significantly higher levels of fibulin-1 mRNA (p < 0.05) and significantly lower levels of tenasin-C mRNA (p < 0.05) compared to fibroblasts from subjects without lung disease. Fibulin-1 in whole lung lysate and cellular fibroblast protein was increased in patients with IPF (p < 0.01), and their fibroblasts showed a different pattern of surface stiffness. Treatment with TGFβ1 increased cellular fibulin-1 production in fibroblasts from only patients with IPF (p < 0.01).

Fibroblast stiffness of fibroblasts from patients with IPF was increased under basal conditions. Fibulin-1 may play a role in the pathogenesis of lung fibrosis resulting in increased stiffness of the lung parenchyma and perpetual loss of lung function.

LUNG DISEASE IS FREQUENT FOLLOWING ALLOGENIC BONE MARROW TRANSPLANTATION

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Chronic graft versus host disease (GVHD) is an important non-infectious complication following allogenic bone marrow transplant (BMT). Pulmonary GVHD is increasingly being recognized as an important cause of morbidity and mortality, so pre- and post-transplant respiratory function tests (RFT) are recommended.

Aim: The aim of this study was to document the respiratory abnormalities in consecutive patients undergoing BMT from a 5 year period.

Method: Lung function measures were performed pre-transplant and then in follow-up after 1, 3, 6, 9 and 12 months. Those with significant clinical or spirometric deterioration were reviewed by a Respiratory Physician, with chest radiographs, CT scans and bronchoscopies performed as clinically indicated.

Results: 288 patients, (173 males) were recruited between 1/1/08 and 1/1/13. 42 patients (15%) died within the first 3 months, leaving 246 followed up with repeated lung function. In this group, lung function decreased by >10% in more than 15% of patients. The majority developed obstruction with decreases in FEV1, but stable FVC, though some developed decreases in both FEV1 and FVC. In those with an obstructive picture, CT scans generally demonstrated air trapping, sometimes with features of bronchiectasis. In those with reductions in FEV1, and FVC, CT scans showed various features including gas trapping ± bronchiectasis ± interstitial infiltrates. Bronchoscopy was performed if there were signs of possible infection but was generally unhelpful. Early treatment with increased immunosuppression and prednisolone, reversed the deterioration in some but not all patients.

Conclusion: Pulmonary involvement remains common following BMT and requires ongoing surveillance for early recognition and intervention. Bronchiectasis is a new finding in pulmonary GVH and warrants further investigation.

A RARE SYSTEMIC CONDITION POST LUNG TRANSPLANTATION

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Introduction: This is a case presentation of a rare systemic condition post lung transplantation that can mimic sepsis.

Case Report: A 63 year old female received a bilateral sequential lung transplant in 2010 for COPD. In 2013, she presented with 2 weeks of fevers, dyspnoea and cough, initial blood investigations revealed pancytopenia and acute renal failure. CXR and CT chest showed evidence of pulmonary oedema and left lower lobe patchy consolidation. Bronchoscopy showed normal anatomies and no organisms on washings or BAL. She was commenced on broad spectrum intravenous antibiotics and cautious diuretic therapy. No specific pathogens found on extensive investigations including nosopharyngeal swab, blood and urine cultures. She continued to deteriorate with ongoing high fevers and worsening pancytopenia, and later developed disseminated intravascular coagulation. Further specific blood investigations revealed high ferritin 52702, hypertriglyceridemia 3.8 and non-specific hepatitis. Bone marrow biopsy confirmed the diagnosis of haemophagocytic syndrome (HPS).

Discussion: HPS is a distinct clinico-pathologic entity, which most commonly occurs following infection in lung transplant patients, but can also occur ‘de novo’. HPS is characterized by increased proliferation and activation of benign macrophages engulfing erythrocytes, leukocytes, platelets and their precursors. There are strict diagnostic criteria of which 5 or more criteria need to be met. This patient fulfilled 6 criteria: fever, splenomegaly, cytopenia of 2 or more cell lines, hypertriglyceridaemia, serum ferritin > 500, hepatitis and haemophagocytosis. Treatment for HPS includes intravenous dexamethasone and etoposide. HPS has a poor prognosis, which may improve with specific treatment.

Conclusion: HPS is a rare complication following lung transplantation. HPS is often misdiagnosed as the presentation is non-specific and can mimic sepsis. HPS should be suspected in patients with sepsis not responding to therapy as expected, with ongoing high fevers and pancytopenia.
THE SOUTH AUSTRALIAN LUNG TRANSPLANT UNIT OUTCOMES FROM A SATELLITE CENTRE

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Aim: The South Australian (SA) Lung Transplant Unit is a non-surgical ‘satellite’ state-wide centre which works closely with interstate surgical units. This enables expertise to be centralized without patients needing to relocate for prolonged periods of time. This study assessed outcomes of transplant recipients managed by the South Australian Lung Transplant Unit, and compared these with available data from a national and international level.

Method: A retrospective, single-centre observational study was performed. Data was obtained through review of case notes, medical correspondence, computerized pathology and pulmonary function tests. Indication for transplant, age at transplant, length of survival, complications, renal function, pulmonary function and cause of death were recorded.

Results: One hundred and fifty five SA patients received lung transplants from 1990 until 1st July 2013. Median age of transplant was 44 years. The main indications for transplantation were COPD and Cystic Fibrosis. One hundred and seventeen (75%) patients received bilateral lung transplants, 25 (17%) received single lungs transplant, and 13 (8%) received heart-lung transplant. 91 (59%) patients remain alive today. One year, five year and ten year survival were 93%, 66% and 51% respectively. Median survival for all recipients was 10.0 years (10.0 and 7.3 years for bilateral sequential and single lung transplants respectively). Thirty-one percent of South Australian patients had documented bronchiolitis obliterans syndrome after 5 years, and 41.2% after 10 years. Complication rates including BOS, length of survival and cause of death were all comparable to international and national data.

Conclusion: South Australian patients have at least equivalent outcomes post lung transplantation, compared to international and national lung transplant recipients. The role of the satellite centre is highlighted and supported by outcomes shown in this study.

PAEDIATRIC SIG – ORAL PRESENTATIONS

ESTABLISHMENT OF THE VICTORIAN PRIMARY CILIARY DYSKINESIA DIAGNOSTIC SERVICE

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Aim: To describe the establishment of a state wide diagnostic service for Primary Ciliary Dyskinesia (PCD), an inherited condition where ciliary dysfunction leads to impaired mucociliary clearance, recurrent upper and lower respiratory tract infections, and bronchiectasis. In 2012 we received funding for the establishment of the states first diagnostic PCD service.

Method: Referrals are accepted from consultant physicians and ENT surgeons. Though situated at RCH the service is funded for all ages. An adult diagnostic outpatient clinic has been established. All patient testing is completed within one day. Initially nasal nitric oxide (nNO), a known good screening tool for PCD, is determined. A ciliary nasal brush biopsy is then taken. Cell strips obtained are then viewed directly under light microscopy and recorded using a high speed video recorder. Playback at slower speeds allows determination of beat frequency, and beat pattern. This is Australia’s first and currently only high speed video recording cilial assessment technique. Cell strips are then submitted for electron microscopy to determine cilia ultra structure. A QI initiative has been established with a referral centre in the UK where a subset of studies each 6 months are submitted for assessment.

Results: Prior to the first adult OPD 25 referrals from adult based services were obtained. In addition 16 referrals were received from paediatricians. 5 adults have been tested all had a history of bronchiectasis without known cause. In children two children who have been previously labelled as having PCD have been found to have no evidence of PCD from nNO measurement, ciliary beat frequency analysis and electron microscopic assessment of cilia ultra structure.

Key words: Primary Ciliary Dyskinesia, Cilia, microscopy, diagnostics.

QUANTITATIVE ANALYSIS OF COMPUTED TOMOGRAPHY AND X-RAY IN BRONCHIECTASIS

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Introduction: Bronchiectasis (BX) is often only diagnosed with extensive disease and/or after recurrent chest infections. Radiologist reads of chest x-rays (CXRs) miss 66% of high-resolution computed tomography (HRCT) diagnosed cases of bronchiectasis. We need better use of routine chest imaging to allow earlier detection or suspicion of BX in children.

Aim: This study uses quantitative image analysis to determine whether changes in pulmonary tissue in BX can be identified automatically from CXR imaging.

Methods: Concurrent HRCT and CXRs, and pulmonary function in 24 children aged 5 years with cystic fibrosis were used for analysis. The diameters of artery and blood vessel pairs passing perpendicular to the imaging plane and Bhalla scores were calculated from HRCT to assess BX. For each subject the mean, standard deviation and coefficient of variation of pixel intensity were calculated from HRCT and CXRs in the whole lung, and in three sub-regions in the gravitational direction.

Results: Radiological scoring did not correlate with pulmonary function measures (FEV1, FVC, or FEV1/FVC). As the ratio of airway to blood vessel diameter increased FEV1/FVC decreased (p < 0.05). Also as mean Hounsfield value (0.05) in HRCT increased FEV1/FVC increased (p < 0.05). CXR measures of tissue heterogeneity correlated significantly with HRCT measures (p < 0.01).

Conclusions: We have shown a quantitative analysis of HRCT and CXR imaging, which could be calculated automatically, correlates with pulmonary function, and that CXR measures correlate with HRCT. This illustrates the potential use of computed CXR measures to detect pulmonary abnormalities in BX. In the future we will identify specific BX features in HRCT and CXR to determine whether a digital footprint for these features can be identified.

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Subjects were part of the ACFB Study (ACTRN 126050065639).
FACTORS ASSOCIATED WITH RESPIRATORY MORBIDITY IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH CEREBRAL PALSY

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Introduction: Although respiratory disease is the most common cause of mortality in individuals with cerebral palsy (CP), little is known about respiratory morbidity and its causes in CP.

Aim: To describe respiratory symptoms in individuals from birth to 25 years diagnosed with CP, and to determine which factors are associated with respiratory morbidity.

Methods: Cross sectional survey of respiratory symptoms in people with CP aged 0–26 years, using a self or parent/carer completed questionnaire. Questionnaires were received concerning 552 eligible participants aged 0 to 26 years, (mean 11 years, 1 month (SD = 5 years, 11 months)), (57% of those directly solicited), with a GMFCS distribution representative of the total Western Australian CP population and representation across the age range. Univariate and multivariate logistic regression were used to determine associations between self/carer-reported respiratory morbidity and respiratory-related hospitalizations or courses of antibiotics for respiratory infections over the previous 12-month period.

Results: In univariate analyses, factors significantly associated with respiratory hospitalizations were age (inversely), gross motor function (GMFCS), frequency of cough, chestiness and wheeze, respiratory signs at meals, difficulty managing saliva, reflux, seizures, scoliosis, and asthma, but not presence of a smoker in the household. Multivariate analysis demonstrated that those individuals with the highest motor disability (GMFCS IV and V) were only at increased risk of respiratory hospitalization if they required modifications to feeding (OR 5.36 (95% CI 2.89 to 9.96)). Those who took nutrition only by tube had the highest risk (OR 12.63 (95% CI 5.11 to 31.00)).

Conclusion: Respiratory hospitalizations are common in children and young people with CP. Feeding in-coordination rather than level of motor disability is the most important predictor of respiratory illness in this group.

CAN eNO HELP TO PREDICT CHILDREN AT A PARTICULARLY HIGH RISK FOR RESPIRATORY COMPLICATIONS?

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Perioperative Respiratory Adverse Events (PRAE) is a major cause of morbidity and mortality in paediatric anaesthesia. Airway inflammation is a known risk factor (RF) for PRAE and the degree of inflammation can be assessed non-invasively by exhaled Nitric Oxide (eNO).

Aim: This study aimed therefore at measuring eNO preoperatively and assessed its ability to improve the prediction of PRAE.

Methods: 280 children (6–16 years) undergoing elective minor surgery were recruited. 100 children had no RF for PRAE and 180 children had ≥2 RF. eNO level was measured using a hand held portable device (Niox Mino, aerocrine) prior to surgery and any PRAE was recorded afterwards.

Results: Prediction capacities were assessed using binary logistic regression. The odds ratio for the prediction capacity of eNO was 3.050 (p = 0.002, CI: 1.5–6.1) in the RF group while it was not significant in the no RF group (p = 0.508). If presence of RF was the only predictor used, the odds ratio for PRAE prediction was 3.63 (p = 0.001, CI: 1.7–7.5). Receiver Operating Characteristic curves yielded an area under the curve of 0.60, 0.63 and 0.69 respectively when RF and eNO were considered alone and combined.

Conclusion: eNO was a fair predictor of PRAE when RF were present. RF and eNO together only slightly improved the prediction capacity. For routine clinical practice the presence of RF can therefore be considered as a clinically more adequate predictor for PRAE.

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SLEEP QUALITY IN CHILDREN WITH CYSTIC FIBROSIS: ASSOCIATIONS WITH MOOD

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Introduction: In adults with cystic fibrosis (CF) sleep disturbance is common and associated with depressed mood however there is a paucity of international data regarding children.

Aim: To determine sleep patterns and quality in children with clinically stable CF and healthy controls and to examine the relationship to mood.

Methods: Children with CF, free from pulmonary exacerbation and age matched healthy control children (age range 7–18 y) were recruited. Each completed 2 weeks of sleep diary together with sleep questionnaires (OSA-18, Paediatric Daytime Sleepiness Scale (PDSS), Sleep Disturbance Scale for Children (SDSC)). Overnight SpO2 was measured using pulse oximetry. Questionnaires were used to assess mood (Children’s Depression Inventory (CDI), Beck Depression Inventory-Youth (BDI-Y)). Data were compared between groups with one way ANOVA with Student Newman Keuls posthoc analysis if normally distributed or Kruskal-Wallis one way ANOVA on Ranks with Dunns posthoc analysis if not.

Results: 46 CF (24 M/22 F) and 39 control (19 M/20 F) children well-matched for age completed the study. Mean (± SD) FEV1 in the CF group; 80 ± 19% predicted. CF and control subjects reported no significant differences in sleep duration or frequency of night waking. Children with CF had significantly lower mean SpO2 than controls (96.9 ± 1.7% vs. 98.4 ± 0.8%, p < 0.001). Children with CF had higher total scores than controls for the OSA-18 (median 28 vs. 24, p < 0.05), PDSS (mean 14.3 ± 4.5 vs. 10.2 ± 4.4, p < 0.001) and SDSC (median 45.5 vs. 35.0, p < 0.05). Young children (7–12 y) with CF (n = 28) exhibited higher mood scores on the CDI (reflecting lower mood) than controls (n = 24) (mean 45.8 ± 7.3 vs. 41.3 ± 5.1, p = 0.01). In the CF group, there was no correlation between mood scores and any of the sleep questionnaire scores or FEV1.

Conclusion: Children with clinically stable CF report significantly more sleep problems than healthy children despite similar durations of sleep. Young children with CF have lowered mood compared to controls however it is not directly associated with poor subjective sleep quality. This relationship needs to be examined in children with more severe CF lung disease.

LUNG FUNCTION DECLINE IN SCHOOL-AGE CHILDREN WITH A NEONATAL CLASSIFICATION OF BRONCHOPULMONARY DYSPLASIA (BPD)

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Introduction: BPD remains the most significant pulmonary complication of preterm birth with the contemporary disease pathology reflecting prematurity rather than the treatment induced lung injury seen in classical BPD. The long term respiratory sequelae of children born extremely preterm with ‘New BPD’ is currently unknown.

Aim: To examine how lung function tracks over the school years in children born extremely preterm.

Methods: Term controls (N = 32) and children born <32 weeks gestational age (GA) with (+BPD, N = 74) and without (-BPD, N = 44) a neonatal classification of BPD performed lung function at 4–7 and/or 9–11 years. Outcomes from spirometry (FEV1, FVC, FEV1/FVC, FEF25-75%) and the forced oscillation technique (area under reactance curve (AX), resonant frequency (Fres)) were expressed as Z-scores and preterm children compared to controls using one-way ANOVA. Paired t-test and Fisher’s exact test were used to assess change in lung function and change in the proportion of children with lung function outside normal limits (1.64 Z-scores) between visits.

Results: Compared to term controls, children born preterm demonstrated lower lung function at both visits by spirometry (FEV1, FEV1/FVC, FEF25-75%) and the FOT (AX, Fres, X8) regardless of BPD classification (P < 0.05). To date, longitudinal data is available in 15 term and 68 preterm children (39+BPD; 29-BPD). The +BPD group had a decline (mean Z-score difference ± SD) in FEV1 (~0.47 ± 0.92; P = 0.011) and FEF25-75% (~0.61 ± 0.76; P = 0.001) between the two visits and the proportion of children with abnormal FEV1/FVC and FEF25-75% increased from 32% at visit 1 to 52% and 68% at visit 2, respectively. In contrast, AX and X8 showed significant improvement over time in both preterm groups (P < 0.05), though the proportion of children outside the normal limit was not different between the two time points. No longitudinal changes were found in the term or –BPD groups.

Conclusion: Children born <32 weeks GA have lower lung function than their term counterparts. Those classified with BPD experience further lung function decline during childhood which may warrant intervention.
SUPPORTING SMOKING CESSION IN PRIMARY CARE:
RESULTS OF THE QUIT IN GENERAL PRACTICE STUDY
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Aim: Primary care interventions to support smoking cessation can be effective but new models are needed to increase uptake and effectiveness. The aim of this study was to determine if personalized smoking cessation support provided primarily by the practice nurse (PN) is more effective than Quitline referral or usual GP care.

Method: The study was a three arm cluster randomized controlled trial conducted in general practices in Sydney and Melbourne. Participants were adult smokers presenting to see their general practitioner (GP). Quit support primarily provided by the PN was compared to Quitline referral and usual GP care. PNs in the study undertook six h of education and were then supported by mentoring phone calls. Outcome measures were sustained abstinence and point prevalence abstinence at 3 month and 12 month follow-up collected by telephone interviewers blind to group allocation.

Results: Follow-up at 12 months was 82%. Assuming all those lost to follow-up relapsed, the sustained and point prevalence abstinence rates respectively at three months by group were: PN intervention 13.1% and 16.3%; Quitline referral 10.8% and 14.2%; Usual GP care 11.4% and 15.0%. At 12 months the rates were: PN intervention 5.4% and 17.1%; Quitline referral 4.4% and 18.6%; Usual GP care 2.9% and 16.4%. Only 43% of participants in the PN intervention group attended to see the nurse. Multilevel regression analysis showed no effect of intervention group overall but participants who received partial or complete PN support were more likely to report sustained abstinence (partial support OR 2.27; complete support OR 5.34).

Conclusion: The results show no difference by intervention group on intention to treat analysis. Those patients who received more intensive nurse intervention were more likely to quit. This suggests that PN led cessation support can be effective if patients are engaged and attend for follow-up.

WHAT ROLE CAN THE COMMUNITY NURSE PLAY IN REGARD TO ASTHMA, COPD AND DEMENTIA?
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Introduction: Between 2005 and 2008, 77% of Australia’s asthma deaths occurred in those over 60 years old. In 2007, 4% of all deaths occurring in those over 55 years were attributed to COPD. By 2020, COPD is expected to become the 3rd leading cause of death. The long-acting inhaled anti-cholinergic tiotropium, combination long-acting beta-agonists and inhaled corticosteroids are used in the treatment of both asthma and COPD. Older people are likely to have multimorbidities, cognitive and functional decline and are more susceptible to adverse effects of these treatments. However, Pharmaceutical Benefit Scheme data demonstrate that dispensing of inhaled and oral corticosteroids increases with age and that guideline-based use of medication is likely compromised by cognitive impairment. We aimed to determine the prevalence of cognitive impairment among clients over the age of 60 years with respiratory illness.

Method: A review of a Victorian home nursing service database was undertaken to establish: the overall number of clients, their age and gender, how many received support for medicines management, and how many over the age of 60 years had the co-diagnosis of respiratory illness and cognitive impairment.

Results: Between the July 2012 and June 2013, 31,921 clients (47% male, mean age 71 years) received home nursing visits. Fifty-two percent were for the purpose of supporting medicines management, including to those with cognitive impairment many of whom do not yet have a diagnosis of dementia. Ten percent of visits were to those with a diagnosis of asthma or COPD of these only 645 (2%) had a diagnosis of dementia.

Conclusion: Community nurses could play an important role in identifying potential side effects caused by respiratory medications and ensuring appropriate use and accessibility in those with cognitive impairment. Evidence-based respiratory education for community nurses could enhance the delivery of optimal care to older people.
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RESPIRATORY HEALTH SERVICE DELIVERY AND UTILIZATION BY ABORIGINAL AND TORRES STRAIT ISLANDER AUSTRALIANS: A QUALITATIVE ANALYSIS OF THE BARRIERS AND EnableS TO OPTIMAL MEDICAL MANAGEMENT

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Aim: To explore the barriers and enablers to optimal respiratory health service utilization by Aboriginal and Torres Strait Islander (TSI) Australians.

Method: Semi-structured interviews developed in consultation with Aboriginal Elders, researchers and healthcare workers were conducted with respiratory consultants, community stakeholders and Aboriginal Elders between March and October 2013. Quantitative data was also collected. Data was analyzed using QSR NVivo version 10.

Results: Data saturation was researched with recruitment of n = 5 respiratory consultants and n = 10 Aboriginal community Elders, researchers and healthcare workers across four states and one territory in Australia. Participants agreed that improvements in healthcare practices have occurred through computerization of medical records and sharing of data across communities, provision of outreach services and increased funding. However, inherent racism in Indigenous health still exists with perceptions that ‘...people think it’s all a bit harder and they just shouldn’t bother ...’ which is impeding optimal medical management. Barriers to communication between respiratory consultants and Indigenous people were identified including difficulties with numeracy, literacy and concerns around discussing personal problems with a doctor. A more strategic healthcare strategy is required for the ‘language of disadvantage’ that is adaptive and responsive to people’s linguistic, cultural and social needs, irrespective of whether they are Indigenous, from non-English speaking backgrounds or a particular socio-economic group. It was considered important that health professionals take every opportunity to provide education because ‘...if we stop asking, we stop giving any opportunity to respond.’ Focusing on youth to improve education around healthy lifestyle messages are believed to be an important strategy to improving health service utilization and recognising problems before they progress.

Conclusion: There have been many improvements to healthcare delivery for Indigenous patients; however, a more strategic healthcare strategy incorporating education is needed to target ‘disadvantaged’ populations as a whole rather than focusing on the Indigenous.

ELECTRONIC REMINDERS IMPROVE ADHERENCE WITH PREVENTER INHALERS IN AUSTRALIAN PRIMARY CARE PATIENTS

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Aim: Poor asthma control is associated with poor preventer adherence. GP-led interventions which promote adherence in primary care are needed. We tested the effectiveness of Inhaler Reminders with adherence Feedback (IRF) and/or GP-delivered Personalized Adherence Discussions (PAD) for improving preventer adherence and asthma control in primary care.

Method: In a 6-month cluster randomized controlled trial, we compared IRF, PAD and IRF + PAD with active usual care; all GPs were trained to provide active usual care with a written action plan and an inhaler technique check. Sydney GPs enrolled patients with a suboptimal Asthma Control Test (ACT) ≤19 and already prescribed a combination controller inhaler for ≥3 months. Electronic inhaler monitors recorded time/date of each puff and uploaded medication use data to a secure website. In IRF groups, monitors also provided reminder ringtones for missed doses, displayed time last dose taken, and patients and their GPs could access graphs of medication use online. PAD group GPs received 2 h communication training, telephone booster training, and support tools to facilitate brief adherence discussions. ACT was collected at baseline, 2, 4 and 6 months. Intention to treat mixed model analysis incorporated cluster effect and repeated measures.

Results: 43 GPs (56% male) enrolled 143 patients (mean age 40.3 yrs ± 15.2; FEV1% predicted 77 ± 20; ACT 14.6 ± 3.8). Over 6 months, ICS adherence was higher in IR (73% ± 28%) than non-IR groups (46% ± 28%, p < 0.0001). Asthma control improved in all groups (overall mean change in ACT 4.5 ± 4.9, p < 0.0001) but there was no significant difference between groups (p = 0.14). Interventions were valued by GPs.

Conclusion: In this pragmatic primary care study, inhaler reminders were feasible and substantially improved ICS adherence, compared with adherence discussions or usual care. The complex relationship between prescription, dose taken, and asthma control needs further exploration.

WHAT FACTORS CONTRIBUTE TO PARTICIPANT RECRUITMENT BY GPs IN PRIMARY CARE RANDOMIZED CONTROLLED TRIALS?

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Aim: Primary-care based randomized controlled trials (RCTs) build an important evidence base relevant to general practice, but little evidence exists on causes of recruitment problems which often hamper such trials. Our aim was to investigate issues that impede and facilitate recruitment in one such trial.

Method: Sydney GPs participating in a 6-month primary care-based cluster RCT, testing interventions for improving medication adherence and asthma control, completed a survey about barriers to recruiting patients. The survey comprised Likert scale and free text questions about GPs’ individual recruitment issues. Univariate and multivariate analyses (Spearman’s rho, Chi square, Backward linear regression), identified variables predicting participant recruitment by GPs.

Results: 37 of 40 GPs (age 54.3 ± SD 9.0; 40% female) who enrolled ≥1 patients (mean no. patients 2.6 ± 2.5) completed the survey, versus 5 of 15 GPs (age 52.3 ± SD 11.5; 67% female) who enrolled zero patients. Enhanced recruitment was associated with GPs ‘inviting a greater number of patients to participate’ (rho 0.327, p = 0.039), and poorer recruitment with ‘working in a training practice for medical students’ (Chi-square, p = 0.012). After adjustment in multivariate regression, poor recruitment was predicted only by longer duration to first patient enrolled, and enhanced recruitment by GPs perceiving that they ‘saw eligible patients in their practice’ (b=0.920 and 0.346 respectively); explained variance of the model was 44.3%. Free text recruitment barriers included: ‘GPs in group practices are not empowered to recruit’ and ‘GPs perceive their patients to be unsuitable for research participation’, while facilitators included ‘good support from the research team’.

Conclusion: Barriers to participant recruitment in primary-care based RCTs seem related to GPs’ personal resources/attitudes, participant factors, practice culture and level of support from research teams. Future research is needed to investigate potential solutions to these varied issues.
CONCURRENT SYMPOSIUM 2: COPD – ORAL PRESENTATIONS

RESULTS OF THE SECOND UPDATE OF THE COPD SELF-MANAGEMENT COCHRANE REVIEW

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Background: New studies have been published and new opinions have been formed concerning the contents of self-management for patients with Chronic Obstructive Pulmonary Disease (COPD), since the latest COPD self-management Cochrane review (2008).

Aim: This update assesses whether COPD self-management reduces health care utilization and improve health outcomes.

Methods: Trials were identified using the Cochrane Airways Group Specialized Register of trials. Randomized and controlled clinical trials published after 1994 that assessed efficacy of COPD self-management programmes were included. Interventions excluded were those: 1) containing less than two contact moments between patient and health-care provider; 2) defined as pulmonary rehabilitation (PR) offered in hospital or rehabilitation centre; and 3) community- or home-based PR solely directed towards exercise. When appropriate, meta-analyses using data from randomized controlled trials were performed.

Results: 1300 Abstracts were screened for eligibility. 29 studies were included of which 23 compared self-management to usual care (6 compared self-management components head-to-head). Patients who participated in a self-management programme were less likely to have one or more respiratory-related hospital admissions compared to patients receiving usual care (OR: 0.57 (95%CI (0.43, 0.75)). All studies that measured health-related quality of life (HRQoL) with the St. George’s Respiratory Questionnaire (SGRQ) showed lower (meaning better quality of life) total scores in the intervention group compared to the control group (weighted mean difference (WMD) −3.51 (95%CI −5.37, −1.65)). WMDs for the SGRQ domains were −3.09 (95%CI −5.42, −0.77), −2.75 (95%CI −4.93, −0.56), and −5.71 (95%CI −9.17, −2.25) for symptoms, activities, and impacts respectively.

Conclusions: Results of this update strengthen the conclusions of the present Cochrane review. Patients participating in a COPD self-management programme are less likely to be hospitalized for a respiratory-related cause than patients who receive usual care. Moreover, these programmes increase HRQoL.

CURRENT STATUS OF ASThma IN PRIMARY CARE

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Introduction: While the management of asthma from a clinical perspective is well defined, in primary care, there are many challenges.

Aim: The aim of this study was to capture the current status of asthma of people in the community and to identify key areas of suboptimal management.

Methods: This study utilized a cross-sectional design and was conducted in May 2012–October 2013. Through a convenient sample of GP practices, people with asthma were identified and underwent a comprehensive asthma review. At the review visit data was collected through an electronic survey and included a large range of variables ranging from asthma control to beliefs and concerns about regular inhaled therapy.

Results: Asthma reviews were completed for 140 patients, with a diagnosis of asthma. The median age of patients was 51 years with the median number of years of having asthma being 22 years. Based on symptoms and 44% of patients were classified as having partially controlled or uncontrolled asthma respectively. However, 60% of patients perceived their asthma to be well controlled. Fifty percent of patients had a diagnosis of allergic rhinitis while 89% of patients reported mild to severe symptoms. While 42%, 37% and 20% were using a Turbuhailer, pMDI and Accuhaler respectively to administer their combination therapy, only 7% were regularly using a spacer device within the last 12 months only 6% of patients had their inhaler technique assessed and only 13% of patients had received an asthma review by a respiratory specialist or nurse outside their general practice.

Conclusions: This study has uncovered issues with the management of asthma in primary care. The high proportion of those with allergic rhinitis symptoms suggests this is an area of need.

EXPLORING THE ROLE OF FEEDBACK IN INHALER TECHNIQUE EDUCATION

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Introduction: Feedback is a critical component of any educational intervention. When it comes to feedback associated with inhaler technique education, there is a lack of knowledge on its role or its potential to solve the major issue of poor inhaler technique.

Aims: This study aims to explore the role of feedback in inhaler technique education and its impact on inhaler technique of patients over time.

Methods: A parallel group, repeated measures study was conducted in the community pharmacy in which the effectiveness of current best practice inhaler technique education utilising qualitative visual feedback (Group 1) was compared with a combination of qualitative and quantitative visual feedback (Group 2). The impact of these two interventions on inhaler technique maintenance was evaluated.

Community pharmacists were randomly allocated to recruit people with asthma using a dry powder inhaler. At Visit 1 their inhaler technique was evaluated, education delivered and followed up at Visit 2 (one month later).

Results: Both educational interventions resulted in an increase in the proportion of patients with correct inhaler technique from 4% to 51% for Group 1 and 6% to 83% for Group 2 (Pearson’s Chi-Squared, p = 0.03, n = 49 and Pearson’s Chi-Squared, p = 0.01, n = 48, respectively). The magnitude of improvement was statistically significantly higher for Group 2 compared with Group 1 (n = 97, p = 0.02, Pearson’s Chi-Square test). A significant improvement in asthma control was observed for both Groups 1 and 2 over time (1.6±1.0) to 1.4±0.8) and 1.7±1.0) and 1.3±1.0) respectively Wilcoxon Signed Rank test, p < 0.05, n = 49 and n = 48 respectively.

Conclusion: The nature of feedback impacts on the effectiveness of inhaler technique education with regards to correct inhaler technique maintenance over time. This has significant implications for clinical outcomes.
EXAMINATION OF VARIATIONS IN RESPONDER RATES IN COPD CLINICAL TRIAL OUTCOMES

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Aim: The MCID (minimum clinically important difference) is used to identify responders to treatment in clinical trials, enabling a comparison of responder rates between treatment arms. Relatively little is published about responder rates and their variation between trials.

Method: Data from three clinical trials with once-daily QVA149 (glycopyrronium (GLY) + indacaterol (IND)), GLY, IND, open-label tiotropium (TIO) and placebo (PB) was compared to examine the size of the variation in responder rates.

Results: High responder rates were seen with PB, ranging from 44.2% to 57.5% (Table). Very high TDI and SGRQ responder rates were observed with QVA149 but that study also had the highest PB responder rate. Using TIO as an active comparator, the range of response to treatment was wide (47.3–59.4). Spearman’s ρ = 0.66 between TIO and PB suggested an association between their response rates, but the difference between TIO-PB responder rates varied in the range −0.02 to 10.7 between outcomes and trials.

Conclusion: Placebo responder rates vary across studies. Studies in which more than half of the patients have a clinically significant response to placebo may be particularly problematic to interpret, especially when exploring differences between treatments.

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*p < 0.05; †p < 0.01 versus placebo

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CONSERVATIVE VS. INVASIVE TREATMENT OF PRIMARY SPONTANEOUS PNEUMOTHORAX: A RETROSPECTIVE COHORT STUDY

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Aim: The best management of primary spontaneous pneumothorax is unclear. Conservative treatment has been proposed, but no studies comparing conservative with invasive management have been done where pneumothorax size has been numerically quantified. This study aimed to investigate the hypothesis that conservative management is non-inferior to invasive treatment for primary spontaneous pneumothoraces of any size.

Method: Retrospective cohort study of adult patients with primary spontaneous pneumothorax treated at an Australian tertiary hospital from 2006–2011, conducted by case-note and chest radiograph review. Patient demographics, smoking status, and outcome data (complications, recurrences, resolution and length of stay) were collected. Pneumothorax size, as a percentage of lung volume lost, was calculated using the Collins method which is based on the sum of interpleural distances.

Results: 127 cases from 116 patients were identified. Males comprised 75% of patients, and the median age at presentation was 37. 82% of cases were ever-smokers. Of the cases in which pre-treatment radiographs were available, 53 were treated conservatively and 58 invasively with tube thoracostomy. All were clinically stable. When stratified by pneumothorax size, age, sex, ethnicity, and smoking status had no effect on outcome. Compared to invasive treatment, conservative management resulted in zero complications (vs. 25%), an equal recurrence rate (11% vs. 10%), and a significantly shorter mean length of stay (0.6 vs. 6.5 days). Eight conservatively-treated cases had post-treatment radiographs demonstrating complete resolution, with a further six showing a reduction in size within two weeks. 39 invasively-managed cases had radiographs showing full lung re-expansion.

Conclusion: This study suggests that conservative management is safer than, and not inferior to, tube thoracostomy in pneumothoraces of any size. It appears more cost-efficient, and may be the optimal first-line treatment in clinically stable patients. Given the limitations of this study, a large randomized controlled trial is required to conclusively prove this assertion.

Key words: conservative, pneumothorax, Collins.

Nomination for Young Investigator Award: No.

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SPONTANEOUS PNEUMOTHORAX; A MULTICENTRE RETROSPECTIVE ANALYSIS OF EMERGENCY TREATMENT, COMPLICATIONS AND OUTCOMES

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Introduction: Approaches to the initial management of spontaneous pneumothorax vary amongst clinicians.

Background: We aimed to determine the clinical features of spontaneous pneumothorax presenting to the emergency department (ED), interventions, outcomes and potential risk factors for poor outcomes after treatment.

Methods: Retrospective chart review from EDs of three major referral and two general hospitals in Australia of presentations with primary spontaneous pneumothorax (PSP) or secondary spontaneous pneumothorax (SSP) between 2006 and 2011. Main outcome measures were prolonged air leak (chest drainage >5 days) and pneumothorax recurrence within 1 year.

Results: We identified 225 people with PSP and 98 with SSP. There were no cases of clinical tension pneumothorax with absolute hypotension (SBP <90 mmHg). Significant hypoxaemia (SpO2 <92%) was observed only in SSP and in older patients (age ≥ 50 years) with PSP. The commonest initial drainage procedure was underwater seal drainage via Seldinger catheter or thoracostomy tube. Prolonged air leak occurred in 16% (95% confidence interval 10%–23%) of PSP and 31% (21%–42%) of SSP. Independent risk factors for prolonged drainage were non-asthma SSP and large pneumothorax on presentation. Complications of drain insertion and/or management were recorded in 11% (7.5%–16%) of those having drains inserted. Recurrences occurred in 5/91 (5%, 1.8%–12%) in those treated without drainage versus 40/232 (17%, 13%–23%) in those treated by drainage of which half occurred in the first month after drainage.

Conclusion: Pneumothorax drainage is associated with significant morbidity including prolonged air leak and complications of tube insertion and/or management. Because PSP is well tolerated in younger people even with large pneumothoraces, conservative treatment in this subgroup may be a viable option to improve patient outcomes and should be tested in a clinical trial.

FLEXIBLE FIBRE-OPTIC BRONCHOSCOPY, OBESITY AND SLEEP DISORDERED BREATHING: PATIENTS CHARACTERISTICS AND COMPLICATIONS IN 221 CASES

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Introduction: Fibre-optic bronchoscopy (FOB) is an essential diagnostic and therapeutic tool in Pulmonary Medicine. There are limited data on patients’ characteristics including body mass index (BMI) and presence of obstructive sleep apnoea (OSA) in relation to bronchoscopic complications.

Aim: To evaluate patients’ characteristics, types of sedation, diagnostic yield and complications in FOB in a non-intensive care unit (ICU) setting.

Method: Retrospective chart review of consecutive patients undergoing FOB over a twelve-month period in a tertiary care teaching hospital. Patients’ characteristics, sedation details, endobronchial interventions, diagnostic outcome and adverse events were reported.

Results: 227 patients underwent FOB from 10th January to 18th December 2012. Six patients were excluded from analysis because FOB was performed in ICU. 128 patients (57.9%) were male. The mean age was 61.1 ± 14.4 years. 13 patients (5.9%) had known OSA. The mean BMI was 25.8 ± 5.3 kg/m². 44 patients (19.9%) had BMI ≥ 30. 99% of patients received midazolam and fentanyl, the average doses were 3.6 mg (range 1–7 mg) and 70.5 μg (range 25–100 μg), respectively. 10.4% of patients received propofol. Interventions including biopsies and brushings were performed in 32.1% of patients. The overall diagnostic yield was 52.0%, of which 21.7% were confirmed malignancies. 98% of FOB sedation were performed by trained nurse sedationists. 0.9% of FOB (2/221) were associated with adverse outcomes. Both patients did not have OSA and had BMI <30. Those two individuals had persistent hypoxia and tachycardia, and a post biopsy pneumothorax, respectively. The overall mortality rate was 0%.

Conclusion: FOB appears to be a valuable diagnostic tool with a low rate of complications. Our chart review did not find an association between obesity and presence of OSA with adverse outcome in FOB.

AN AUDIT OF A METROPOLITAN HOSPITAL PLEURAL SERVICE

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Introduction: In 2011 Box Hill Hospital (BHH) introduced a referral based pleural service for the diagnosis and management of pleural disease.

Aim: To review our pleural service’s consistency of practice and complication rates.

Method: Retrospective audit of patients referred to BHH pleural service between January 2013 and October 2013. We identified baseline patient demographics, procedural characteristics and pathology results from patient records.

Results: 49 cases were referred to the pleural service. 33/49 (85%) had ICCs inserted (31 pleural effusions, 2 pneumothoraces). 33/33 (100%) had written consent. 16/49 (15%) had no ICC attempted due to insufficient fluid. 2/33 (6%) were performed by a consultant, 21/33 (64%) by a registrar, and 10/33 (30%) by a supervised RMO. Minor complications included introduction of air on inser- tion 5/33 (15%). More serious complications included tube-site infection 1/33 (3%), empyema 1/33 (3%), haemothorax 1/33 (3%), dislodgement of tube 1/33 (3%) and delayed bronchopleural fistula 2/33 (6%). There was no difference in complication rates between the three types of operators (p = 0.5).

There were no organ punctures or mortality attributed directly to tube insertion. 33/33 (98%) of ICCs were inserted after-hours. Mean LOS was 17.2 days (95% CI, 13.3–21.1). Whilst ICCs were in-situ for 2.9 days (95% CI, 1.9–3.9). Of the pleural effusions drained 30/30 (100%) had appropriate investigations of pleural fluid recommended by BTS guidelines, but 12/30 (40%) had inadequate investigations of paired serum. However, in all cases (30/30) we were able to differentiate an exudate 26/30 (87%) from a transudate 4/30 (13%). Of 10 cases with positive pneumococci, 5/10 (50%) helped establish a new diagnosis of malignancy, 2/10 (20%) upstaged a known malignancy.

Conclusion: Compliance with consensus guidelines for consent and analy- sis of pleural fluid was excellent, but more consistency is required for paired serum samples. Complication rates were similar to the published literature. Our team provided a useful service in the management of pleural disease.

DIAGNOSTIC YIELD AND UTILITY OF BRONCHOSCOPIC SAMPLING IN IMMUNOCOMPROMISED PATIENTS WITH PULMONARY INFILTRATES

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Introduction: Immunosuppressed patients frequently present with pulmo- nary infiltrates and life threatening pulmonary symptoms. Infiltrates could be secondary to infective or non-infective causes. While empirical treatment is often instituted as early as possible, obtaining a diagnosis has been associated with improved mortality. Bronchoscopy and Bronchoalveolar lavage (BAL) have been shown to be successful methods of diagnosis of pulmonary infiltrates.

Aim: To determine the diagnostic yield and utility of bronchoscopy and BAL in immunosuppressed patients with radiological evidence of pulmonary infiltrates at the Alfred Hospital and to determine if the results of BAL changed subsequent management.

Method: This was a retrospective chart audit of patients with Haematological malignancies, Bone Marrow Transplant (BMT) and Human Immunodeficiency Virus (HIV) with pulmonary infiltrates. 95 bronchoscopies fulfilling the inclusion criteria performed at the Alfred Hospital between April 2008 and August 2010 were selected. Clinical details regarding BAL results and pre and post bronchoscopy treatment were collected.

Results: An organism or other pathology was identified in 65% of bronchoscopies. Bacteria, viruses and fungi were identified in 12, 35 and 31% of bronchoscopies respectively. In 2% of bronchoscopies a non-infective pathology was identified. The Charlson Index (BMI) and the presence definite or probable change in treatment in 27% of patients. Complications occurred in 2% of bronchoscopies. There was one death within 24 h of bronchoscopy.

Conclusion: Bronchoscopy is safe with minimal complications. We demon- strated that bronchoscopies and BAL have a good diagnostic yield and result in treatment modifications in 27% of patients.
EFFICACY OF MACITENTAN ON LONG-TERM OUTCOMES IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH): SUB-ANALYSIS OF SERAPHIN COMPARING INCIDENT AND PREVALENT PATIENT POPULATIONS NOT TREATED WITH PAH-SPECIFIC THERAPY AT BASELINE

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Aim: In SERAPHIN macitentan significantly reduced the risk of morbidity and mortality, and death due to PAH or hospitalization for PAH (DHPAH). This sub-analysis examined the effects of macitentan on long-term outcomes in incident and prevalent patients who were treatment-naïve at enrolment.

Method: 742 PAH patients (≥ 12 years) were randomized to placebo, 3 mg or 10 mg macitentan, once daily. According to the delay between PAH diagnosis and study enrolment, treatment-naïve patients were classified as incident (>6 months) or prevalent (≥6 months). Unadjusted hazard ratios (HR, 95% confidence intervals) were calculated using Cox regression models to determine the effect of macitentan on morbidity and mortality, and DHPAH.

Result: The 265 treatment-naïve patients comprised 108 incident and 157 prevalent patients, and study enrolment, treatment-naive patients were classified as incident (6 months) or prevalent (>6 months). Unadjusted hazard ratios (HR, 95% confidence intervals) were calculated using Cox regression models to determine the effect of macitentan on morbidity and mortality, and DHPAH.

Conclusion: Despite similar baseline disease severity, the natural history (placebo arm) of incident patients showed a higher risk of morbidity and mortality as compared to prevalent patients. Macitentan 10 mg significantly reduced the risk of morbidity and mortality, and DHPAH in both patient groups.

IMPACT OF BMPR2 THERAPY ON DOWNSTREAM CELL SIGNALLING IN A PAH MODEL: A MICROARRAY STUDY

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Introduction: Pulmonary arterial hypertension (PAH) is caused by pulmonary vascular remodelling, as a result of abnormal cellular signalling. Reduced expression of the bone morphogenetic protein receptor type-2 (BMPR2) is causally linked to familial, idiopathic and secondary forms of PAH. Previously we have attenuated the disease using BMPR2 targeted gene delivery.

Aim: Using microarray technology, we now investigate possible novel pathways involved in the amelioration of the disease process.

Methods: Adenoviral BMPR2 gene delivery was targeted to the pulmonary vascular endothelium in the monocrotaline (MCT) rat model of PAH and PAH amelioration was assessed through hemodynamic measurements. RNA was isolated and purified from lung tissue (n = 4 each group) and ran on an Affymetrix DNA microarray. Significant genes were analyzed through the use of IPA (Ingenuity Pathways Systems) to examine the downstream effects and impact on cellular function in the treatment group compared to the disease state.

Results: Reduced PAH was confirmed in the BMPR2 treated group. 2197 significant genes were identified between the disease only and treatment groups. Pathways involved in up-regulation of DNA repair and replication as well as increased activity of cell cycle regulation and checkpoint control were seen in the BMPR2 group. Haematological changes involved an increase in activity of T-cells (z = 2.341) and natural killer cells (z = 2.028) and normal cytokeratin organization (z = 3.741) in the BMPR2 group. Additionally this group had increased quantity (z = 3.346) and differentiation (z = 3.344) of hematopoietic progenitor cells. Molecular networks involved in these changes include known key mediators of angiogenesis, cell proliferation and apoptosis such as vascular endothelial growth factor (VEFG), MAP Kinases and ERK1/2.

Conclusion: This study has identified many novel cellular signalling pathways, which may contribute to the attenuation of PAH following BMPR2 therapy. Confirmation of changes using alternate techniques is required and is ongoing.

THE NEED FOR DEDICATED RIGHT VENTRICULAR ECHOCARDIOGRAPHY PROTOCOLS IN PULMONARY ARTERIAL HYPERTENSION

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Introduction: Right ventricular dysfunction (RVD) is a predictor of morbidity and mortality in pulmonary arterial hypertension (PAH). The accuracy of echocardiography parameters of RVD has not been validated in patients with PAH. We have previously reported the concerning anomaly of normalization of quantitative parameters of annular motion in the setting of severe RVD characterized by the “rocking right ventricle”.

Aim: To evaluate a right ventricular echocardiography protocol reliably reflects RVD in PAH using pulmonary hemodynamics and cardiac magnetic resonance imaging (CMRI)-derived RV ejection fraction (RVEF) as a gold standard.

Method: 51 (72%) patients from tertiary PAH centre, 20 IPAH, 1 FPAH, 6 PAH-CHD, 12 PAH-CVD, 5 CTEPH, 1 porto-pulmonary & 6 out of proportion therapies. Echocardiography confirmed PHT, RHC and CMRI-derived RVEF as a gold standard.

Results: Mean age 56.8 ± 17.7 years, mNYHA-FC 2.9 ± 0.6; m6MWT 414 ± 150.3 metres with 57% prescribed mono, 29% dual & 14% triple PAH therapies. Echocardiography confirmed PHT with mRVSP 85.5 mmHg ± 24, mPAP 25.4 cm² ± 7.6, 29% paracardial effusion, TAPSE 18.9 ± 2.3, S’ velocity 10.8 cm/s, RV FAC 18.9% ± 6.6, 1.6 mglobal strain –18.2% (range –9.3 to –30%) and mRV free wall strain –19.6% (–11.4 to –25%) compared to mPAP 49.4 mmHg, PVR 9.4 WU and CI 2.3 L/min/m². Sub-group analysis 14 patients with cardiac MRI (mRVEDV 141.7 ± 35 ml (BSA corrected) & RVEF 32.8% ± 7.3 were compared with mRVSP 98.2 mmHg ± 18.4, mPAP 27.4 cm² ± 5.5, and again mean TAPSE and S’ were preserved 19.9 mm ± 3.7, 11.6 cm/s ± 1.8

Conclusion: This study adds to the notion of standardized echocardiography RV protocols and reporting in the assessment and monitoring PAH patients and removal of reliance of TAPSE and S’ velocity from guidelines.

Key words: Right ventricular dysfunction, echocardiography & pulmonary hypertension
COMPUTATIONAL MODELS TO STRATIFY PATIENTS WITH ACUTE AND CHRONIC PULMONARY EMBOLISM

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Introduction: Both acute and chronic pulmonary embolisms are difficult to manage, due to variability in response between patients with apparently similar level of disease. The consequences result in increased pulmonary artery pressure and ventilation perfusion mismatch due to the combined influence of mechanical obstruction and local vessel remodelling (chronic cases) or vasoactive responses (acute cases). The ability to determine the functional influence of these conditions from computed tomography (CT) imaging and to predict a patient’s response to treatment would allow clinicians to make improved decisions on treatment.

Aim: This study aims to create patient specific models of the response of an individual to acute and chronic pulmonary embolism.

Methods: Subject specific models of 12 patients with acute and 4 patients with chronic pulmonary embolism were constructed from CT pulmonary angiograms. Central blood vessels, emboli and regions of low perfusion were segmented via semi-automated algorithms. Occlusion locations were mapped to the computational model of the individual’s lungs and the hemodynamic response to this occlusion was predicted.

Results: Model prediction of hypoxemia and pulmonary artery pressure correlated closely with clinical metrics for these measures (r < 0.01 in each case), whereas the clot load defined by number of segmental vessels occluded only weekly correlated. The model predicts that large central occlusions have more impact on function than smaller distributed occlusions.

Conclusions: We have developed subject specific models that predict function from CT pulmonary angiograms in individuals with acute and chronic pulmonary embolism. The effect of redistribution of blood from its normal pattern—and hence the potential effect on gas exchange—is represented in the model. The model can therefore be used to predict the impact of surgical or pharmacological treatments on an individual’s pulmonary function, and provides a novel tool in the stratification of patients with these conditions.

SUSTAINED EFFECT OF MACITENTAN ON EXERCISE CAPACITY AND THE ASSOCIATION OF ITS MEASURE WITH LONG-TERM OUTCOMES IN PULMONARY ARTERIAL HYPERTENSION

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Aim: In SERAPHIN, macitentan significantly reduced the risk of mortality and mortality, and death due to PAH or hospitalization for PAH (DHPAH). This sub-analysis examined the effect of macitentan on 6-min walk distance (6 MWD) and the association between 6 MWD and DHPAH.

Method: 742 PAH patients were randomized to placebo, 3 mg or 10 mg macitentan, once daily. Treatment-by-visit interaction and placebo-corrected treatment effects were calculated using repeated measures analysis on change in 6 MWD from baseline to months 3, 6, 12. Hazard ratios were calculated to measure associations between quartiles of baseline 6 MWD, absolute 6 MWD at Month 6, 6 MWD changes at Month 6, and DHPAH; performed in patients with available 6 MWD data at Month 6 and DHPAH data from Month 6 up to end of treatment.

Results: Baseline mean ± SD 6 MWD for placebo (n = 249), macitentan 3 mg (n = 248) and macitentan 10 mg (n = 243) was 352 ± 111 m, 364 ± 96 m and 363 ± 93 m, respectively. No significant treatment-by-visit interaction (p = 0.47) suggested beneficial effects of macitentan on 6 MWD (3 mg: +21.5 m (10.0–33.0); p = 0.0003 and 10 mg: +25.4 m (13.8–37.0); p < 0.0001 vs. placebo) were maintained over 12 months. The Table shows associations between 6 MWD and DHPAH.

Conclusions: Macitentan provided sustained improvements in 6 MWD over 12 months. No association between 6 MWD changes and long-term clinical outcome was demonstrated.

Table: Association of 6 MWD with risk of DHPAH

<table>
<thead>
<tr>
<th>6 MWD</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q2 vs. Q1</th>
<th>Q3 vs. Q1</th>
<th>Q4 vs. Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>≤300</td>
<td>&gt;300–372</td>
<td>&gt;372–430</td>
<td>&gt;430</td>
<td>0.56</td>
<td>0.39</td>
<td>0.23</td>
</tr>
<tr>
<td>(n = 742)</td>
<td>0.44</td>
<td>0.27</td>
<td>0.15</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute at Month 6</td>
<td>≤48</td>
<td>&gt;48–348</td>
<td>&gt;348–455</td>
<td>&gt;455</td>
<td>0.55</td>
<td>0.40</td>
<td>0.33</td>
</tr>
<tr>
<td>(n = 599)</td>
<td>0.38</td>
<td>0.27</td>
<td>0.19</td>
<td>0.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at Month 6</td>
<td>≤9</td>
<td>&gt;9–≤20</td>
<td>&gt;20–≤57</td>
<td>&gt;57</td>
<td>1.02</td>
<td>1.01</td>
<td>1.37</td>
</tr>
<tr>
<td>(n = 596)</td>
<td>0.62</td>
<td>0.63</td>
<td>0.60</td>
<td>1.20</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Cox proportional model; ** adjusted for baseline 6 MWD and sex.

RIGHT VENTRICULAR GLOBAL STRAIN IN PULMONARY HYPERTENSION IS RELATED TO RESTING MEASURES OF GAS EXCHANGE

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Introduction: The measurement of right ventricular global strain (RVGS) is a relatively new estimate of right ventricular (RV) dysfunction in pulmonary artery hypertension (PH). Similarly, recent evidence suggests that measurements of gas exchange, specifically breathing efficiency (VE/VCO2) and PETCO2 are related closely with clinical metrics for these measures (p < 0.01). These results suggest that individuals with higher VE/VCO2 and lower PETCO2, tend to have poorer RV function as measured using an index of ventricular dysfunction. This strengthens the argument that measures of gas exchange may be sensitive indices to disease severity and potentially track changes in disease status in patients with PH.

Aim: The aim of this study was to examine the relationship between RVGS and resting and exercise measures of VE/VCO2 and PETCO2 in PH.

Methods: 12 patients with PH were recruited; all were on long term oxygen therapy and had RVGS measurements and resting and during a 6 min walk test. Gas exchange measurements (VE/VCO2 and PETCO2) were made on the same day that of the exercise test. RVGS measurements were made on the same day that of the exercise test. Gas exchange, specifically breathing efficiency (VE/VCO2) and PETCO2 are weakly correlated. The model predicts that large central occlusions have more impact on function than smaller distributed occlusions.

Results: Model prediction of hypoxemia and pulmonary artery pressure correlated closely with clinical metrics for these measures (p < 0.01 in each case), whereas the clot load defined by number of segmental vessels occluded only weekly correlated. The model predicts that large central occlusions have more impact on function than smaller distributed occlusions.

Conclusions: We have developed subject specific models that predict function from CT pulmonary angiograms in individuals with acute and chronic pulmonary embolism. The effect of redistribution of blood from its normal pattern—and hence the potential effect on gas exchange—is represented in the model. The model can therefore be used to predict the impact of surgical or pharmacological treatments on an individual’s pulmonary function, and provides a novel tool in the stratification of patients with these conditions.
DOMINATION OF THE LOWER AIRWAY MICROBIOTA BY VEILLONELLA SPECIES IS PREDICTIVE OF Frequent EXACERBATION IN NON-CYSTIC FIBROSIS BRONCHIESTASIS

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Aim: To determine the clinical and prognostic significance of the bacterial species that constitute the lower airway microbiota in adults with non-cystic bronchiectasis.

Method: The lower airway microbiota in sputum samples from 96 adults with non-cystic bronchiectasis was assessed using standard diagnostic microbiology, 16S rRNA gene pyrosequencing, and quantitative (q) PCR. Relationships between microbiota characteristics, prior clinical course, disease severity at sampling, and markers of disease progression over the following 12 months were determined. The clinical significance of detected bacterial taxa was assessed and compared with that of Pseudomonas aeruginosa.

Results: P. aeruginosa detection was associated with poor lung function and exacerbation frequency, irrespective of analytical strategy, with P. aeruginosa predominance the single best predictor of exacerbation frequency (β = 0.501, p < 0.001). The second best predictor was predominance of Veillonella, a genus not detected by conventional culture-based microbiology (β = 0.385, p < 0.005). The relative risk of ≥5 exacerbations in the 12 months following analysis was greater by a factor of 1.60 when P. aeruginosa was dominant and 1.44 when a Veillonella species was dominant. By comparison, the relative risk associated with P. aeruginosa culture positivity was 1.35.

Conclusion: Dominance of the lower airway microbiota by members of the Veillonella genus is predictive of poor clinical course. Whether this relationship is causal, or reflects a competitive advantage in the lower airway environment associated with more severe disease, is not yet known. The association between worse clinical course and P. aeruginosa infection was confirmed.

ENHANCED CASE DETECTION OF LEGIONNAIRES’ DISEASE BY PCR TESTING OF INDUCED SPUTUM AND THROAT SWAB SPECIMENS

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Introduction: We recently demonstrated a four-fold increase in case detection of Legionnaires’ disease through a laboratory-initiated strategy of routine systematic PCR testing of lower respiratory specimens for Legionella species. The present study aimed to further enhance case detection of Legionnaires’ disease by actively identifying patients with community-acquired pneumonia and by collecting induced sputum from those who could not expectorate.

Methods: Patients admitted with community-acquired pneumonia during a Legionnaires’ disease season were approached and a throat swab, sputum (expectorated or induced), urine sample, clinical data, laboratory and radiology results and relevant exposures were collected.

Results: Sputum samples were obtained from 114 patients admitted with community-acquired pneumonia, 46 of whom were initially unable to expectorate. There were 22 cases (19%) of Legionnaires’ disease, of whom 8 (36%) would not have been detected without assisted or induced sputum collection. Throat swabs were positive in only 3 patients, all of whom were also positive on sputum sample. Recent gardening, gastro-intestinal symptoms, elevated C-reactive protein levels and hyponatremia were associated with Legionnaires’ disease.

Conclusion: Active collection of sputum samples for PCR testing, including by induction, in patients with community-acquired pneumonia enhanced the case detection of Legionnaires’ disease, and is useful in high-prevalence regions. Throat swabs are insufficiently sensitive for routine clinical use.
PROLONGED ANTIBIOTICS FOR NON-CYSTIC FIBROSIS PURULENT BRONCHIECTASIS IN CHILDREN AND ADULTS: A COCHRANE REVIEW

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Aim: Bronchiectasis, a chronic respiratory condition characterized by the abnormal dilatation of the bronchial lumen, is being diagnosed with increasing frequency. This review aims to determine the effectiveness of prolonged antibiotic therapy in the treatment of patients with non-cystic fibrosis bronchiectasis.

Method: We searched the Cochrane Airways group specialized register in June 2013, which included searches of Medline, EMBASE, PsychINFO and CINAHL in addition to multiple sources of grey literature. Randomized controlled trials of adult or paediatric participants diagnosed with bronchiectasis who underwent prolonged antibiotic therapy (> four weeks) compared to placebo or usual care was considered for inclusion. The primary outcome was exacerbations with a number of secondary outcomes also assessed including lung function, exercise capacity, quality of life, symptom diary cards, sputum volume and purulence, bacterial colonization, systemic markers of infection, hospital utilization, number of courses and duration of antibiotics, deaths and other adverse events. Data was extracted by a combination of two independent review authors.

Results: A total of 695 citations were retrieved from the search producing 14 studies (18 citations) meeting the pre-specified inclusion/exclusion criteria, 12 were parallel randomized controlled trials and two were cross-over studies. For the primary outcome of acute exacerbations seven parallel studies contributed to the meta-analysis reporting the 'number of participants with exacerbations at follow-up' (odds ratio 0.49; 95%CI 0.30 to 0.81; p < 0.0001), producing a statistically significant effect in favour of the intervention arm for both analyses at final follow-up (range 6 to 52 weeks for follow-up).

Conclusion: The available evidence shows some benefit in favour of prolonged antibiotic use in the treatment of bronchiectasis with reductions in exacerbations. More studies are required to assess the effectiveness of the different types of antibiotics available.

Key words: Bronchiectasis, antibiotics, prolonged treatment, adult, paediatric.

Grant Support: Nil.

AN AUDIT OF ANTIBIOTIC USE FOR COMMUNITY ACQUIRED PNEUMONIA AT AN AUSTRALIAN TERTIARY HOSPITAL

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Aim: To describe antibiotic use in community-acquired pneumonia (CAP) at a major tertiary hospital prior implementation of a computerized antibiotic stewardship program, and determine concordance with national therapeutic guidelines.

Method: We conducted a single-centre, retrospective audit of consecutive patients admitted to Royal North Shore Hospital with CAP between October and December 2012. Cases were identified by the principle DRG E62. The 3 highest volume admitting specialties were used for the purposes of this analysis. Relevant patient characteristics, antibiotic use and clinical outcomes were measured. A retrospective SMART-COP score was calculated for all cases.

Results: 98 CAP cases were identified (Respiratory 57, General Medicine 24, Geriatrics 17). There were 69 Mild, 20 Moderate and 9 Severe cases. Intravenous Cephalosporin was used to target “typical” pathogens in the majority of CAP cases, irrespective of admitting specialty and pneumonia severity. Only 12% of these patients satisfied criteria according to national guidelines based on CAP severity, allergies and available gram stain results. 41% of patients received intravenous Azithromycin for “atypical” cover, with only 15% of these prescriptions occurring in accordance with guidelines. 25% of patients received no atypical cover despite being included, indicating 4 patients with severe CAP. There was no significant difference in mean length of stay of patients with mild CAP receiving Cephalosporin versus penicillin-based treatment (5.98 vs. 5.36 days respectively). Reasons for discordance with national guidelines included inappropriate antibiotic choice for CAP severity, incorrect route of administration, and omission of antibiotics despite indication.

Conclusion: This study confirms poor concordance with recommended antibiotic guidelines for the treatment of CAP in our hospital. A computerized antibiotic stewardship program is being implemented and future studies will allow comparison in trends of antibiotic use and help evaluate the effect of such interventions.

ATTITUDES TOWARDS TREATMENT OF LATENT TUBERCULOSIS INFECTION AMONG HOSPITAL STAFF

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Introduction: Healthcare workers (HCWs) have an increased risk of latent tuberculosis infection (LTBI). However, previous studies suggest that they might be reluctant to accept treatment for LTBI.

Aim: To examine the experience of doctors and nurses with tuberculosis (TB) screening at a TB clinic of a tertiary hospital in Sydney and to explore HCWs’ attitudes towards treatment of LTBI.

Methods: We conducted a survey among HCWs at a tertiary hospital in South-West Sydney, using a paper-based questionnaire. Anonymous questionnaires were sent out with pay slips to all doctors and randomly selected nurses. Additionally, questionnaires were randomly handed out to doctors and nurses in the hospital.

Results: A total of 1304 questionnaires were distributed and 311 responses were received (response rate of 24%). Of 258 HCWs that had undergone screening with a Tuberculin Skin Test and/or Interferon Gamma Release Assay, 116 (45%) reported a positive test result, indicating LTBI. Of these, 14 were offered treatment of LTBI and 42 were not (the remainder did not provide any information related to this question). Nine HCWs (64%) accepted treatment for LTBI.

When asked about their personal opinions, 67% of all respondents, but only 48% of staff in respiratory medicine, wished to be offered LTBI treatment if they had evidence of LTBI (p < 0.001). When asked whether HCWs with LTBI in general should be offered LTBI treatment, only 29% of staff in respiratory medicine agreed, compared to 78% in other disciplines (p < 0.001).

Conclusion: The prevalence of LTBI among responding HCWs in this survey was high. A majority of HCWs (but not respiratory medicine staff) wished that treatment of LTBI was offered to HCWs with LTBI in general and to them personally if they had evidence of LTBI. This contrasted with low actual rates of offered LTBI treatment, indicating a need for more client-oriented TB screening services in this setting.

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Airway closure with bronchoconstriction is greater in older asthmatics than young asthmatics. The causes of increased airway closure with bronchoconstriction are unknown.

**Methods:** Asthmatics with airway hyperresponsiveness had measures of baseline spirometry, lung volumes, multiple breath nitrogen washout to measure ventilation heterogeneity in conducting (Scond) and acinar (Sacin) airways, and methacholine challenge. The closing index, calculated as (% fall FVC – % fall FEV1/FVC) / % fall FEV1, was used to assess excessive airway closure during bronchoconstriction relative to the fall in FEV1. Correlations between closing index and asthma outcomes, anthropometry, ventilation heterogeneity and lung volumes, were analyzed.

**Results:** In the group as a whole (r = 58, aged 19–80, 29 females) closing index was related to age (r = 0.29, p = 0.03), longer disease duration (r = 0.32, p = 0.001), higher BMI (r = 0.39, p = 0.003) and worse asthma control (r = 0.25, p = 0.059). Second predicted excessive airway closure with bronchoconstriction (r = 0.32, p = 0.018) but Sacin did not (r = 0.04, p = 0.8). Residual volume predicted excessive closure with bronchoconstriction in asthmatics over 55 years of age (n = 15, r = 0.55, p = 0.035) but not in the younger asthmatics (n = 44, r = 0.09, p = 0.6).

**Conclusions:** Excessive airway closure with bronchoconstriction increases with increasing disease duration and BMI. Increased ventilation heterogeneity in the conducting airways may lead to excessive airway closure with bronchoconstriction, consistent with imaging and modelling studies that suggest that random heterogeneities in airway dimensions predispose to catastrophic collapse of localized lung regions with bronchoconstriction (1). The association between baseline residual volume and excessive airway closure in older asthmatics is consistent with previous findings that residual volume is an important predictor of AHR severity in older asthmatics (2).

(1) Venegas, NEJM, 2005
(2) Hardaker, Chest, 2011
SHORT TERM ORAL CORTICOSTEROID THERAPY DOES NOT INCREASE APPETITE, DIETARY INTAKE, BODY WEIGHT AND BODY COMPOSITION IN ADULTS WITH ASThma – A RANDOMIZED-CONTROLLED TRIAL

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Introduction: Oral corticosteroids used to treat exacerbations of asthma are efficacious, yet the risk of adverse effects may decrease patient compliance with therapy. In particular, changes in appetite and dietary intake, which may lead to weight gain and changes in body composition are considered to be undesirable.

Aim: To determine whether 10 days oral corticosteroid therapy in adults with asthma causes changes in appetite, dietary intake, body weight and body composition.

Methods: Double-blinded cross-over trial of 10 days prednisolone (50 mg)/ placebo administered in random order to subjects with stable asthma (n = 55). Pre and post assessment included spirometry, sputum induction, body weight, body composition measured by dual energy x-ray absorptiometry (GE, Lunar), bioelectrical impedance analysis (InBody720), appetite measured using a validated visual analogue scale and dietary intake assessed using 4-day food records. A fasting blood sample was used to measure leptin as a biomarker of appetite and eosinophils as an adherence biomarker. Outcomes were analyzed by generalized linear mixed models.

Results: Subject adherence was confirmed by a significant decrease in blood eosinophils (>10^3/L) following prednisolone compared to placebo (Coef. −0.29 95% CI: (−0.39, −0.19) p < 0.001). There was no difference in serum leptin (ng/ml) (Coef. 0.13 95% CI: (−3.47, 3.72) p = 0.945) or appetite measured by visual analogue scale (mm) (Coef. −3.47, 3.72) p = 0.945) or appetite measured by visual analogue scale (mm) (Coef. −13.64, 3.79) p = 0.267) following prednisolone vs. placebo. There was no difference in dietary intake (kj/day) (Coef. 255, 95% CI: (−380, 891) p = 0.431), body weight (kg) (Coef. −0.38 95% CI: (−0.81, 0.05) p = 0.083) or body fat (%) (Coef. −0.31 95% CI: (−0.81, 0.20) p = 0.230). Waist circumference (cm) increased significantly in females after prednisolone compared to placebo (Coef. 2.85 95% CI: (0.79, 4.90), p = 0.006).

Conclusion: A 10 day oral corticosteroid intervention in stable asthmatics did not induce changes in appetite, dietary intake, body weight or composition. This evidence may assist clinicians and health professionals in increasing compliance of asthmatics prescribed oral corticosteroids for asthma exacerbations.

Key words: Asthma, corticosteroids, leptin, appetite, diet

Conflicts of Interest: Nil

PROTEOMIC IDENTIFICATION OF HOST-PATHOGEN INTERACTIONS: IN VIVO CHARACTERIZATION OF BACTERIAL SURFACE AND ADHERENT HOST PROTEINS IN A NATURAL INFECTION

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Introduction: Caseating lymphadenitis (CLA) is a hallmark of tuberculosis. Host-pathogen interactions involve cross-talk of surface and secreted molecules of both bacteria and host cells. In vivo characterization of bacterial surface proteins can be achieved by ‘membrane shaving’: proteomic identification of peptide fragments directly cleaved from surface proteins of live bacteria. We applied membrane shaving to bacteria obtained from naturally infected tissue, using CLA in sheep caused by the mycobacteriaceae Corynebacterium pseudotuberculosis (C.ptb) as a disease model.

Aim: To identify surface expressed proteins of C.ptb from clinical specimens of naturally occurring CLA and concurrently expressed sheep proteins.

Method: Caseous material was harvested from lymph nodes of diseased sheep (n = 3), bacteria were then separated and concentrated. Controls were prepared from uninfected animals (n = 3). Peptide fragments were generated from surface proteins by trypsin treatment, separated by liquid chromatography and analysed by online mass spectrometry. Proteins were identified by comparison to the predicted proteomes of C.ptb and Ovis Aries (Sheep) with MASCOT.

Results: Twenty nine bacterial surface proteins were consistently identified in caseous lymph nodes and were absent from normal sheep, including twenty four with a close homolog in M.tb and six of these have established roles in virulence. Thirty one host proteins were recurrently identified exclusively in the caseous lymph nodes, including immune mediators such as complement components and MHC class1 antigens. In addition, antimicrobial peptides were identified consistently in the caseous material including Regakine 1-like protein and Cathelicidin.

Conclusion: We have characterized proteins expressed in vivo at the interface between host cell and pathogen in a natural occurring infection. Given the histopathological and microbial similarities of this infection system to human CLA, these results may provide insights into tuberculosis.
Increased cell-secreted fibulin-1 production is an intrinsic quality of fibroblasts with IPF (p < 0.05). Levels of fibulin-1 and periostin were increased in the serum and tissue of patients with IPF (p < 0.05) but only levels of fibulin-1 inversely correlated with lung function (r = −0.9, p < 0.05). In addition, only cell-secreted fibulin-1 production was increased in IPF fibroblasts compared to subjects without lung disease (p < 0.01). The dysregulated levels of secreted ECM proteins can be reflected in the serum and act as biomarkers of activated fibroblasts and disease progression. Increased cell-secreted fibulin-1 production is an intrinsic quality of fibroblasts from patients with IPF and dysregulation was not seen in periostin or tenascin-C levels.

Prediction of disease progression in idiopathic pulmonary fibrosis (IPF) remains challenging in the clinical setting. We have previously shown that the matricellular protein fibulin-1 enhances proliferation of mesenchymal cells. Increased levels of extracellular matrix (ECM) proteins may be a consequence of activated fibroblasts that produce excessive ECM proteins in the context of fibrotic disease.

The aim of this study was to compare the utility of the ECM proteins fibulin-1, periostin, tenascin-C and fibronectin as biomarkers of disease progression in patients with IPF.

Primary parenchymal fibroblasts derived from 8 patients with IPF and 7 subjects without lung disease were assessed for levels of cell-secreted ECM protein production. Serum and cell-secreted fibroblast proteins were measured by western blot (fibulin-1) and sandwich ELISA (periostin, tenascin-C, fibronectin) in 72 patients with IPF and 17 subjects without lung disease. Levels of the proteins were measured in the distal lung parenchyma of 20 patients with IPF and 5 subjects without lung disease using immunohistochemistry. Disease progression in patients with IPF was defined as a significant reduction in lung function or death within the first year of blood draw.

Fibulin-1 was the only of the 4 ECM proteins to accurately predict disease progression in patients with IPF (AUC 0.71, 95%CI 0.6 to 0.9, p = 0.01). Levels of fibulin-1 and periostin were increased in the serum and tissue of patients with IPF (p < 0.05) but only levels of fibulin-1 inversely correlated with lung function (r = −0.9, p < 0.05). In addition, only cell-secreted fibulin-1 production was increased in IPF fibroblasts compared to subjects without lung disease (p < 0.01). The dysregulated levels of secreted ECM proteins can be reflected in the serum and act as biomarkers of activated fibroblasts and disease progression. Increased cell-secreted fibulin-1 production is an intrinsic quality of fibroblasts from patients with IPF and dysregulation was not seen in periostin or tenascin-C levels.

**Conclusion:** Smoking exposure caused clear differences in the patterns of airway contraction to 5-HT and BK in mice. Exposure to cigarette smoke in these diseases may alter contractile signalling pathways, including changes in intracellular Ca²⁺ release and/or changes in Ca²⁺ sensitivity.

**Aim:** To assess the effects of sub-chronic cigarette smoke exposure on mouse small airway reactivity to methacholine (MCh), serotonin (5-HT) and bradykinin (BK).

**Methods:** Balb/C mice were exposed to 3 cigarettes (smoke) or air (sham) 3 times a day for 4 days. On day 5, mice were euthanized with sodium pentobarbitone (i.p.) and lung slices prepared. Small airway contraction was assessed using phase-contrast microscopy. The contribution of Ca²⁺ sensitivity pathways to contraction was measured after treatment with caffeine/ryanodine to abolish intracellular Ca²⁺ oscillations. Protein expression was assessed in whole lung extracts.

**Results:** All constrictors induced stable monophasic contractions in airways from sham mice (n = 4–6). After smoke exposure, MCh responses were unchanged but contractions to 5 HT were biphasic and BK elicited transient oscillations. Protein expression was assessed in whole lung extracts.

**Conclusion:** Smoking exposure caused clear differences in the patterns of airway contraction to 5 HT and BK, but not MCh, despite all agonists mediating contraction via GPCR signalling. Biphasic and twitchy contractions to 5 HT and BK were associated with altered intracellular Ca²⁺ release, as they were absent when this pathway was inhibited. Further exploration of the differences in signalling downstream of MCh, 5-HT and BK receptors, in particular changes in Ca²⁺ signalling as a potential mechanism for the altered reactivity, could identify novel therapeutic targets to minimize the contribution of smoking to altered small airway contraction in chronic lung diseases.
**Introduction:** The alarmins LL-37 and β-Defensin-1 promote the chemotaxis and activation of several immune cells, and are believed to contribute to the pathology of several chronic inflammatory diseases, yet their role in asthma and chronic obstructive pulmonary disease (COPD) remains unclear.

**Aim:** To determine the airway expression of the alarmins LL-37 and β-Defensin-1 in asthma and COPD when individuals are divided by either inflammatory phenotype or by disease severity.

**Methods:** Induced sputum was collected from healthy controls, asthmatics and individuals with COPD. Participants were divided by disease group, inflammatory phenotype and disease severity. LL-37 and β-Defensin-1 expression was quantified by qPCR and ELISA.

**Results:** LL-37 protein was specifically increased in the neutrophilic subgroup in both asthma and COPD, and positively correlated with airway inflammatory phenotype or by disease severity. LL-37 and β-Defensin-1 expression was negatively associated with BMI in severe asthma, and gender in severe asthma and COPD.

**Conclusion:** LL-37 elevation is specific to the neutrophilic phenotype of asthma and COPD, which clarifies disagreement in the literature and suggests distinct phenotype-specific disease mechanisms. Alternately, elevated β-Defensin-1 protein is a feature of COPD and severe asthma regardless of inflammatory phenotype. Consequently, while β-Defensin-1 may be an effective general therapeutic target, the efficacy of modulating LL-37 may be phenotype-specific.
THE BUSSELTON HEALTH STUDY—GENOME WIDE ASSOCIATION STUDY (GWAS) OF LONGITUDINAL CHANGES IN LUNG FUNCTION

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Aim: To identify Single Nucleotide Polymorphisms (SNPs) associated with longitudinal changes in lung function.

Methods: The genotypes of 4167 individuals were analyzed using the Illumina 660W bead array and data imputed using the 1000 genome project. Spirometry was performed in the same individuals when they attended the Busselton Health Studies. A total of 12,695 observations from up to 8 different time points spanning up to 30 years were analyzed. Fixed effects and random effects models using age, height, height^2, sex, time and SNPxSNPxtime interactions were used to identify signals for longitudinal change in lung function measures.

Results: Regions with P < 5 × 10^{-6} were identified in independent regions (defined as 500 kb either side of the sentinel SNP) for FEV1, FVC and FVC. Region plots were examined for all SNPs to assess association with neighbouring SNPs. Regions of potential interest were identified as those with at least one SNP (either the top SNP or a proxy with R^2 > 0.2) with P < 5 × 10^{-6} and population frequency of >1%. Based on these criteria, 52 regions were selected. For regions with a significant interaction (P < 0.05) between ever and never smokers, the most significant SNP in the smoking function. Replication of these regions is currently being undertaken in the regions of interest. None has been previously associated with longitudinal changes in lung function.

Conclusion: This GWAS of longitudinal change in lung function identified 62 regions of interest. None has been previously associated with longitudinal lung function. Replication of these regions is currently being undertaken in the Copenhagen City Heart Study/Copenhagen Population Health Study where individuals with 2–3 measures spanning up to 20 years are available.

THE EFFECT OF SERUM AMYLOID A ON DIFFERENTIATION AND GENE EXPRESSION IN C2C12 SKELETAL MUSCLE CELLS

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Skeletal muscle wasting is an important comorbidity associated with Chronic Obstructive Pulmonary Disease (COPD). Patients who experience recurring acute exacerbations of COPD (AECOPD) have more severe muscle wasting and reduced recovery of muscle mass and function following an AECOPD. Serum amyloid A (SAA) is an acute phase protein that is dramatically elevated in the serum of patients during the onset of an AECOPD (Bozinozki et al. 2012); its effect on skeletal muscle mass and function is not yet known. The aim of the current study was to investigate the effect of SAA on skeletal muscle cell differentiation.

C2C12 mouse myoblasts were treated with SAA (0.1–10 mg/ml) for 24 or 48 h, and the effects on myoblast proliferation and differentiation into multinucleate myotubes was assessed. Cell viability and proliferation were assessed by MTT assay and differentiation was analysed microscopically by counting the percentage of nuclei fused into myotubes. Gene expression was measured by Q-PCR.

SAA treatment of C2C12 myoblasts for 48 h did not affect cell proliferation, but resulted in decreased myoblast differentiation into myotubes from 9.4% (control) to 5.1% (SAA, 10 mg/ml, n = 3, p = 0.02). Differentiating myoblasts treated with SAA (10 mg/ml) for 24 h showed a significant 5-fold increase in IL-6 mRNA levels (p < 0.05). TNF-a was modestly upregulated and the differentiation factors MyoD and Myogenin were downregulated in SAA treated cells.

Reduced differentiation and changes in gene expression observed in SAA treated myoblasts indicates that acute elevations in systemic SAA during AECOPD may have direct signalling effects in skeletal muscle and could contribute to impaired regeneration and recovery of muscle mass following an exacerbation. Targeting of these pathways in skeletal muscle represents a potential therapeutic strategy to reduce loss of muscle mass and function in COPD.

ASTHMA AND ALLERGY SIG 2 – ORAL PRESENTATIONS

EARLY LIFE AND CHILDHOOD RISK FACTORS FOR ASTHMA IN YOUNG ADULTS IN THE WESTERN AUSTRALIA PREGNANCY COHORT (RAINE STUDY)

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Introduction: Early-life factors associated with adult asthma remain largely unexplored despite the significant health burden of adult asthma on individuals and the community. Identifying factors occurring during infancy and childhood that are associated with adult asthma may allow for more targeted treatment of children at risk.

Aim: This study aimed to identify factors that may determine whether a child is more likely to be asthmatic in early adulthood.

Methods: Participants of the Raine study completed questionnaires and pulmonary function testing during the 23 year cohort follow-up. Participants also completed pulmonary function testing at ages 6 and 14 years, and they or their parents completed similar questionnaires during early life(1, 2 & 3 years), childhood (6, 8 & 10 years), and adolescence (14 & 16 years). Participants were classified as current asthmatics at age 23 if they reported ever having asthma and in the past 12 months had asthma symptoms and used asthma medication. Binary logistic regression was used to determine which factors from questionnaires and lung function results were associated with current asthma in early adulthood.

Results: 496 participants completed questionnaires and pulmonary function tests at the 23 year follow-up. Several early life factors significantly associated with current asthma at age 23 were identified. In early life: male gender, wheezing with or without a cold and having dermatitis/eczema. In childhood: Wheezing with a cold, having hay fever or dermatitis/eczema and maternal wheeze or asthma. In adolescence: History of wheeze and having allergic rhinitis or allergic conjunctivitis. Asthma in childhood or adolescence was also significantly correlated with current asthma at age 23 years.

Discussion: This study highlights a range of early-life factors that may identify those at risk for adult asthma. This could lead to early intervention and treatment strategies to reduce the incidence and significant health burden of adult asthma.
SPUTUM GENE EXPRESSION OF SIX MARKERS IDENTIFIES ASTHMA INFLAMMATORY PHENOTYPE AND CORTICOSTEROID RESPONSE

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Introduction: Airway inflammation is associated with asthma exacerbation risk, treatment response, and disease mechanisms.

Aim: This study aimed to identify and validate a sputum gene expression signature that differentiates asthma inflammatory phenotypes.

Method: An asthma phenotype biomarker discovery study generated gene expression profiles from induced sputum of 47 asthmatics. A clinical validation study (n = 59 asthmatics) confirmed differential expression of key genes. A 6 gene signature was identified and evaluated for reproducibility (n = 30 asthmatics, n = 20 controls), and prediction of inhaled corticosteroid (ICS) response (n = 71 asthmatics). Receiver operating characteristic curves were calculated and area under the curve (AUC) values reported.

Results: From 277 differentially expressed genes between asthma inflammatory phenotypes, we identified 23 genes that showed highly significant differential expression in both the discovery and validation populations. A signature of 6 genes, including CLC, CPA3, DNASE1L3, IL1B, ALPL, and CXCR2, was reproducible and could significantly (p < 0.0001) discriminate eosinophilic asthma from each other phenotype including non-eosinophilic asthma (AUC = 89.6%), paucigranulocytic asthma (AUC = 92.6%), neutrophilic asthma (AUC = 91.4%) and healthy controls (AUC = 97.6%), as well as neutrophilic asthma from paucigranulocytic asthma (AUC = 85.7%) and healthy controls (AUC = 90.8). The 6 gene signature predicted ICS response (<12% change in FEV1, AUC = 91.5%). ICS treatment reduced the expression of CLC, CPA3 and DNASE1L3 in eosinophilic asthma.

Conclusion: A sputum gene expression signature of 6 biomarkers reproducibly and significantly discriminates inflammatory phenotypes of asthma, and predicts ICS treatment response. This signature has the potential to become a useful diagnostic tool to assist in the clinical diagnosis and management of asthma.

DIETARY INFLAMMATORY INDEX IS RELATED TO ASTHMA RISK, LUNG FUNCTION AND SYSTEMIC INFLAMMATION IN ASTHMA

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Introduction: Asthma prevalence has increased in recent years and evidence suggests that diet may be a contributing factor. Increased use of processed foods has led to a decrease in diet quality, which may be creating a pro-inflammatory environment, thereby leading to the development and/or progression of various chronic inflammatory diseases and conditions. Recently, the Dietary Inflammatory Index (DII) has been developed and validated to assess the inflammatory potential of individual diets.

Aim: To examine the DII in subjects with asthma compared to healthy controls and to relate the DII to asthma risk, lung function and systemic inflammation.

Methods: Subjects with stable asthma (n = 99) and healthy controls (n = 61) were recruited. Blood was collected and spirometry was performed. The DII was calculated from food frequency questionnaires administered to study subjects.

Results: The mean DII score for the asthmatics was higher than the DII score for healthy controls (−1.40 vs. −1.86, p = 0.04), indicating their diets were more pro-inflammatory. For every 1 unit increase in DII score the odds of having asthma increased by 62% (OR = 1.62, CI: 1.01–2.60). FEV1 was significantly associated with DII score (β = −3.22, p = 0.04), indicating that for every 1 unit increase in DII score, FEV1 decreased by 3.22 times. Furthermore, plasma IL-6 concentrations were positively associated with DII score (β = 0.21, p = 0.03).

Conclusion: The usual diet consumed by asthmatics in this study was pro-inflammatory relative to the diet consumed by the healthy controls, as assessed using the DII score. The DII score was associated with lower lung function and increased systemic inflammation. Hence, consumption of pro-inflammatory foods in the diet may contribute to worse asthma status.

TOBACCO USE AND ASTHMA CONTROL IN A REPRESENTATIVE SAMPLE OF AUSTRALIANS LIVING WITH ASTHMA

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Aim: Smoking impacts asthma control and treatment responses. We set out to determine the relationship between smoking and asthma control at a population level in Australia.

Methods: Members of a large panel were invited to participate in an online survey. Eligibility criteria were age > 15, health professional-diagnosed asthma and asthma symptoms or medication use in the past year. Sample data were weighted by age, gender and State to be representative of the national asthma population. Self-reported smoking rates for current daily, less than daily, ex-smoker or never-smoker (NS) were compared to national data. Using the Asthma Control Test (ACT), asthma control was categorized as well-controlled (WC) (20–25), not well controlled (16–19) or very poorly controlled (VPC) ≤16. The odds ratio (OR) for asthma control (by ACT level) and emergency department (ED) visits for asthma was determined for each smoker group compared to NS.

Results: 9388 respondents with ever-diagnosed asthma were identified. 3033 subjects with current asthma were selected and 2686 completed the survey.

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Daily smoker</th>
<th>Less than daily</th>
<th>Ex-smoker</th>
<th>Never smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(National 15+)</td>
<td>(17.5%)</td>
<td>(2.0%)</td>
<td>(34.1%)</td>
<td>(46.4%)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(National 15+)</td>
<td>(13.9%)</td>
<td>(1.7%)</td>
<td>(25.5%)</td>
<td>(58.9%)</td>
</tr>
<tr>
<td>OR(95% CI) WC</td>
<td>0.47 (0.4–0.6)</td>
<td>0.54 (0.3–0.8)</td>
<td>0.75 (0.6–0.9)</td>
<td>1</td>
</tr>
<tr>
<td>vs. never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR(95% CI) VPC</td>
<td>2.65 (2.1–3.4)</td>
<td>2.17 (1.4–3.3)</td>
<td>1.52 (1.22–1.9)</td>
<td>1</td>
</tr>
<tr>
<td>vs. never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR(95% CI) – ED visit vs. never smokers</td>
<td>2.11 (1.5–2.9)</td>
<td>2.22 (1.3–3.7)</td>
<td>1.26 (0.9–1.7)</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion: More females with asthma are daily smokers than the national average, while both males and females have higher rates of less than daily smoking. Current smokers are more likely to have poor asthma control and asthma requiring ED care. These risks are less in those who have stopped smoking, but not in those with continuing less than daily smoking.

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SNEEZING LEADS TO WHEEZING: RHINOVIRUS INFECTION IN THE STUDY OF ASTHMA, VIRUSES AND ENVIRONMENT (SAVE) COHORT

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Aims: Viral infections are the main cause of exacerbations and acute hospital admissions in children with asthma. Little is known about viruses circulating in the community and their impact on day-to-day fluctuation of asthma symptoms. The Study of Asthma, Viruses and Environment (SAVE) is a longitudinal study investigating how and why respiratory viral infections, with host and environmental factors, can cause worsening of asthma.

Methods: 67 children aged 5–12, with moderately severe asthma, were recruited from Sydney Children's Hospital High Risk Asthma Clinic or Emergency Department. They self-collected nasal-wash and exhaled breath samples and recorded asthma and cold symptoms and lung function, twice per week for 10 weeks. The presence of 8 viruses, including human rhinovirus (HRV), was analyzed by PCR. A mixed model, to account for repeated measures, was used to determine the current and delayed impact of viruses on symptoms and lung function.

Results: Of 2463 samples, 25.5% of nasal and 11.5% of breath samples were positive for HRV. Other viruses were detected in only 1.8% of all samples. The presence of HRV in nasal wash, but not in breath, was associated with worsening outcomes; adjusted odds ratios: cough 2.53, 95%CI (1.62–3.94), wheeze 3.05, 95%CI (1.89 to 4.93), febrile symptoms 2.07, 95%CI (1.17 to 3.68) and coryzal symptoms 1.95, 95%CI (1.14 to 3.32) over the previous 3–4 days. These associations remained 3–4 days later, but generally not 7 days later. No association between any virus positivity and changes in lung function.

The presence of hRV in nasal wash, but not in breath, was associated with worsening outcomes; adjusted odds ratios: cough 2.53, 95%CI (1.62–3.94), wheeze 3.05, 95%CI (1.89 to 4.93), febrile symptoms 2.07, 95%CI (1.17 to 3.68) and coryzal symptoms 1.95, 95%CI (1.14 to 3.32) over the previous 3–4 days. These associations remained 3–4 days later, but generally not 7 days later. No association between any virus positivity and changes in lung function.

THE ROLE OF DIETARY FATTY ACIDS IN TRANSPORT OF SALBUTAMOL ACROSS CALU-3 EPITHELIA

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Western diets are characterized by the use of processed foods, high in dietary fat. The effect of consuming high fat meal (mixture of saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs)) in asthmatic subjects demonstrated a reduced bronchodilator response to salbutamol. A potential mechanism by which FAs may interfere with bronchodilation involves inhibition of drug transport across the airway epithelium.

The aim of this study was to investigate the impact of FAs (arachidonic acid, palmitic acid and eicosapentaenic acid) exposure on salbutamol transport through Calu-3 sub-bronchial epithelial cells. Calu-3 cells were seeded on Transwells using a fat-free medium and were used for transport study after 12 days. The cells were incubated for one h with 30 μM of each FA and the basal medium was replaced with Hanks buffer. Salbutamol solution was then added to the apical to a concentration of 100 μM. After 4 h the concentration of salbutamol was analyzed using high performance liquid chromatography. To investigate the influence of FAs on cell stiffness related to membrane structure/ permeability, cells were probed using molecular force probe.

Analysis of data suggested that the amount of salbutamol transported in presence of PUFAs to be significantly higher compared to incubation with SFA or transport in the fat-free culture medium. No significant differences were observed between n-6PUFA and n-3PUFA. Furthermore, the analysis of cell stiffness showed a significant drop in stiffness following incubation with PUFAs.

The findings of this study suggest that the presence of PUFAS is essential for membrane fluidity. It was observed that under physiologically relevant conditions, the transport of salbutamol is sensitive to alterations in the FA environment. This provides the first evidence that the transport of β2-agonist can be modified by dietary fat consumption.
TRIGGERS RESULTING IN RELAPSE: COHORT ANALYSIS FROM THE SMOKING TERMINATION OPPORTUNITY FOR INPATIENTS (STOP) TRIAL

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Triggers resulting in relapse: Cohort analysis from the Smoking Termination Opportunity for inpatients (STOP) trial

Aim: Smoking is a modern day epidemic and a major cause of premature mortality worldwide. Using the cohort of inpatients recruited into the STOP smoking trial we aimed to identify the leading triggers resulting in relapse and examine the potential differences in these triggers between the two arms of the study, being the PBS approved schedule of varenicline tartrate plus Quitline-counselling (VT+C) compared to Quitline-counselling (C-alone) at various time periods.

Methods: Adult patients (18–75 years) admitted with a smoking-related illness to one of three hospitals in South Australia, were randomized to receive either 12-weeks of VT+C (n = 196) or 12-weeks of C-alone (n = 196), with 52-week follow-up.

Results: The triggers perceived likely to have resulted in past relapses by subjects at baseline were: being with other smokers (reported by 90% of the VT+C group and 86% of the C-alone group), feeling stressed (86% VT+C; 87% C-alone), boredom (80% VT+C; 79% C-alone) and taking a work break (79% VT+C; 79% C-alone). However, by the end of the study the most commonly reported triggers actually resulting in relapse at 52-weeks were: feeling stressed (54% VT+C; 58% C-alone), during or after a meal (46% VT+C; 64% C-alone), being with other smokers (39% VT+C; 63% C-alone) and feeling down/upset (42% VT+C; 53% C-alone).

Conclusion: Smoking cessation counselling combined with the inpatient opportunity to reflect on the associated illness episode has succeeded in suppressing the smoking triggers of feeling stressed, being with other smokers, desire to smoke during or after a meal and other triggers at 52-weeks follow-up. Administration of VT+C has had an additional benefit to C-alone in relation to suppressing these triggers commonly resulting in relapse. The inpatient setting coupled with counselling and/or VT+C offers an opportunistic and effective environment to initiative smoking cessation attempts where triggers commonly resulting in relapse can be suppressed.

Funding: None.

PROVISION OF SMOKING CESSATION SERVICES IN AUSTRALIAN COMMUNITY PHARMACIES – A SIMULATED PATIENT STUDY

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Introduction: Pharmacists can play a key role in implementing evidence-based smoking cessation interventions.

Aim: To investigate how community pharmacists respond to requests of quitting smoking from smokers seeking assistance and treatment within the pharmacy venue.

Method: A simulated patient methodology was utilized. Two scenarios were developed and enacted by two trained simulated patients in 100 randomly selected community pharmacies located within Sydney greater metropolitan area, New South Wales. Scenario 1 involved a 28-year-old pregnant female who presents with a request for help in quitting smoking. Scenario 2 involved a 22-year-old female requesting a quit smoking product for her 55-year-old father who has cardiovascular problems. A standardized scoring key was designed to assess the performance of pharmacists during each encounter. Major anticipated outcomes included pharmacists’ skills in eliciting patient history and dependence level, pharmacists’ knowledge about the safety of nicotine replacement therapy (NRT) in the corresponding scenario and the adequate dispensing of a product(s).

Results: A product(s) was supplied in 42% of the 100 encounters, while a product was adequately suggested pending doctor’s referral in 39%. In 13% of the cases, a product was not supplied based on incorrect notions of NRT not being safe in the presented scenario. Pharmacists performed better in dispensing scores (counselling about product use) as compared to pre-dispensing scores (eliciting patient history), generating a mean (±SD) total performance score of 51.4 ± 20.3 for scenario 1 and 59.6 ± 19.2 for scenario 2 (p = 0.04, independent sample t-test). ANOVA followed by regression analyses indicated that the estimated age and gender of the pharmacist and the visibility of the pharmacy quality assurance program symbol were significant predictors affecting total scores.

Conclusion: Whilst pharmacists’ counselling about smoking cessation aids seems satisfactory, further education is required to improve practice standards in terms of matching patient’s history and smoking status to an appropriate product.
EVALUATION OF THE HOSPITAL SMOKE-FREE IMPLEMENTATION POLICY: A CROSS-SECTIONAL COHORT ANALYSIS

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Aim: To evaluate the implementation of The Queen Elizabeth Hospital (TQEH) smoke-free policy on inpatient smoking status, (behaviours), knowledge and attitudes.

Method: Two cross-sectional mail-out surveys were administered to all patients admitted to the Queen Elizabeth Hospital during a three day period in April 2010 and May 2011. The TQEH Smoke-free policy was implemented in May 2010, which included a ban on cigarette smoking anywhere on hospital grounds, increased advertising for smoke-free zones and increased access to nicotine replacement therapy for inpatient smokers on discharge. Survey data was analyzed using Microsoft Excel 2010 and SPSS version 18.

Results: A total of n = 177 letters were mailed to discharged patients at baseline with a 60% response rate (usable data on n = 89 subjects) and n = 115 letters were sent at 12-month follow-up with 82% response rate (n = 94 subjects). Mean age at baseline was 46.98 ± 20.27 years, 46% were male and 48% were current or ex-smokers, with similar demographics in the follow-up cohort. Using ten-point Likert scales (10 being ‘strongly agree’) participant responses strengthened post-implementation of the policy with responders believing second-hand smoke to be harmful (baseline mean 8.51 ± 2.29; follow-up mean 9.27 ± 1.52; p = 0.009), implementation of the smoke-free policy was a good move (baseline 8.99 ± 2.41; follow-up 9.62 ± 1.54; p = 0.04), smoking was bad for their health (baseline 9.38 ± 1.84; follow-up 9.92 ± 0.38; p = 0.007), and smoke-free policy will make the hospital a safer place to visit (baseline 8.84 ± 2.54; follow-up 9.61 ± 1.67; p = 0.02). However, baseline responders were undecided about whether they were likely to quit smoking because of the policy (5.71 ± 4.04).

Conclusion: Introduction of a hospital smoke-free policy strengthened participant attitudes and knowledge about the negative health effects of tobacco use and positive effects of a tobacco-free environment. However, participant smoking behaviour was not influenced by the policy. Data is limited to the perceptions of survey responders only, which is likely to cause bias.

ASSESSING THE PERFORMANCE OF TWO LUNG AGE EQUATIONS ON THE AUSTRALIAN POPULATION: USING DATA FROM THE CROSS-SECTIONAL BOLD-AUSTRALIA STUDY

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Introduction: Lung age, a simple concept for patients to grasp, is frequently used as an aid in smoking cessation programmes. However, lung age equations should be continuously updated and made relevant for target populations.

Aim: To observe how new lung age equations developed for Australia performed when utilising the BOLD-Australia dataset compared to more commonly used equations.

Methods: Data from cross-sectional population study of non-institutionalized Australians aged ≥40 years with analysis restricted to Caucasians ≥75 years. Lung age calculated using equations developed by Newbury et al and Morris & Temple, was compared with chronological age by smoking status and within smoking status.

Results: There were 2,793 participants with a mean age of 57 (SD = ±10) years. Over half (52%) ever smoked and 10.4% were current smokers. Prevalence of COPD Stage 1 or higher was 13.4% (95%CI: 12.2, 14.7). For both genders, newer Newbury equations estimated lung ages significantly higher than actual age across all smoking groups (p < .05). Morris & Temple equations resulted in lung age estimates significantly lower than chronological age for non-smokers (p < .05), but no difference among current smokers. Both equations showed exposure to smoking had lung ages higher than never smokers (p < .001). Lung age also increased with increased pack-years.

Conclusions: This supports the use of updated equations suited to the population of interest. The Australian Newbury equations performed well in the BOLD-Australia dataset providing more meaningful lung age profile, compared to chronological age, among smokers. Using equations not developed or ideally suited for our population, is likely to produce misleading results.

Support: NHMRC (Project Grant: 457385); TSANZ – The Robert Pierce Grant-in-Aid for Indigenous Lung Health (2010); Air Liquide (2005); AstraZeneca (2005); GlaxoSmithKline (2005); and Boehringer Ingelheim (2005).
PHYSICAL TRAINING FOR ASTHMA: A COCHRANE SYSTEMATIC REVIEW

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Aim: To determine the level of evidence supporting the use of physical training (of at least 20 min undertaken twice per week for four weeks) as a treatment for asthma through: reducing asthma symptoms and improving bronchodilator usage, pulmonary function testing, exercise tolerance and quality of life.

Method: We systematically searched the Cochrane Airways Group specialized register, reference lists of included studies and online clinical trial registries for studies meeting the pre-specified inclusion/exclusion criteria. Randomized controlled trials of people over eight years of age with diagnosed asthma were considered. Data extraction was performed by two independent researchers into a standardized abstraction template.

Results: A total of 1948 citations were identified with 21 studies (772 participants) meeting all of the criteria for inclusion within the review. Physical training showed marked improvement in cardiopulmonary fitness with significant increases in VO₂ max (mean difference (MD) 4.92 ml/kg/min, 95%CI 3.98–5.87; p < 0.00001) and maximum heart rate (MD 3.67 bpm, 95%CI 0.90–3.44; p = 0.01), though no statistically significant effects were observed for FEV₁, FVC or V′E max. Meta-analysis was not possible for quality of life due to heterogeneity, however, there was some evidence to suggest that physical training may produce a benefit with four of five studies producing statistically and clinically significant benefits. Physical training was reported to be well tolerated with no worsening of asthma symptoms identified.

Conclusion: This review demonstrates that physical training showed significant improvements in quality of life and maximum oxygen uptake though not other measures of pulmonary function. No asthma exacerbations were reported as being related to physical training, suggesting that people with stable asthma should be encouraged to participate in regular exercise training without fear of symptom exacerbation.

BENEFIT OF TREATMENT OF LATENT TUBERCULOSIS INFECTION IN INDIVIDUAL PATIENTS: A DECISION AID

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Background: Previous decision analyses dealing with the treatment of latent tuberculosis infection (LTBI) have taken a population perspective, which does not assist clinicians in giving advice to patients about whether the benefits to them, personally, outweigh the risks of treatment.

Aim: To develop a clinical decision aid that estimates the net gain or loss in quality-adjusted life expectancy that an individual patient is likely to experience with treatment of LTBI.

Methods: A life-course Markov model was constructed to simulate the life experience of patients with LTBI as they progress through a series of health states. Estimates of risk for developing TB and for developing adverse effects of treatment for LTBI were derived from the published literature. Each health state was assigned a utility allowing the estimation of cumulative quality-adjusted life expectancy. Benefits (gains) and risks (losses) were estimated for a range of patient profiles.

Results: In most cases treatment of LTBI was associated with a net gain in quality-adjusted life expectancy. The threshold levels for annual risk of active TB above which giving treatment for LTBI was favoured over withholding treatment increased with age.

Threshold annual risks for TB (per 100,000) by age and sex

<table>
<thead>
<tr>
<th>Age</th>
<th>Females</th>
<th>Males</th>
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<tr>
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<td>70 years</td>
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As older people have higher case-fatality rates due to TB, those aged ≥35 years have a net gain in quality-adjusted life expectancy with treatment for LTBI in many case scenarios, despite the increased risk of isoniazid-induced hepatitis.

Conclusions: This model shows that, from an individual risk-benefit perspective, many patients with LTBI should be offered treatment. The model can be used to give patient-specific advice on the balance of risks and benefits of treatment for LTBI.

Supported by: University of Sydney Postgraduate Award for CCD.
MASS MEDIA INTERVENTIONS FOR PREVENTING SMOKING IN YOUNG PEOPLE: A COCHRANE SYSTEMATIC REVIEW

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Aim: To search and critically appraise the relevant literature in order to determine the strength of the evidence that mass media interventions aimed at preventing smoking in young people may: reduce smoking uptake, improve tobacco-related attitudes, behaviours and knowledge, improve self-efficacy and improve perceptions about smoking.

Method: We searched the Cochrane Tobacco Addiction group's specialized register and conducted additional searches of Medline and EMBASE in January 2013. Randomized controlled trials, controlled clinical trials and time-series studies assessing the effectiveness of mass media campaigns (defined as channels of communication not dependent on person to person contact) designed to prevent smoking in young people (≥25 years) were included. Data abstraction was performed by two independent researchers into standardized extraction templates.

Results: Seven studies met all of the criteria for inclusion from a total of 707 citations with all studies employing a controlled trial design. Meta-analysis was not possible due to significant amounts of heterogeneity (I2 60%) and as such the studies were analyzed using narrative synthesis. Three of these trials reported a reduction in smoking behaviour amongst youth in the intervention arm, whilst the remaining four studies observed no evidence of any effect for the intervention.

Conclusion: There is some evidence to support the use of mass media as a vehicle for tobacco use prevention messages aimed at youth. However, this data is limited due to identification of substantial methodological flaws. Despite the increasing popularity of mass media as a form of communication amongst youth (particularly social media such as Facebook and Twitter) no new studies have been identified by this systematic review that evaluates this form of mass media. Rigorous trials evaluating social for delivering tobacco use prevention messages need to be performed.

Key words: Tobacco, paediatric, prevention, evidence-base, media.
Grant Support: Nil.

COMPLIANCE WITH THE BRITISH THORACIC SOCIETY GUIDELINES IN THE MANAGEMENT OF PNEUMOTHORACES

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Aim: To determine compliance with the British Thoracic Society (BTS) guidelines in the management of pneumothoraces in the public hospital setting.

Method: We performed a retrospective critical appraisal of The Queen Elizabeth Hospital’s electronic database for people who presented with spontaneous, traumatic and iatrogenic pneumothoraces between 2007 and 2012. This was supplemented by manual screening of hospital case records, with data extraction by two independent doctors using a standardized pilot tested template. Data collection included demographics, hospital utilization, admissions details, diagnosis and variables that could be used to compare current practice with the BTS guidelines for the management of pneumothoraces. Data analysis was conducted using Microsoft Excel and Access.

Results: Twenty-two patients identified as being diagnosed with a pneumothorax were included in the analysis. Of these, 13 were compliant with the BTS guidelines and nine were non-compliant. Baseline characteristics were similar across groups including age and Charleston Comorbidity Index. The BTS compliant group recorded four (30.7%) complications compared to two (22.2%) in the non-compliant group. Associated daily costs of admissions and length of stay per patient were $2,043.00 with a mean of 8.31 days compared to $1,518.00 and 6.33 in the compliant and non-compliant groups respectively. Nine (69.2%) patients in the BTS compliant group had an interventional chest drain, with eight (61.2%) having large pneumothoraces determined by radiological criteria versus six chest drains (66.6%) in the BTS non-compliant group with only two (22.2%) deemed large.

Conclusion: These observational results may be influenced by the small number of included subjects and high proportion of large pneumothoraces in the BTS compliant group, resulting in more associated complications, incurring costs and prolonging admissions. Evaluations with larger patient samples across multiple sites are required to improve generalizability of the findings and determine the level of compliance to the BTS guidelines on a broad scale.

Key words: Pneumothorax, pneumothoraces, compliance, guidelines, review.
Grant Support: Nil.
EXPOSURE TO IRON LADEN GEOGENIC DUST EXACERBATES THE RESPONSE TO INFLUENZA INFECTION

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Aims: There are many communities around Australia that are exposed to high ambient concentrations of geogenic (earth derived) PM10 (<10 μm diameter particulate matter). There is anecdotal evidence that exposure to high concentrations of iron (Fe) laden PM10 has adverse health effects. We have shown previously that the concentration of Fe in community sampled geogenic PM10 is the primary determinant of the inflammatory and lung function response, however it is unclear how the concentration of Fe impacts on the response to a pre-existing infection. In this study we aimed to determine whether the concentration of Fe in community sampled geogenic PM10 impacts on the response to influenza infection.

Methods: The PM10 fraction was extracted from surface soil samples from four communities across Western Australia. BALB/c mice were intranasally exposed to 10 μg of PM10 (or saline) daily for 10 days. On the 6th day mice were exposed to influenza A (A/Mem/1/71) or a control preparation. 24 h after the last exposure we measured inflammation in the bronchoalveolar lavage (cells, MIP-2, IL-6, IFN-g), lung function and the responsiveness to methacholine (MCh).

Results: Both geogenic PM10 and influenza induced inflammation impaired lung function and increased the response to MCh. Co-exposure to particles exacerbated the response to influenza; particularly the influx of macrophages, the production of cytokines (IL-6 and IFN-g) and the response to MCh. After accounting for particle size and other metals the concentration of Fe was positively correlated with the number of macrophages (p = 0.04) and the maximum response to MCh (p = 0.01) and was negatively correlated with baseline airway resistance.

Conclusions: Collectively these data demonstrate that repeated low level exposure to geogenic PM10 exacerbates the response to a common respiratory infection. The magnitude of this response was altered by the concentration of Fe in the particles.
PNEUMONIA IN THE ELDERLY MAY CAUSE DETERIORATION IN FUNCTIONAL LEVELS THREE MONTHS AFTER THE ILLNESS

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Aim: Pneumonia is the sixth most common cause of death worldwide. The mortality and morbidity associated with pneumonia are increased in the elderly in the presence of chronic diseases. The Pneumonia in Elderly study evaluated the role of comprehensive geriatric assessment on long term outcomes.

Method: In this prospective longitudinal observation study, 61 patients were recruited from July 2011 to September 2012. All participants received usual care prescribed by the multidisciplinary teams. Comprehensive functional assessments were conducted during their inpatient stay and at 3 months. The primary outcome measure was deterioration including death by 3 and 12 months following discharge. In addition, demographic and clinical information was recorded.

Results: Final outcomes were determined for 57 patients; mean age 79 SD7 years, 56% male. Co-morbidities were common with 38% of participants having 2 or more while 40% had COPD. Twelve-month mortality was 15%. This group of elderly patients were unwell with high inflammatory markers (mean CRP 173 SD130 mg/L, mean procalcitonin 3.1 SD4.2 mcg/L), high prevalence of multilobar involvement (34%) and hypoxia (42%). Fever (52%), hypotension (23%) and sputum diagnostic yield was similar in both groups. Initial analysis showed that 25% of our cohort had lower functional levels when assessed at three months post discharge. Possible significant variables for predictors of deterioration at 3 months include male gender, higher length of stay and presence of congestive cardiac failure. The presence of COPD, CRP level, severity scores or frequency of cardiac or pulmonary admissions prior did not influence functional levels at 3 months.

Conclusion: Pneumonia in the elderly causes significant morbidity. Common features of the clinical presentation included hypoxia and multilobar involvement. Pneumonia can lead to a prolonged deterioration in functional levels. Patients with a higher length of stay, male gender and have congestive cardiac failure at higher risk and require close monitoring for functional deterioration.

CHRONIC RESPIRATORY CONDITIONS IN A COHORT OF METROPOLITAN FIREFIGHTERS: ASSOCIATIONS WITH OCCUPATIONAL EXPOSURE AND QUALITY OF LIFE

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Aims: To assess the prevalence of chronic respiratory conditions in metropolitan firefighters, and study associations between occupational exposure, use of respiratory protection, and health-related quality of life (HRQoL) in firefighters with and without chronic respiratory conditions.

Methods: Cross-sectional cohort analysis. Respiratory symptoms, medical conditions, occupational exposures, and respiratory protection were inquired by questionnaire. The SF12 V2 Health Survey was used to measure physical (PCS12) and mental (MCS12) HRQoL. Fire-fighters were categorized in subgroups: asthma; COPD/emphysema/chronic bronchitis; no chronic respiratory conditions, and as being ‘protected’ or ‘not protected’ from exposures. PCS12 and MCS12 scores were compared between subgroups using linear regression.

Results: 570 fire-fighters were analyzed, 24 (4%) fulfilled the criteria for asthma, 39 (7%) for COPD/emphysema/chronic bronchitis. Fire-fighters with asthma were older than those in the other two subgroups and had been employed in the fire-service longer. Respiratory subgroups did not differ in their involvement in fire-fighting tasks. 91% of fire-fighters reported relevant occupational exposure in the past year. Mean PCS12 scores for fire-fighters with no chronic respiratory conditions, asthma, and COPD/emphysema/bronchitis were 49.2 (SD 6.5), 47.0 (8.5) and 48.1 (9.4). For PCS12 (but not for MCS12) interaction between having a chronic respiratory condition and not being protected from occupational exposure was observed (p < 0.001).

Conclusions: 10% of metropolitan fire-fighters reported underlying chronic respiratory conditions. Presence of such a condition in combination with sub-optimal protection from inhaled exposures may lead to poorer physical HRQoL.

BIO DIESEL EXHAUST INDUCED CYTOTOXICITY AND PRO-INFLAMMATORY MEDIATOR PRODUCTION IN HEALTHY HUMAN AIRWAY EPITHELIAL CELLS

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Aim: In this study, we aimed to assess the comparative effects of exposure to diluted exhaust generated by the combustion of ultra-low-sulphur-diesel (ULSD), unprocessed canola oil (POO), 100% canola biodiesel (B100) and a blend of 20% canola biodiesel mixed with 80% ultra-low-sulphur-diesel (B20) in vitro.

Method: Human epithelial cell cultures (10 KT and NuLi-1) were exposed to one of the above exhaust types (or control) for one h. The physio-chemical characteristics of the exhaust were monitored and we compared cellular viability, apoptosis and levels of relevant cytokines in cultured cells at a number of timepoints post exposure.

Results: Different fuel types produced significantly different amounts of exhaust gases and different particle characteristics. All exposures resulted in significant cellular apoptosis and loss of viability compared to control, with an increasing proportion of biodiesel being correlated with a decrease in viability. In virtually all cases, exposure to any exhaust resulted in an increase in mediator production. The greatest increases in IL-6, IL-8 and RANTES were most often in response to B100 exposure, followed by ULSD exhaust exposure. Exposure to PCO exhaust did not increase production of IL-6 at any time point in either cell line, nor did it increase production of IL-8 or RANTES at any time-point in NuLi-1 cells. PCO exhaust exposure resulted in a significant decrease (below control) in IL-8 and RANTES in some cases.

Conclusion: The results of this study show that canola biodiesel exhaust exposure elicits increased inflammation and reduces viability of human epithelial cell cultures in vitro compared to ULSD exhaust exposure. This may be related to an increase in particle surface area and number in B100 exhaust compared to ULSD exhaust. Exposure to PCO exhaust elicited the greatest loss of cellular viability, but virtually no inflammatory response, likely due to an overall increase in average particle size.
GEOGENIC DUST IMPACTS CELL VIABILITY AND INFLAMMATORY CYTOKINES IN HUMAN AIRWAY EPITHELIAL CELLS

CLIFFORD H1, KICIC A1,2,3,4, PERKS K1, BERRY L1, LING K1, SUTANTO E1, LARCOMBE A1, ZOSKY G1
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Introduction: Environmental particulate matter (PM) exposure has been linked epidemiologically to exacerbations of lung disease. We have previously shown using in vivo animal models that geogenic (earth-derived) PM can exacerbate the response to respiratory infection. However, the specific impact of geogenic PM10 on human airways is not known.

Aim: To determine the effects of community-sampled geogenic dust PM10 (PM <10 μm diameter) in human airway epithelial cells.

Methods: Geogenic dust was sampled from four remote Western Australian communities (Kalgoorlie, Karratha, Tom Price and Port Hedland), and the PM10 fraction was extracted. Two immortalized human airway epithelial cell (AEC) models (NuLi-1 – healthy; CuFi-1 – cystic fibrosis) were exposed in vitro to geogenic PM10 (10 μg/mL in PBS). After 24 h incubation, cell viability and inflammatory cytokine production (IL-6, IL-8, RANTES) were assessed using MTS assay and ELISA, respectively.

Results: Cell viability was significantly decreased in the cystic fibrosis CuFi-1 AECs, when exposed to geogenic PM10 from Kalgoorlie (18.5% ± 7.8; p = 0.008), Karratha (18.9% ± 3.6; p = 0.007), Tom Price (20.7% ± 6.0; p = 0.003) and Port Hedland (19.2% ± 5.7; p = 0.006), compared with control. No loss of viability was observed in the healthy NuLi-1 cells. In CuFi-1 AECs, IL-6 levels were significantly higher compared with control when exposed to geogenic PM10 at all sites (all p < 0.001). IL-8 was detectable only in the NuLi-1 cells, where levels were also significantly increased compared with control in all four towns (all p < 0.001).

Conclusion: Geogenic dust particles impact on human AECs, affecting viability and cytokine production. This has important implications for respiratory health in individuals living in the remote, arid regions of Australia that are exposed to high particulate loads of geogenic origin, particularly those with pre-existing respiratory conditions.

Supported by: University of Western Australia

OXIDATIVE CHANGES TO SUB-CELLULAR LOCALIZATION AND FUNCTION OF MANNOSE BINDING LECTIN ON ALVEOLAR MACROPHAGES MAY CONTRIBUTE TO THEIR DECREASED PHAGOCYTIC FUNCTION AND INCREASED INFLAMMATION IN COPD

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Aim: Disorders implicated in COPD include decreased phagocytosis by alveolar macrophages associated with secondary necrosis and chronic inflammation, increased oxidative stress, and deficiency of mannose binding lectin (MBL) in the airway. This project aimed to study effects of oxidation on the structure of the MBL molecule and its functional interactions with macrophages.

Method: Oligomeric structure of plasma derived MBL before (pdMBL), and after oxidation (oxMBL) with 2,2′-azobis(2-methylpropionamide) dihydrochloride (AAPH) was investigated by blue native PAGE. Binding of pdBML/oxPBL to THP-1 macrophages, and MBL localization in human alveolar macrophages from BAL and lung biopsies were studied by flow-cytometry and immunofluorescence. Functional capacity of pdMBL/oxMBL was assessed by measuring their effects on expression of macrophage scavenger receptors, and phagocytosis of apoptotic bronchial epithelial cells and non-typeable Haemophilus influenzae (NTHi).

Results: Oxidation disrupted higher order MBL oligomers. Following binding to THP-1 macrophages, pdMBL was detected mostly at the cell surface, consistent with patterns of MBL sub-cellular localization in alveolar macrophages from non-smokers. In contrast, following binding in vitro oxMBL sequestered in intracellular bodies, which mirrored sub-cellular localization in macrophages from smokers and COPD patients. An increase of scavenger receptor A1 (SR-A) expression in THP-1 macrophages in presence of pdMBL was abrogated by using oxMBL (mean ± SEM control 15.84 ± 4.45; pdMBL 20.37 ± 3.98; oxMBL 14.41 ± 4.52). Finally, oxidation of MBL resulted in reduced capacity of THP-1 and alveolar macrophages to phagocytose apoptotic cells (by 11.4 and 17.7%) and NTHi (by 55.9 and 27.0%, respectively).

Conclusion: Our findings suggest that (a) MBL can be taken up by macrophages, induce expression of SR-A, and be mounted at the cell surface to facilitate phagocytosis; (b) oxidative stress-induced structural changes to MBL may be a potential cause for reduced efficiency of MBL in the postulated interactions, which results in impaired phagocytic function in the airways in COPD.
REGULATION OF INNATE IMMUNE RESPONSES TO INFLUENZA A VIRUS BY ENDOosomal NOX2 OXIDASE AND TLR7 IN MACROPHAGES

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Introduction: Influenza A virus (IAV) infects resident alveolar macrophages (AMs) via dynamin-dependent endocytosis, resulting in endosomal TLR7 activation and release of antiviral IL-1β and type 1 IFNs. Although ROS promote the lung injury to IAV, it is completely unknown in which subcellular compartment ROS production occurs and whether it is due to TLR7 activation.

Aim: To establish whether IAV and TLR7 stimulate endosomal ROS production and influence the oxidative burst and cytokine expression in macrophages.

Methods: RAW 264.7 macrophages and AMs were infected with HKx31 (H3N2) IAV strain (MOI 0.1–10) or treated with the TLR7 agonist, imiquimod (1–10 μg/ml). Superoxide production was assessed using chemiluminescence and Oxyburst fluorescence microscopy. IAV, endosome and nuclear localization were examined by triple labelling immunocytochemistry and cytokine expression quantified by qPCR.

Results: X-31 virus internalized into early endosomes, which was blocked by the dynamin inhibitor dynasore (100 μM), and caused an increase in endosomal superoxide production that was abolished by extracellular SOD (300 U/mL) and deletion of the Nox2 gene. One-hour post X-31 infection significantly (P < 0.05) enhanced the phorbol dibutyrate (PDB; 10−7 M)-induced oxidative burst and this ‘priming’ effect was abolished by a novel competitive HIV-tat containing peptide targeted at the Ser346 residue on the Nox2 organizer protein, p47phox. Similar to X-31, imiquimod increased endosomal ROS production by Nox2 oxidase, and caused priming that was blocked by the Ser346 inhibitor. Finally, AMs taken from Nox2−/− mice displayed a substantial increase in IL-6, TNF-α, IFN-β and IL-1β expression compared to WT controls following IAV infection in macrophages.

Conclusion: This study demonstrates a hitherto unappreciated TLR7-Nox2 signalling axis in the endosome that regulates the oxidative burst and antiviral cytokine expression following IAV infection in macrophages.

HCK ACTIVITY PROMOTES AN ALTERNATIVELY ACTIVATED MACROPHAGE PHENOTYPE AND IS ASSOCIATED WITH COPD AND CANCER

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Introduction: Activation of haematopoietic cell kinase (Hck) promotes inflammatory disease and airspace enlargement in the lungs of mice similar to COPD in humans, in addition mutations in Hck have been observed in lung cancer.

Aim: To investigate the role of Hck to pulmonary inflammation and cancer in mice and COPD patients.

Method: This study used a genetic complementation approach to investigate the contribution of the innate and adaptive immune systems to inflammation in Hck mutant mice (Hck499F). Inflammation was characterized by cellular and cytokine measurements derived from recovered BAL bronchoalveolar lavage (BAL) fluid. Macrophage phenotype was assessed by gene expression analysis of cells recovered from BAL and bone marrow-derived macrophages (BMM). Pulmonary adenoma formation was assessed in Cre inducible KrasG12D mutant mice by image analysis and Hck activity was assessed in tissue sections from COPD patients.

Results: Hck499F mice developed macrophage and eosinophil dominant inflammation as indicated by an increase BAL fluid cellularity compared to wt mice. A contribution of the adaptive immune system to disease was discounted after lymphocyte and Th2-deficient mice, Hck499F; Rag1−/− and Hck499F; Stat6−/− respectively, showed no reduction in macrophage content of BAL fluid. Genetic depletion of TNF-α or MyD88 partially rescued the inflammation phenotype of Hck499F mice, while complete rescue was observed in Hck499F;Gcsf−/− mice. Hck499F mutation increased alternatively activated macrophage gene expression in BAL cells and BMMs. Hck may promote tumour growth as Hck499F; KrasG12D mutant mice had a higher tumour burden than KrasG12D control mice and phosphorylated Hck was immunolocalized to inflammatory and tumour foci in COPD tissue.

Conclusion: Hck is involved in inflammatory pulmonary disease and promotes tumour progression in mice and is associated with COPD and lung cancer in humans.
Conclusion: These results indicate that S1P can reverse the inhibiting effect of CSE on efferocytosis, but not LPS. Further investigation is required to determine the mechanisms involved.

Method: SPHK1 and 2 activities were measured in differentiated THP-1 macrophages post-treatment with cigarette smoke extract or LPS. Activity was measured using an isofrom-selective assay which measures the production of 32P-labelled S1P. Flow cytometry was used to measure efferocytosis.

Results: At 24 h there was a significant decrease in SPHK1 activity in CSE (0.659 ± 0.065), and LPS (0.656 ± 0.047) exposed THP-1 macrophages vs controls (1.0 ± 0.067), with no significant differences between CSE and LPS treatments. Likewise, there was a significant decrease in SPHK2 activity at 24 h post CSE (0.677 ± 0.098) and LPS (0.425 ± 0.070) exposure vs controls (1.0 ± 0.081). There was a significant decrease in efferocytosis following 24 h of CSE and LPS exposure (13.85 ± 0.82% and 12.85 ± 1.45%, respectively). Following S1P treatment, efferocytosis significantly increased to control levels (28.90 ± 3.13%) in CSE exposed THP-1 macrophages at 1nM S1P (27.32 ± 2.57%). However, S1P had no effect on LPS-induced repression of efferocytosis.

Conclusion: These results indicate that S1P can reverse the inhibiting effect of CSE on efferocytosis, but not LPS. Further investigation is required to determine the mechanisms involved.
RISK FACTORS FOR DEVELOPMENT OF ANTIBIOTIC-RELATED LIVER ENZYME DERANGEMENT IN ADULTS WITH CYSTIC FIBROSIS (CF)

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Aim: Antibiotic-related liver enzyme derangement can limit treatment options for acute infective exacerbations in CF bronchiectasis. The aim of the study was to identify risk factors for the development of elevated liver enzymes.

Methods: All patients who received parenteral antibiotic therapy in 2012 attending The Prince Charles Hospital (TPCH) Adult CF Centre were identified by searching the CF Research Database and CF Data Registry. All biochemical and haematology panels were retrieved from the Queensland Health Pathology Service and from private pathology providers. Patients who had any liver enzyme elevation >3 times the upper limit of normal were identified. For each laboratory test, the concurrently administered antibiotic(s) were analyzed from TPCH pharmacy dispensing system. Pathology results for patients not receiving parenteral antibiotics were also retrieved.

Results: In patients who received parenteral antibiotics in 2012, 28% of patients (44 of 158) developed abnormal liver enzyme(s) compared with 16% (15 out of 96) of patients who did not receive parenteral antibiotics (Fisher exact test p = 0.03). Patients who received parenteral antibiotics had higher rates of CF related liver disease (CFLD) and lower mean lung function (Table 1).

Conclusion:

Comparison of patient factors between patients who received versus patients who did not receive parenteral antibiotics in 2012

<table>
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</tr>
<tr>
<td>CFLD (%)*</td>
<td>6 (13.6%)</td>
<td>8 (7.0%)</td>
</tr>
<tr>
<td>Mean (sd) best FEV1</td>
<td>54.7 (20.4)</td>
<td>58.2 (23.8)</td>
</tr>
<tr>
<td>Mean (sd) best BMI*</td>
<td>22.8 (3.2)</td>
<td>23.0 (4.6)</td>
</tr>
<tr>
<td>Mean (sd) Total</td>
<td>47.3 (46.9)</td>
<td>29.2 (29.0)</td>
</tr>
<tr>
<td>Hospital Days</td>
<td>47.3 (46.9)</td>
<td>29.2 (29.0)</td>
</tr>
</tbody>
</table>

*ANOVA with post hoc t-tests. No IVs different from both IV groups (p < 0.001)

Ceftazidime was prescribed in 70% of patients who developed significant liver enzyme derangement versus 59% of patients who did not have significant liver enzyme derangement. Meropenem was prescribed in 50% of patients in the elevated liver enzyme group versus 42% of patients in the non-elevated liver enzyme group. The use of dual therapy with ceftazidime and meropenem had higher rates of CFLD with elevated liver enzymes compared with meropenem alone (28% versus 21%, p < 0.05).

Conclusion: Elevated liver function tests are common during parenteral antibiotics for CF exacerbations. Pre-existing CFLD is a risk factor for developing acute abnormal liver function. Lung function and specific antibiotic exposure are being further explored as potential additional risk factors.

PRAAGMA: A NEW METHOD OF QUANTIFYING STRUCTURAL LUNG DISEASE IN YOUNG CHILDREN WITH CYSTIC FIBROSIS

ROSENOW T 1, 2, TIDDENS H 3, DE BRUIJNE M 1, 2, STICK S 1, 2, 5
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Introduction: Computed tomography (CT) is the gold standard for assessing structural lung disease (SLD) in cystic fibrosis (CF). Current systems for scoring SLD are not appropriate for early SLD in very young children with CF. Quantitative assessments of SLD should be developed for this important age group.

Aim: To develop a quantitative method of assessing SLD in children with CF aged less than 5 years.

Methods: Children were included from the Australian Respiratory Early Surveillance Team for CF (AREST-CF) cohort that had bronchoaveolar lavage (BAL) and volumetric inspiratory chest CT scans at both age 1 and 3 years. For CT scans, a square grid was overlaid on top of 10 equidistant slices. Grid cells within the lung field were annotated with one of the following hierarchical categories: for inspiratory scans a) bronchiectasis, b) ‘abnormal’ airway, c) mucus plugging, d) atelectasis, or e) healthy lung. For expiratory scans, a) more than 50% trapped air, b) less than 50% trapped air. The results were presented as the proportion of the lung that is made up of a) bronchiectasis (%Bx) or b) any disease (%Dis) for inspiratory scans, and the proportion of the lung with trapped air (%TA) for expiratory scans, and compared to CT scores.

Results: 31 patients had paired scans. Patients with neutrophil elastase (NE) levels at age 3 had a larger change in %Dis (p < 0.01). %Dis at age 1 was associated with greater progression of %Bx by age 3 (p = 0.44, p = 0.01). Increase in %TA was associated with increase in %Dis (p = 0.03, p < 0.001) and with NE presence at age 3 (p < 0.01). These relationships were not significant with CT scores.

Conclusion: This new method of quantifying structural lung disease in young children with CF is more strongly related to inflammatory markers and bronchiectasis progression than CT scores.
**COPD SIG 2 – ORAL PRESENTATIONS**

**OMEGA-3 FATTY ACIDS AND COPD: HOW HAS CITING A RETRACTED RCT IMPACTED THE LITERATURE?**

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**Introduction:** The only randomized controlled trial (RCT) to explore the effects of omega-3 polyunsaturated fatty acids in people with chronic obstructive pulmonary disease (COPD) was published in 2005 but was retracted in 2008 due to falsified data. Despite the retraction, this article has continued to be cited in both respiratory and nutrition fields.

**Aim:** The aim of this study was to determine the frequency and nature of citations of this retracted paper in order to ascertain the potential impact of retractions on the literature.

**Methods:** The number of times the retracted article was cited was determined using the cited reference function of Google Scholar. Citations were classified into two groups to indicate whether the retraction had been acknowledged (‘retraction acknowledged’ or ‘retraction not acknowledged’). Articles not acknowledging the retraction were further classified as ‘specific citation of data’ or ‘cited in passing’.

**Results:** A total of 73 citations were found with 23 of these occurring before the retraction of the article. Of citations occurring after the retraction the majority (48/50) were classified as “retraction not acknowledged.” Even more concerning is that 20 of these discussed specific outcomes from this publication.

**Conclusion:** Journals publish retraction notices to correct the scientific record, in this case due to falsified data. However this information is not always effectively communicated as evidenced by authors continuing to cite an article without acknowledging the retraction. Implementation of a standard approach to report retractions may limit misinterpretation of a field of research, thereby preventing inappropriate management of chronic disease conditions.

**CONSISTENCY OF AIRWAY OBSTRUCTION IN RESPIRATORY SYMPTOMATIC CURRENT AND EX-SMOKERS IN PRIMARY CARE**

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**Introduction:** Diagnosis of COPD is often based on a single spirometry test. However, stability of diagnosis based on FEV1/FVC ratio has not previously been reported.

**Aim:** In subjects at risk of COPD, we investigated shifts in diagnostic category (i.e. shifts between obstructed and non-obstructed) after 1 year, and predictors of these shifts.

**Methods:** We used data from Caucasian respiratory symptomatic ex- or current smokers aged ≥ 40 who were referred to diagnostic spirometry services by Dutch GPs, and for whom two spirometry tests were available 12 ± 2 months apart. Demographics, BMI, smoking status and medication use were recorded. Diagnosis of airway obstruction was based on post-bronchodilator (post-BD) FEV1/FVC < 0.70 (fixed ratio) and FEV1/FVC < lower limit of normal (LLN).

**Results:** 2,352 subjects (54% males, 45% current smokers, mean age 60.5 (SD 10.2) years, post-BD %predicted FEV1 76.5 (16.1)) were studied. By fixed ratio, 46.6% were obstructed at baseline (32% by LLN). At 1 year, 343 (25.5%) of all subjects had changed diagnostic category: 17% of those obstructed at baseline were non-obstructed at 1 year (22% with LLN), and 13% of those non-obstructed at baseline were obstructed at 1 year (9% with LLN). Significant predictors of change were: gender, age, smoking status, BMI, reversibility, %predictedFEV1, and use of respiratory medication.

**Conclusion:** About 1/3 of current/ex-smokers referred for diagnostic spirometry shifted between obstructed/non-obstructed categories after 1 year. Similar shifts were seen with fixed ratio and LLN. Several features were associated with the probability of change. Given the implications of a diagnosis of COPD, it should probably not be based on a single spirometry test.

**THE LUNG CLEARANCE INDEX IS SENSITIVE TO DETECT STRUCTURAL LUNG DISEASE ON COMPUTED TOMOGRAPHY IN PRESCHOOL CHILDREN WITH CYSTIC FIBROSIS**

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**Introduction:** The lung clearance index (LCI) is a global measure of ventilation inhomogeneity from the multiple breath washout test. LCI is elevated in children with CF and is more sensitive than spirometry to detection of structural disease (SLD) in school-aged children. There are currently no data assessing the ability of LCI to detect SLD during the preschool years.

**Aim:** We aimed to determine the ability of LCI to detect the presence and extent of SLD in preschool children with CF.

**Methods:** LCI was assessed in preschool (3–7 years, n = 20) and school-aged (8–16 years, n = 18) children with CF prior to a volumetric chest computed tomography (CT) scan. SLD was assessed using a simplified CF-CT scoring system.

**Results:** 45% of pre-schoolers and 61% of school-aged children had abnormal LCI (≥ 8). LCI was sensitive to detect the presence of bronchiectasis in school-aged (concordance = 72%) and preschool children (concordance = 80%). Preschool children with abnormal LCI had higher total SLD (abnormal LCI = 8.99 ± 4.19; normal LCI = 4.44 ± 2.00; p = 0.02) and bronchiectasis (abnormal LCI = 5.33 ± 4.44; normal LCI = 1.36 ± 2.84; p = 0.01) scores compared with preschool children with normal LCI. There were no differences in the total SLD (abnormal LCI = 24.73 ± 10.12; normal LCI = 16.86 ± 10.96; p = 0.13) or bronchiectasis (abnormal LCI = 4.82 ± 4.47; normal LCI = 3.71 ± 4.19; p = 0.52) scores between school-aged children with normal or abnormal LCI.

**Conclusions:** The LCI was more sensitive to detect the presence and extent of SLD on CT in preschool children with CF compared with school-aged children with CF. LCI may offer a non-invasive method of detecting SLD in early CF lung disease.
SHOULD WE TREAT OBESITY IN COPD? THE EFFECTS OF WEIGHT LOSS AND RESISTANCE TRAINING IN OBSESE COPD

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Introduction: Obesity is an established risk factor for poor health outcomes, but paradoxically in COPD it is associated with improved survival and lung function. Weight loss via caloric restriction can lead to loss of not only fat, but also skeletal muscle mass.

Aim: To determine if weight reduction, combined with resistance training to maintain muscle mass, would reduce inflammation and improve clinical outcomes in obese COPD.

Method: In a before-after clinical trial, obese (BMI ≥ 30 kg/m²) COPD patients (n = 36) received a 12 week weight reduction programme involving meal replacements, dietary counselling by a dietician and resistance strength training prescribed and supervised by a physiotherapist. Patients were reviewed face to face by the dietician and physiotherapist every two weeks for counselling.

Results: 26 participants completed the intervention. The mean (SD) age was 67.9 (6.5) years, 61% were male, and mean FEV1 (% predicted was 63.3 (20.7). Mean BMI was 36.5 kg/m² (4.8) at baseline and reduced by 2.5 kg/m² (p < 0.0001). Body fat mass was reduced, while skeletal muscle mass was maintained during the intervention. There were no patients with muscle wasting either pre or post intervention. Clinical outcomes improved with weight loss: 6MWD (Δ33.9 m; p = 0.0008); St George Respiratory Questionnaire (Δ10.7 units; p = 0.0001); BODE index (Δ1.4 units; p < 0.0001) and MMRC (Δ1.08; p = 0.0001). There was no difference in CRP post intervention (Δ1.9 mg/L; p = 0.7000), but depression scores improved (p = 0.0100).

Conclusion: In obese COPD patients, dietary energy restriction coupled with resistance strength training results in clinically significant improvements in BMI, exercise tolerance and health status, whilst preserving skeletal muscle mass. Importantly, this intervention resulted in an improved prognostic score (BODE), but longer term follow up is required. This novel study provides a framework for development of guidelines for the management of obese COPD patients and in guiding future research.

ADHERENCE TO THE GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD) STRATEGY DOCUMENT FOR INPATIENTS WITH AN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the second leading cause of hospital admissions in Australia. The GOLD strategy document has been available since 2001 to aid clinicians in assessing and managing people with COPD. Little is known about the level of adherence to the GOLD document among hospital-based health professionals assessing and managing inpatients admitted with an AECOPD.

Aim: The aim of the study was to evaluate the level of adherence to GOLD among hospital-based health professionals.

Methods: A retrospective audit of medical histories was completed using a customized audit tool to evaluate the level of adherence to GOLD. The audit was completed on a random sample of 240 patients admitted to two tertiary hospitals with a primary diagnosis of AECOPD within a calendar year. The audit evaluated adherence to GOLD recommendations on appropriateness of both hospital and critical care unit admissions as well as pharmacological and non-pharmacological management.

Results: High levels of adherence to prescription of bronchodilators (100%) and indications for admission to the critical care unit (100%) were observed. However, only 63% of patient admissions met GOLD hospital admission criteria. There were low levels of adherence to non-pharmacological management in areas such as nicotine replacement therapy prescription (25%) and pulmonary rehabilitation referrals (16%). Patients admitted under the care of the respiratory team were 2.6 times (95% CI 1.3 to 5.4) more likely to be referred to pulmonary rehabilitation than patients admitted under the general medicine team.

Conclusions: The results indicated a need to review clinical practice, with specific reference to appropriate admission to hospital and non-pharmacological management for inpatients admitted with AECOPD.
PREFERENCE FOR BATTERY POWERED PORTABLE OXYGEN CONCENTRATORS VERSUS PORTABLE CYLINDERS IN PATIENTS WITH COPD: EVALUATION OF AN EQUIPMENT SURVEY

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Aim: To evaluate preferences between battery powered portable oxygen concentrators (BPPOC) and portable oxygen cylinders (POC) in patients with COPD.

Method: A multi-centre randomized crossover study of BPPOCs compared to POC (one month each) was undertaken across five major hospitals in South Australia. COPD outpatients who were stable on portable oxygen (max. four cylinders per month) were recruited following successful completion of a step test. At trial completion participants (n=22) were asked to complete an equipment survey of 5 questions, each with 7 options, with an additional narrative comment question. Subjects were asked to select the option that most accurately reflected their experience on BPPOC (scale: 1 ‘none of the time’ and 7 ‘all of the time’).

Results: A higher score for four of five questions designated a positive response and experience for BPPOCs relating to 1. Adequate portability to meet their needs (mean 6.1 ± 1.39); 2. Setup and operation (6.9 ± 0.64); 3. Understanding of the equipment functions (6.8 ± 0.61); and 4. The duration of oxygen supplied was adequate for the performance of normal activities (5.6 ± 1.87). A lower score for the remaining question relating to noise designated a positive response (mean 1.6 ± 1.50) indicating that subjects were not affected by the noise of the device. Narrative responses to question six indicated an outright preference for BPPOC primarily due to ease of use, portability, convenience, increase in mobility, weight-light, improved confidence and BPPOC is more ‘socially acceptable’. Negative responses included battery life too short, concerns about electricity bill and delivery of insufficient oxygen for requirements.

Conclusion: These results indicate a strong preference for BPPOCs over POCs. The increased mobility and activity (the ability to “do more things”) resulting from the portability and convenience of this device is an integral factor in improving general feelings of wellbeing in patients with COPD requiring oxygen for exertional purposes.

Key words: Oxygen, concentrator, COPD, portable, survey, equipment, cylinder.

Grant Support: Nil.

SLEEP AND PHYSIOLOGY SIG – ORAL PRESENTATIONS

IMPACT OF CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) ON CHRONIC COUGH IN OBSTRUCTIVE SLEEP APNOEÀ (OSA) – A RANDOMIZED CONTROLLED TRIAL

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Recent studies have suggested that chronic cough is prevalent in patients with sleep-disordered breathing (SDB). We investigated the effect of continuous positive airway pressure (CPAP) on cough in patients with obstructive sleep apnoea (OSA) and chronic cough in a randomized controlled trial. 22 consecutive patients with OSA confirmed on polysomnography (respiratory disturbance index (RDI) >15/h) and chronic cough >2 months were recruited. All patients underwent a CPAP titration study. 1 patient did not tolerate CPAP. 21 Patients were randomized to receive sham CPAP (4 cm H2O) or CPAP at pressures determined by the titration study for 1 month. The primary outcomes were objective 24-h cough count via the Leicester Cough Monitor (LCM), subjective cough severity via the visual analogue scale (VAS) and cough related quality of life via the Leicester Cough Questionnaire (LCQ).

13 (7 males) patients received sham CPAP and 8 (6 males) received titrated CPAP. There were no significant differences between groups (sham vs CPAP(mean(SD)) in age (54.5 (2.8) yrs vs 59.9 (5.2) yrs, p = 0.34), BMI (37.4 (1.9) vs 32.5 (1.3), p = 0.08), RDI (41.5 (7.4) vs 36.5 (6.7), p = 0.65), baseline 24-h cough count (302.9 (66.0) vs 257.4 (57.5), p = 0.64), VAS (56.9 (6.9) vs 54.3(6.7), in mm) and LCQ score (14.0 (1.0) vs 14.3 (1.3)). After 1 month there were no significant changes in 24-h cough count in the sham CPAP group (−93.9 (222.2), p = 0.15) but there was significant improvement in the titrated CPAP group (−192.6 (162.1), p = 0.01). There were no significant changes in VAS in the sham CPAP group (−9.9 (28.5), p = 0.25) but there was significant improvement in the titrated CPAP group (−26.75 (31.9), p = 0.05). There were no significant changes in LCQ in the sham CPAP group (−0.50 (5.0), p = 0.73) or titrated CPAP group (−1.47 (5.1), p = 0.44).

CPAP may reduce objective and subjective cough severity in patients with cough associated with OSA.
CAN IMPULSE OSCILLOMETRY DETECT PERIPHERAL AIRWAY ABNORMALITIES MEASURED USING MULTIPLE BREATH NITROGEN WASHOUT (MBNW) IN ASYMPTOMATIC SMOKERS?

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Introduction: Smoking causes peripheral airways disease, before spirometry becomes abnormal. Impulse oscillometry can detect differences in airway mechanics in smokers and non-smokers with normal spirometry. MBNW is a sensitive measure of ventilation heterogeneity caused by smoking related peripheral airway dysfunction.

Aim: To determine if impulse oscillometry detects peripheral airway abnormalities, as defined by MBNW in smokers with normal spirometry.

Method: 88 smokers aged 41(10), % predicted FEV1 99.5 (11.2)%, 16 (11) pack years of smoking history, had measures of Sacin and Scond using the multiple breath nitrogen washout and resistance (R5, R5-R20) and reactance (X5, AX) using impulse oscillometry. Sacin and Scond are indices of ventilation heterogeneity in diffusion-dependent and convection-dependent peripheral airways, respectively. Resistance and reactance are indices of airway calibre and stiffness of the respiratory system. Receiver operator curves (ROC) were used to determine the sensitivity and specificity of IOS parameters.

Results: Sacin was abnormal in 35 subjects, R5 was abnormal in 31 subjects, but only 12 of these subjects had both abnormalities. Sacin did not correlate with R5 (p = 0.8), R5-R20 (p = 0.49), X5 (p = 0.77) and AX (p = 0.75). None of the IOS parameters could reliably detect an abnormal Sacin (ROC area under curve = 0.43–0.58).

Conclusion: Impulse oscillometry is not a sensitive measure of peripheral airway abnormalities in smokers as defined by Sacin. The lack of correlation between Sacin and IOS parameters suggest that these parameters reflect different abnormalities or differing sites of abnormality due to cigarette smoking. The nature of these differences and their implications for the risk of later development of COPD require further study.

CONTINUOUS POSITIVE AIRWAY PRESSURE FOR OBSTRUCTIVE SLEEP APNOEA: A COCHRANE SYSTEMATIC REVIEW

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Aim: To assess the clinical effectiveness of CPAP (Continuous Positive Airway Pressure) therapy in the treatment of obstructive sleep apnoea (OSA).

Method: In July 2012 we searched the Cochrane Airways Group specialized register, online clinical trial registries, reference lists of included studies and consulted with experts in the field for identification of relevant studies producing n = 1035 citations. Randomized controlled trials comparing nocturnal CPAP (minimum two weeks duration) with an inactive control or oral appliance (OA) in adults with OSA were included. Data was extracted by two independent reviewers.

Results: A total of n = 77 studies were identified for inclusion in the review (n = 42 new studies since last update). Study quality was mixed with the majority of risk of bias categories assessed as unclear. For the primary outcome of sleepiness as measured by ESS (Epworth Sleepiness Scale) a significant improvement was observed for CPAP over the control group in both parallel (mean difference −3.13; 95%CI −4.11 to −2.15; p < 0.00001; n = 18 studies) and cross-over studies (generic inverse variance −2.75; 95%CI −4.36 to −1.14; p = 0.0008; n = 8 studies). No differences were observed for ESS when comparing CPAP to OAs for parallel studies (n = 3) or cross-over studies (n = 5); CPAP therapy produced significant improvements in other objective and subjective measures of sleepiness in comparison to the control group including measures for quality of life, cognitive function, blood pressure, apnoea/hypopnea index, sleep efficacy and other outcomes. A strong preference for the OA was observed, however, participants were also more likely to withdraw on OA than on CPAP therapy.

Conclusion: CPAP is effective in reducing symptoms of sleepiness and improving quality of life in patients with moderate and severe OSA. Long-term data are required for all outcomes in order to determine whether the benefits seen in short-term clinical trials persist.
MEF50 IS RELATED TO VENTILATION HETEROGENEITY IN ASTHMA BUT LESS SENSITIVE PREDICTOR OF FUTURE SYMPTOM CONTROL

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Introduction: One of the primary goals of asthma management is determining the optimal inhaled corticosteroid (ICS) dose to achieve asthma control. However, the physiological factors that determine changes in control are still poorly understood. We have previously shown that small airway ventilation heterogeneity, measured using the multiple breath nitrogen washout (MBNW), can predict changes in symptom control following ICS dose titration. Mid-expiratory flow at 50%FVC (MEF50) is thought to be a surrogate measure of small airway obstruction.

Aim: We investigated whether MEF50 is related to ventilation heterogeneity and its ability to predict changes in symptom control.

Methods: Data from 61 non-smoking asthmatics were analyzed. At visit 1 (baseline), subjects performed a series of tests including MBNW, spirometry, and plethysmography. Symptoms were assessed using the Asthma Control Questionnaire (ACQ5). Subjects with poor symptomatic control at baseline had their ICS dose doubled (up-titration group), whereas well-controlled subjects either quartered or stopped their ICS dose (down-titration group). At visit 2 (8 weeks later), the assessments were repeated. MEF50 was obtained from spirometry whereas Scond (conductive) and Sacin (acinar) ventilation heterogeneity were obtained from MBNW. We first examined correlations between MEF50, Scond, Sacin and ΔACQ5s (visit 2-visit 1). Predictors for ΔACQ5s were then examined using multiple linear regression.

Results: Significant correlations were found between baseline MEF50 and Scond (r = -0.523; p < 0.001) and Sacin (r = -0.478; p < 0.001). MEF50 was significantly related to ΔACQ5s in the whole dataset (r = -0.360; p = 0.005) but not when examined separately in the two titration groups. As previously reported, Scond and Sacin predicted ΔACQ5s in the up- and down-titration groups, respectively.

Conclusions: MEF50 is related to ventilation heterogeneity, suggesting that it provides information regarding the small airways. While MEF50 may be a simpler measure available from spirometry, it is less closely related than it provides information regarding the small airways. While MEF50 may be a simpler measure available from spirometry, it is less closely related than

IDENTIFICATION OF CLINICAL PHENOTYPES IN OBSTRUCTIVE SLEEP APNEA (OSA) USING CLUSTER ANALYSIS: A POPULATION STUDY

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1The Health Observatory, Discipline of Medicine, University of Adelaide, The Queen Elizabeth Hospital Campus, Woodville, South Australia, 2The Men Androgen Inflammation Lifestyle Environment and Stress (MAILS) Study is an urban population biomedical cohort study of men, aged ≥ 40 years (n = 1629) with 10+ years of follow-up. In 2011, randomly selected men from the cohort without previously diagnosed OSA (n = 837), successfully underwent full in-home unattended polysomnography (PSG) (Embletta X100), scored according to current AASM (alternate) criteria and completed questionnaires including the Epworth Sleepiness Scale (ESS). Clinic assessment included anthropometry, blood pressure and fasting lipid assessment, and chronic conditions and risk factors. Phenotypic clusters were determined using spherical (cosine) k-means clustering. The Ratkowsky-Lance indicator determined optimal cluster number.

Methods: The Men Androgen Inflammation Lifestyle Environment and Stress (MAILS) Study is an urban population biomedical cohort study of men, aged ≥ 40 years (n = 1629) with 10+ years of follow-up. In 2011, randomly selected men from the cohort without previously diagnosed OSA (n = 837), successfully underwent full in-home unattended polysomnography (PSG) (Embletta X100), scored according to current AASM (alternate) criteria and completed questionnaires including the Epworth Sleepiness Scale (ESS). Clinic assessment included anthropometry, blood pressure and fasting lipid assessment, and chronic conditions and risk factors. Phenotypic clusters were determined using spherical (cosine) k-means clustering. The Ratkowsky-Lance indicator determined optimal cluster number.

Results: Undiagnosed OSA (apnea-hypopnea index (AHI) ≥ 10 events/hour) was identified in 52.9% (n = 443/837). In OSA population (n = 332 after cancer and depression excluded), four clusters were identified. Cluster 1 (22%) was characterized by predominantly younger age (<50 y), economic advantage, and high burdens of moderate to severe OSA, obesity, hypertension, hypertriglyceridemia, and low testosterone but minimal sleepiness. Cluster 2 (27%) was similar to cluster 1 (with the exception of economic advantage) but with frequent sleepiness and low SF-36 vitality. Cluster 3 (19%) demonstrated more mild OSA, lowest burdens of obesity, hypertriglyceridemia and elevated interleukin 6, and aged >65 years. Cluster 4 (32%) were predominantly aged >65 years, demonstrating high burdens of moderate-severe OSA, economic disadvantage, diabetes, hypertension, nocturia, cardiovascular disease and hypertriglyceridemia, but not sleepiness.

Conclusions: Distinct clinical OSA phenotypic clusters could be identified. Further work can examine if these groupings can prospectively identify outcomes, and be used to identify groups for targeted interventions.
LYMPHOCYTE SENESCENCE IN COPD IS ASSOCIATED WITH LOSS OF GLUCOCORTICOID RECEPTOR EXPRESSION BY PRO-INFLAMMATORY/CYTOTOXIC LYMPHOCYTES

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Background: Glucocorticoid (GCS) resistance is a major barrier in the treatment of COPD and the reason for this unknown. We have shown that COPD is associated with an increase in cytotoxic/pro-inflammatory T and NKT-like cells, particularly CD8+ subsets. Loss of the co-stimulatory molecule CD28 (lymphocyte senescence) from these cells was associated with a further increase in their pro-inflammatory/cytotoxic potential and resistance to GCS. We hypothesized that lymphocyte senescence is associated with downregulation of the GCS receptor (GCR) from these cells.

Methods: Blood was collected from 8 COPD and 10 healthy aged-matched controls. Intracellular pro-inflammatory cytokines and expression of CD28 and GCR were determined using flow cytometry and binding of Dex-Fluorescene to GCR+ lymphocyte subsets following culture.

Results: Loss of CD28 was associated with an increase in the percentage of T and NKT-like cells producing IFNγ or TNFα in all subjects studied. Loss of CD28 was associated with a loss of GCR and Dex-Fluor staining. There was a significant loss of GCR in CD8+CD28 null compared with CD4+CD28null cells in both groups (eg, GCR+CD28+ in COPD: 8% ± 4 vs 17 ± 6, mean ± SEM p = .004). There was a significant negative correlation between GCR expression and the percentage of T and NKT-like cells producing IFNγ or TNFα in all subjects (eg, COPD: R = -.763, p < .001 for T-cell IFNγ) and FEV1 in COPD (R = -.653, p = .043). In GCR+CD28+ T and NKT-like cells GCR translocated from the cytoplasm to the cell nucleus following cell culture but not in CD28null cells.

Conclusions: Lymphocyte senescence in COPD is associated with loss of GCR in CD28null T and NKT-like cells suggesting that alternative treatment options to GCS are required to inhibit these pro-inflammatory/cytotoxic cells. These findings may be relevant to other diseases associated with lymphocyte senescence such as GCS resistant asthma, SLE, CAD, IPF as well as the normal aging process.

POLYSOMNOGRAPHY AND SONOMAT MEASUREMENTS ARE SIMILAR IN SLEEP LABORATORY PATIENTS

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Introduction: The ‘gold standard’ of sleep measurement is in-laboratory polysomnography (PSG). However, due to the increasing prevalence of sleep disorders, home-style sleep studies are emerging. A system to address limitations for in-laboratory PSG has been developed – the Sonomat. The Sonomat is a non-invasive portable mat which contains a microphone and four highly sensitive vibration sensors to detect breath sounds, breathing and body movements. The Sonomat can also identify additional respiratory sounds, such as cracks and wheeze, not detected by PSG.

Aim: The aim of this study is to validate the Sonomat with in-laboratory PSG.

Method: In-laboratory PSG was performed simultaneously with the use of the Sonomat at the Westmead Sleep Investigation and Research Centre. The data from the PSG and the Sonomat were analyzed separately by sleep technicians. Respiratory disturbances were calculated using the PSG Respiratory Disturbance Index (RDI, includes respiratory effort related arousals) and modified Apnoea-Hypopnoea Index (AHI) from the Sonomat.

Results: Twenty-nine patients, 20 male, age 58 ± 10 years (mean ± SD) were recruited. Baseline characteristics included: body mass index (BMI) 28.1 ± 3 kg/m2, Epworth Sleepiness Scale (ESS) 10 ± 5. The PSG RDI (25.9 ± 21.5 events per hour) did not differ from the Sonomat AHI (27.7 ± 21.1 events per hour; p = .61).

Conclusion: Sonomat measurements of AHI in patients with sleep disordered breathing did not differ from simultaneous PSG measurements. The Sonomat can also identify additional respiratory sounds, such as cracks and wheeze, not detected by PSG.

Key words: Polysomnography, obstructive sleep apnoea, AHI.

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MECHANISMS UNDERLYING STAT3-INDUCED LUNG FIBROSIS

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Introduction: We previously examined bleomycin-induced lung fibrosis in mice with different capacities to activate gp130-mediated Erk1/2 and Stat3/3 pathways. We observed increased collagen deposition/fibrosis with exaggerated gp130-STAT signalling in gp130757F mice compared to wild-type (wt) and gp130757F;Stat3−/− mice, demonstrating that STAT3 signalling is fundamental to the development of lung fibrosis.

Hypothesis and Aims: STAT3-mediated lung fibrosis is driven by interleukin (IL)-6 family cytokines through mechanisms including epithelial to mesenchymal transition (EMT). This study examined the roles of IL-6 and IL-11 in bleomycin-induced lung fibrosis and determined whether the lungs of bleomycin-treated gp130757F mice demonstrated increased EMT.

Method: Bleomycin or saline was administered intranasally to wt, gp130757F and IL-6 (IL-6−/−) and IL-11 α-receptor knockout (IL-11αR−/−) mice separately or crossed onto a gp130-757F background (gp130757F;IL-6−/− and gp130757F;IL-11αR−/− respectively). Collagen and fibrosis were examined by HPLC and histology of lung tissue from all genotypes 30 days post bleomycin treatment. IL-6 family cytokines, EMT markers and inflammatory mediator mRNA and protein were measured in lung tissue and serum at 3 and 30 days following bleomycin.

Results: IL-6, OSM, IL-1β and TNFα mRNA were significantly increased in gp130757F lung tissue but not in serum 3 days post-bleomycin compared to saline. Furthermore, a two-fold increase in MMP2 and 9 activity was demonstrated in gp130757F mice. We observed evidence of increased epithelial cell hyperplasia and fibroblast number, possibly due to increased EMT, since snail and slug expression were significantly increased in gp130757F lung tissue at 3 and 30 days post-bleomycin. Genetic ablation of IL-6 but not IL-11αR significantly reduced collagen production/fibrosis in bleomycin-treated mice but eliminating either IL-6 or IL-11R in gp130757F mice reduced bleomycin-induced fibrosis in both genotypes.

Conclusion: These data indicate that IL-6 cytokines play a significant role in bleomycin-induced lung fibrosis and that fibroblast accumulation and activity may be driven by STAT3-mediated EMT.

DOES EXCESSIVE OXIDATIVE STRESS DIRECTLY CONTRIBUTE TO INCREASED SUSCEPTIBILITY TO PNEUMOCOCCAL INFECTIONS?

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Introduction: Excessive oxidative stress is a pathological feature of chronic lung diseases including COPD. A large proportion of COPD patients are chronically colonized with respiratory pathogens, including Streptococcus pneumoniae which can be life threatening. The mechanisms that typically protect against such invading pathogens are thought to become dysfunctional during COPD. However, these dysfunctional processes remain poorly defined.

Aim: To identify the cellular and molecular mechanisms that underlie susceptibility to pneumococcal infections in airways under high oxidant burden.

Methods: An experimental mouse model was used in which C57BL/6 mice were intranasally infected with S. pneumoniae EF3030 and coinfected with influenza A virus (IAV) to trigger pneumococcal disease. To model the increased levels of extracellular superoxide radicals detected in COPD airways, mice lacking SOD3 (superoxide dismutase 3) were used.

Results: Infection of SOD3−/− mice with pneumococci resulted in greater weight loss over a seven-day period compared to infected wildtype (WT) mice. In addition, pneumococcal load in the lung and nasal tissues were also increased in SOD3−/− mice compared to WT mice. Co-infection with IAV resulted in dramatically increased pneumococcal numbers in the lungs and the nose, with more pneumococci in co-infected SOD3−/− mice compared with co-infected control mice. Analysis of bronchoalveolar lavage found that co-infected SOD3−/− mice had two-fold higher numbers of recruited inflammatory cells, in particular neutrophils.

Conclusions: SOD3−/− mice show increased susceptibility to infection with pneumococci, suggesting that pathogenesis of S. pneumoniae may be altered under oxidative stress. We are currently exploring differences in pneumococcal and host gene expression that may explain these changes in susceptibility to pneumococcal infection.

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TIGHT JUNCTION DISASSEMBLY FOLLOWING HUMAN RHINOVIRUS INFECTION RESULTS IN AIRWAY EPITHELIAL PERMEABILITY CHANGES

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Introduction: Junctional protein complexes such as tight junctions (TJ) provide a physical barrier against external insults. Although TJs have been extensively assessed in general terms, few studies have directly addressed the consequence on barrier function following the disassembly of TJ protein post human rhinovirus (HRV) infection. This study aimed to assess TJ expression and barrier function prior to and post HRV infection in both healthy and asthmatic epithelium.

Methods: Primary airway epithelial cells from healthy and asthmatic children obtained via bronchial brushings and cultured as previously mentioned (Kicic et al. 2006) were infected with HRV-1B at various multiplicity of infection (MOI) over 24 h. Barrier integrity as measured by TJ was assessed by protein expression of occludin, claudin-1 and zona occluden-1 (ZO-1) via immunocytochemistry (ICC) and in-cell western (ICW) while barrier function was assessed via transepithelial permeability assay.

Results: Ex vivo TJ protein expression for occludin, claudin-1 and ZO-1 observed via ICC was markedly reduced in asthmatic airway epithelium than healthy controls. Semi-quantitative assessment of occludin, claudin-1 and ZO-1 protein expression via ICW corroborated with ICC findings and demonstrated reduced basal membrane TJ expression in asthmatic compared to healthy controls. However, only the reduction in claudin-1 was considered significant (p < 0.05). A greater effect on TJ disassembly was observed within the asthmatic epithelium post infection and this was concurrent with a marked increase in transepithelial permeability.

Conclusion: This study demonstrated significant differences in basal membrane TJ protein expression between healthy and asthmatic cohorts, suggesting intrinsic differences between healthy and mild-asthmatic epithelium. Furthermore, post HRV infection, an exaggerated disassembly in the asthmatic cohorts, which is concomitant with increased transepithelial permeability suggests elevated trafficking of small sized aeroallergens into sub-epithelial space, contributing to asthma exacerbations.


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Conflict of Interest: No.

FIBULIN-1C PEPTIDE INDUCES CELL ATTACHMENT, PROLIFERATION AND ECM DEPOSITION IN LUNG FIBROBLASTS

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Rationale: Fibulin-1 is an extracellular matrix (ECM) protein which mediates cellular processes and tissue remodelling. In our previous study we have shown that the levels of fibulin-1 are elevated in serum and bronchoalveolar lavage fluid from asthmatic patients compared to healthy volunteers. Furthermore, in vitro we found fibulin-1C, one of four fibulin-1 isoforms, promoted proliferation and wound repair in human airway smooth muscle cells.

Aim: To identify the bioactive regions of fibulin-1C which promote lung fibrosis induced by fibroblasts from patients with COPD, pulmonary fibrosis (PF) or neither disease (Non-C/P).

Methods: Fibulin-1C peptides were designed (seven in total) according to the principles described by Angelatti (1). The peptides were coated on tissue culture plates before lung fibroblasts were seeded. The effects of peptides on fibroblast attachment, mitochondrial activity and proliferation, and ECM deposition were measured.

Results: Among the fibulin-1C peptides, peptide 1C1 (FBLN1C1) increased fibroblast attachment in Non-C/P and COPD, proliferation in Non-C/P, and mitochondrial activity in all three groups. In addition, FBLN1C1 enhanced fibulin-1 deposition in COPD and PF fibroblasts, while it augmented fibronectin and perilacin deposition in all three groups of fibroblasts. The peptides FBLN1C2 to FBLN1C7 were inactive.

Conclusion: FBLN1C1 may be important in fibulin-1 induced lung fibrosis. The active peptide identified from this study will provide a useful tool for future studies in recognition of FBLN1C and receptor binding and exploration of cellular signalling pathways of FBLN1C. Further investigation of this molecule may help reveal the role of Fibulin-1 in the pathophysiology of chronic lung diseases.

(1) R Angeletti. Design of Useful Peptide Antigens. 1999 ABRF.

EXTRACELLULAR ANNEXIN A2 MEDIATES INFLAMMATORY AND FIBRO-PROLIFERATIVE RESPONSES IN MODELS OF PULMONARY FIBROSIS

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Introduction: Interstitial lung diseases (ILDs) have in common elements of pulmonary inflammation and fibrosis. Annexin A2 is a participant of such networks by accelerating the conversion of plasminogen into plasmin, and acting as a plasmin-signal transducer. Annexin A2 also has plasmin(oen)-independent effects involving interactions with Factor Xa and the toll-like receptor-4 (TLR-4).

Aim: To investigate the roles of annexin A2 in pulmonary inflammation and fibrosis.

Method: Human parenchymal fibroblasts (PFbs) were incubated with plasminogen (0.5–50 μg/mL), plasmin (0.5–50 μl/mL) or Factor Xa (25 nM). In selected experiments, levels of annexin A2 were reduced by transfection with siRNA. Levels of interleukin-6 (IL-6) mRNA and protein were assessed by PCR (4 h) and ELISA (24 h) respectively, and cell proliferation was assessed by cell enumeration (48 h). Annexin A2 knock-out mice were used in a model of pulmonary fibrosis. The number of inflammatory cells and levels of IL-6 were measured in the bronchial lavage fluid (BALF), and levels of collagen (ie hydroxyproline) were measured in the lung.

Results: Annexin A2 knock-down or antibody-neutralization attenuated plasminogen activation by PFbs, in turn attenuating plasmin-stimulated cytokine production and proliferation. Our evidence suggests that plasmin binds to and cleaves soluble extracellular annexin A2 in the process of plasmin-evoked signalling. We also have evidence of plasmin(oen)-independent roles of annexin A2 in PFb cytokine production and proliferation involving interactions with Factor Xa or TLR-4. In support of a role of annexin A2 in lung pathophysiology, lung inflammation and fibrosis were reduced in annexin A2 knockout mice as compared to wild-type mice after intranasal administration with bleomycin.

Conclusion: Our study provides the necessary way forward to understanding the role of extracellular annexin A2 in lung (patho)physiology with a strategic impact on the development of new therapies for ILDs.