NURSE SPECIALIST CARE FOR BRONCHIECTASIS: A COCHRANE META-ANALYSIS

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Aim: To determine the effectiveness of specialist nurse-led care in the management of bronchiectasis, with respect to improvements in exacerbations, health-care utilization, pulmonary function testing and courses of antibiotics amongst other outcomes.

Method: The Cochrane Airways Group’s specialized register, electronic databases and the bibliographies of identified studies were searched in August 2013. Included studies were randomized controlled trials of adults and children with CT (computed tomography) defined bronchiectasis comparing care delivered by a nurse specialist to other patterns of care delivery including usual care or inpatient hospital care.

Results: From a total of 12 citations one randomized cross-over study met all of the eligibility criteria for inclusion within the review, with a total of 80 participants. Subjects were randomized to two, one-year blocks of either doctor or nurse practitioner-led care in an outpatient setting. The latter involved specialist training of the nurse practitioner prior to study commencement. The nurse practitioner-led intervention included routine tests for participants followed by a consultation for clinical assessment and discussion of a management plan, with changes to treatment and further tests (such as radiographs or blood tests) as appropriate. The medical care (doctor) comparison arm consisted of care delivery by two consultants and one registrar with two to three years of experience in respiratory medicine. The comparison between nurse-led care and doctor-led care did not yield any statistically or clinically significant changes for any outcomes including number and extent of exacerbations, with CT (computed tomography) defined bronchiectasis comparing care delivered by a nurse specialist to other patterns of care delivery including usual care or inpatient hospital care.

Conclusion: This review highlights the paucity of data with only one study identified. As such, reliable conclusions for treatment efficacy cannot be drawn from this review. Additional studies are required to determine whether nurse specialist-led care provides the same outcomes in the community or secondary care setting.

Key words: nurse, bronchiectasis, specialist care, meta-analysis, review, nurse-led.

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MANAGEMENT OF BRONCHIECTASIS: A RETROSPECTIVE HOSPITAL AUDIT OF PATIENT CARE COMPARED TO BRITISH THORACIC SOCIETY GUIDELINES

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Aim: To retrospectively evaluate documented clinical care and management of non-CF (non-cystic fibrosis) bronchiectasis in adults compared with the current British Thoracic Society (BTS) guidelines.

Method: A retrospective audit of medical records was performed for patients attending the Queen Elizabeth Hospital between January and December 2011. Subjects were classified with either primary or secondary non-CF bronchiectasis. Hospital case notes were screened and data were extracted into a standardized pilot-tested template, which was supplemented by screening of electronic hospital records and internal respiratory databases.

Results: Forty-eight patients were identified based on DRG (diagnosis related group) code screening. Thirty one per cent had a primary diagnosis of bronchiectasis, gender was comparable between groups. Number and type of microorganism growth in sputum was similar in both groups. Referral to respiratory nurse (6%; 37%), respiratory physician (89%; 73%) and physiotherapy (28%; 37%) were similar between primary and secondary groups respectively. Referral to the multidisciplinary team was comparable between groups.

Conclusion: Results from this audit indicate a low level of adherence to the BTS guideline for the management of bronchiectasis by multidisciplinary teams. BTS guidelines recommending a team approach to management with physiotherapy and respiratory nurse involvement, this seldom occurred in practice. A larger multicentre evaluation is required to improve generalizability of these findings.

Key words: bronchiectasis, audit, BTS, guideline, non-CF, management.

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IS TRANSFORMING GROWTH FACTOR BETA DRIVING AIRWAY EPITHELIAL-MESENCHYMAL TRANSITION IN COPD VIA ITS CLASSIC PATHWAY?

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Aim: We previously reported epithelial-mesenchymal transition (EMT), a process in which epithelial cells change into a mesenchymal phenotype with migratory potential, is active in smokers, especially in those with chronic obstructive pulmonary disease (COPD). These migrating cells can digest their way through the reticular basement membrane (Rbm) into the sub-epithelial lamina propria (LP). One potentially important driver of EMT may be transway through the reticular basement membrane (Rbm) into the sub-epithelial obstructive pulmonary disease (COPD). These migrating cells can digest their way through the reticular basement membrane (Rbm) into the sub-epithelial lamina propria (LP). One potentially important driver of EMT may be transforming growth factor beta (TGFβ). If so, then its ‘classic’ pathway Smad proteins should be elevated. In this study, our aim was to examine the expression of Smad2/3 in COPD airway epithelium, Rbm, and underlying blood vessels.

Method: Endobronchial biopsies (ebb) from current smokers with COPD (COPD-CS; n = 23) and non-smokers with healthy lungs (Normal-NS; n = 14) were immunostained for phosphorylated (p) (activated) Smad2/3. Computer-assisted image analysis was used to measure the percentage of positive staining in the epithelium, and the number of stained cells and vessels in the Rbm and lamina propria for pSmad2/3. The results were compared between the two groups using either a Student t test or Mann-Whitney U test as appropriate.

Results: There was no significant difference in percentage area of the epithelium stained for pSmad2/3 between the COPD-CS and Normal-NS groups (median values 7.87 vs 7.34, respectively; p = 0.9). However, pSmad2/3 stained vessels in the Rbm were increased in the COPD-CS group compared to controls (median values 5.08 vs 2.46, respectively; p < 0.01). Stained vessels deeper in the LP were also increased in the COPD-CS group (mean values 5.40 vs 2.39, respectively; p < 0.02).

Conclusion: These data suggest that TGFβ is not active as a driver of EMT in COPD. However, it may be inducing COPD airway vessel changes. If TGFβ is involved in EMT, it would have to be working through ‘alternative’ pathways.

LOW SELF-EFFICACY IS ASSOCIATED WITH HIGHER LEVELS OF DYSPNOEA AND DEPRESSION IN PATIENTS WITH COPD

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Introduction: Self-efficacy describes an individual’s coping skills and may influence the outcomes of pulmonary rehabilitation, but the relationship between self-efficacy, functional status and health-related quality of life in people with chronic obstructive pulmonary disease (COPD) is unclear.

Aim: To describe the relationship between self-efficacy and measures of functional exercise capacity, symptoms, mood and health-related quality of life in people with COPD.

Method: Participants with COPD undergoing initial assessment at commencement of an 8-week home- or hospital-based pulmonary rehabilitation programme completed the Pulmonary Rehabilitation Adapted Index of Self-Efficacy (PRAISE), with scores ranging from 15 to 60 and higher scores indicating greater self-efficacy. Disease severity was classified according to the Global Initiative for COPD (GOLD) criteria. Exercise capacity was measured using the 6-minute walk distance (6MWD). Other measures included the modified Medical Research Council (mMRC) dyspnoea scale, the Chronic Respiratory Disease Questionnaire (CRDQ) and the Hospital Anxiety and Depression scale (HADS).

Results: One hundred and thirty-three participants (mean age 71[SD]9 years and FEV1 49.5[19.1]% predicted) were included. Mean (SD) PRAISE score was 47(9.2) points, and ranged from 15 to 60. Lower self-efficacy was associated with a greater level of functional dyspnoea according to the mMRC (p = 0.04) but was unrelated to the 6MWD (r = 0.02, p = 0.81), age (r = 0.27, p = 0.43) and gender (p = 0.37). Self-efficacy did not differ according to disease severity based on GOLD criteria (p = 0.18). Worse scores on the PRAISE were associated with significantly greater fatigue and worse mastery on the CRDQ, but correlations were weak (r = 0.25–0.27). Lower self-efficacy correlated fairly with depression (r = −0.395, p < 0.001) but not anxiety (r = −0.16, p = 0.07).

Conclusion: Some people with COPD have low self-efficacy at the commencement of pulmonary rehabilitation, which is associated with greater dyspnoea and fatigue, lower mood and less mastery.

COMORBIDITY IS ASSOCIATED WITH REFERRAL TO PULMONARY REHABILITATION IN PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Aim: Comorbid conditions are common in people with chronic obstructive pulmonary disease (COPD) and may affect their therapeutic management. The aim of this study was to examine the association of comorbidity in people with COPD with referral to a pulmonary rehabilitation (PR) programme.

Method: Cross-sectional data were analysed from an observational study of 88 people admitted to hospital with a primary diagnosis of COPD. Demographic and admission related data were extracted and comorbidity scores (Charlson and Rx-risk-V) calculated.

Results: Total comorbidity scores were not associated with referral to PR; however, individual comorbid conditions were associated with referral. Documentation of anxiety in the medical record was more frequent in those referred to PR (χ2 = 4.20, p = 0.04, odds ratio (OR) = 7.0, 95% CI 0.8–59.0). Patients with Rx-risk-V category of hypertension (according to medication prescription) were more likely to have been referred to PR (χ2 = 6.69, p = 0.01, OR = 6.8 95% CI 1.6–29.1), and those with Rx-risk-V category of arrhythmia less likely (χ2 = 4.22, p = 0.04, OR = 0.28, 95% CI 0.08–0.99). Patients who had been referred to PR had lower FEV1% predicted (p = 0.002) and greater hospital bed days in previous three years (p = 0.051). In multivariate analysis, FEV1% predicted, bed days in last three years, and Rx-risk-V categories of hyperten- sion and arrhythmia accounted for 25% of the variance in referral to PR.

Conclusion: People with COPD and documented anxiety (but not managed pharmacologically for anxiety), pharmacologically managed hypertension, or with more severe disease and greater hospital bed days were more likely to have been referred to PR in this cohort.

Key words: COPD, comorbidity, pulmonary rehabilitation, referral.

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Conflict of Interest: None.
INTERVENTIONS TO IMPROVE PHYSICAL ACTIVITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)—A SYSTEMATIC REVIEW

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Aim: To determine the efficacy of interventions aimed at improving physical activity (PA) of people with chronic obstructive pulmonary disease (COPD).

Methods: The Cochrane Central Register of Controlled Trials, Physiotherapy Evidence Databases (PEDro), EMBASE, MEDLINE and CINAHL were searched using the keywords COPD, ‘intervention’, and ‘physical activity’. All randomized controlled trials (RCTs) aimed at increasing PA of individuals with COPD were included, regardless of the nature of the intervention. The PEDro scale was used to rate study quality. Standardized mean differences (effect sizes) with 95% confidence intervals were determined.

Results: Fifteen RCTs were included (n = 1167 individuals). Mean PEDro score was 5.8 (SD 1.4). Interventions included exercise training, nutritional supplements, activity counselling, self-management and combinations of these elements. PA levels were measured objectively using tri-axial accelerometers and pedometers or subjective questionnaires. The six studies which compared an intervention with usual care all tended to show positive effects on PA levels (effect sizes: 0.17 to 1.05), however most effects were not statistically significant. In contrast, addition of an intervention to improve PA to an exercise training programme showed no additional benefits on PA levels when compared to exercise training alone (effect sizes ranged from −0.03 to 0.2; five studies). Overall, effect sizes were larger for exercise-based interventions compared to other interventions.

Conclusion: Exercise training, nutritional supplements and activity counselling may improve PA in people with COPD compared to usual care, however existing trials have been underpowered and there are few statistically significant effects. Non-exercise related interventions do not appear to improve PA more than exercise training alone. Larger trials are needed to establish the clinical benefits of interventions designed to improve PA levels in people with COPD.

Key words: COPD, physical activity, interventions.

STANDARD CLINICAL MEASURES USED IN A PRE-PULMONARY REHABILITATION ASSESSMENT FAIL TO PREDICT LEVELS OF PHYSICAL ACTIVITY IN COPD

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Introduction: Inactivity and low physical activity levels (PAL) are associated with greater mortality and disease burden in patients with chronic obstructive pulmonary disease (COPD). In order to address this increase in disease burden it would be beneficial to be able to predict levels of PAL in individuals upon entry to pulmonary rehabilitation (PR).

Aim: The aim of this study was to determine if standard clinical measures for COPD patients entering PR could predict levels of physical activity.

Method: Participants with COPD from a single-centre PR programme were recruited and all measures were collected in the first week of the programme. PAL was measured with the Sensewear Pro 3 armband using a standardized protocol. PAL was expressed as the mean daily energy expenditure divided by the sleeping energy expenditure. Standard clinical measures included age, lung function (forced expiratory volume in 1 second % predicted—FEV1% pred), body mass index (BMI), 6 minute walk distance (6MWD), quadriceps strength, modified Medical Research Council (MRC) dyspnoea score and quality of life as measured by Chronic Respiratory disease Questionnaire (CRQ).

Results: 82 participants (male = 52) with a mean (SD) age 67(8) years, FEV1% pred 52%(22%), BMI 27(5), 6MWD 418 m (118), MMRC 44 ± 2 were studied. PAL was 1.50(0.19) METS. Using a multivariate linear regression model, we found that BMI (p = 0.03) and baseline MMRC (p = 0.02) were the only independent predictors of baseline levels of physical activity (r² = 0.12, adjusted r² = 0.10).

Conclusion: In our population of COPD patients pre-PR, standard clinical measures do not strongly determine levels of physical activity. This gives weight to the argument that physical activity should be measured in its own right as part of a PR assessment.

TUMOUR NECROSIS FACTOR RELATED APOTOPSIS INDUCING LIGAND (TRAIL) REGULATION OF PROTEIN PHOSPHATASE (PP)2A IS CRUCIAL FOR THE DEVELOPMENT OF BLEOMYCIN INDUCED PULMONARY FIBROSIS IN MICE

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Introduction: Regulation of protein phosphatase (PP)2A by tumour necrosis factor apoptosis inducing ligand (TRAIL) is crucial for the development of acute and chronic allergic airways disease models in mice (Collison, Hatchwell et al., Nat Med 2013).

Aim: To determine the role of TRAIL dependent PP2A deactivation in the development of bleomycin induced pulmonary fibrosis.

Method: Wild type and TRAIL−/− BALB/c mice were treated intratracheally with bleomycin. Experimental groups of WT mice also received either a single or daily administration of AALw, a FTY720 analogue capable of synthetically reactivating PP2A activity or vehicle control. Mice were sacrificed 21 days post bleomycin administration for lung measurements using a Buxco forced manoeuvres apparatus with lung sections collected for histological examination, qPCR and protein quantification by ELISA.

Results: Mice challenged with bleomycin had significantly reduced PP2A activity which was reversed by daily AALw treatment or TRAIL deficiency. Increased PP2A activity correlated with improved lung function as determined by FVC and was inversely proportional to peripheral bronchial fibrosis as determined by quantitative analysis of Masson’s Trichrome stained lung sections.

Conclusion: TRAIL-dependent PP2A deactivation plays a fundamental role in the development of bleomycin induced pulmonary fibrosis in this model.

A RANDOMIZED CONTROLLED TRIAL OF TELEPHONE HEALTH-MENTORING INCLUDING HOME-BASED WALKING (TELE-REHAB) BEFORE GROUP REHABILITATION VERSUS USUAL CARE AND SUBSEQUENT GROUP REHABILITATION (GROUP-REHAB)

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Introduction: There is a need to widen delivery of rehabilitation using models that foster integration of exercise into daily life. This is especially of the us usually wasted period between referral and formal pulmonary rehabilitation (PR).

Aim: To compare the effect of Tele-Rehab including home-based walking plus Group-Rehab versus Group-Rehab (self-management education and exercise plus a walking diary) alone on physical capacity and self-reported walking and to ascertain additional benefits of Tele-Rehab or walking diaries.

Methods: Adults with COPD referred for PR were recruited and randomized to 8–12 weeks of Tele-Rehab plus Group-Rehab (Intervention) or Group-Rehab (Control). In the intervention, community nurses, trained in self-management support, facilitated home-walking via telephone before hospital-based PR. Data were collected at baseline (Time-point One, TP1), after Tele-Rehab/usual care and before Group-Rehab (TP2) and post 8 weeks Group-Rehab (TP3). Participants logged home-walking action plan diaries. Outcomes were 6 minute walk test distance (6MWD) and self-reported physical activity (days per week; daily minutes walked) and walking score. Analysis was by intention-to-treat, using Mann Whitney U or t-tests.

Results: Of 65 recruits (35 intervention, 30 control), 25 withdrew (19 pre-Group-Rehab, 4 attended self-management education (23 Intervention, 17 Control), 17 (9 intervention, 8 control) attended supervised exercise. There was no significant effect of Tele-Rehab (TP1-TP2) on the intervention group. There were no significant differences between groups in the change in 6MWD or walking score (TP1-TP3). During Group-Rehab both groups walked 4 ± 2 days/week for similar daily periods (Intervention: 17 minutes ± 7; Controls: 14 minutes ± 7).

Conclusion: This small study found no benefit to Tele-Rehab before formal PR on daily physical activity or exercise capacity. Walking plans and diaries used during Group-Rehab added little improvement to 6MWD or walking scores. The challenge is encouraging people with COPD to choose to attend supervised exercise and integrate exercise into daily life.
PHYSICAL FUNCTION MEASURED WITH THE GROCERY SHELVING TASK (GST) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Introduction: The GST was developed to measure physical performance, including upper limb function, in patients with COPD. It involves components of sit-to-stand, bending over, lifting objects from the floor and reaching overhead. It has previously been validated by comparison with tests of unsupported upper limb work.

Aim: To describe the relationship between GST performance and other subjective and objective measures of functional activity, symptoms and quality of life in patients with COPD.

Method: Participants completed the GST along with measures of functional exercise capacity (6-minute walk distance, 6MWD), functional dyspnoea (modified Medical Research Council dyspnoea scale, mMRC), disease impact (COPD Assessment Test, CAT), quality of life (SF-36 and Chronic Respiratory Disease Questionnaire, CRDQ), and mood (Hospital Anxiety and Depression scale, HADS) at commencement of an 8-week home- or hospital-based pulmonary rehabilitation programme. Test outcomes were compared using Spearman’s rho and stepwise linear regression analysis was performed to determine independent contributors to GST performance.

Results: Seventy-four participants with COPD (mean FEV1% predicted 56.3 ± 21.3) were assessed of whom six were unable to perform the test, due predominantly to musculoskeletal problems. Mean (SD) time for GST performance was 37.86 (11.54) seconds. The significant correlates of GST time were 6MWD (r = −0.548), mMRC (r = 0.384), CAT (r = 0.362) and the physical component score of the SF-36 (r = −0.393). The GST did not correlate with measures of lung function or anthropometry, CRDQ, HADS or other component scores of the SF-36. The only independent predictor of GST time was mMRC.

Conclusion: GST performance is consistently associated with measures of function, supporting the conceptualization of the GST as a measure of functional activity in COPD.

THE INVOLVEMENT OF HISTONE ACETYLATION ENZYMES IN A MOUSE MODEL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, affecting around 25–30% of all cigarette smokers, with disease numbers likely to increase due to increased use of tobacco products. High doses of steroids are widely used to suppress symptoms (ineffectively), but there are no treatments that halt the progression of disease. Epigenetic changes through aberrant acetylation of cellular factors have been implicated in COPD pathogenesis. Histone acetyltransferases (HATs) acetylate lysine residues are associated with gene activation and inflammation. They are counteracted by histone deacetylases (HDACs), which have been implicated in COPD pathogenesis. Histone acetyltransferases (HATs) acetylate lysine residues are associated with gene activation and inflammation. They are counteracted by histone deacetylases (HDACs), which have been implicated in COPD pathogenesis. Histone acetyltransferases (HATs) acetylate lysine residues are associated with gene activation and inflammation. They are counteracted by histone deacetylases (HDACs), which have been implicated in COPD pathogenesis. Histone acetyltransferases (HATs) acetylate lysine residues are associated with gene activation and inflammation. They are counteracted by histone deacetylases (HDACs), which have been implicated in COPD pathogenesis. Histone acetyltransferases (HATs) acetylate lysine residues are associated with gene activation and inflammation. They are counteracted by histone deacetylases (HDACs), which have been implicated in COPD pathogenesis. Histone acetyltransferases (HATs) acetylate lysine residues are associated with gene activation and inflammation. They are counteracted by histone deacetylases (HDACs), which have been implicated in COPD pathogenesis.

Aim: To investigate the roles of HDACs and HATs in COPD pathogenesis. The elucidation of their roles and their therapeutic modulation may identify effective ways to treat COPD.

Method: Our lack of understanding of COPD pathogenesis and consequently the development of therapies has been severely hampered by the lack of an appropriate animal model that recapitulates aspects of human disease in a reasonable time frame. We have generated a novel mouse model of COPD that displays airway inflammation, mucus hypersecretion, emphysema-like tissue destruction, and altered lung function in just 8 weeks. Using this model we will analyse the aberrant changes in acetylation that occur due to disease development and progression.

Results/Conclusion: In pioneering studies we demonstrate that in experimental COPD, HATs are selectively increased, with a corresponding decrease in some HDACs, mimicking human disease. These specific changes in enzymes involved in acetylation may reflect potential targets to treat COPD or improve the effectiveness of symptom treatments.
AIRWAY EPITHELIAL PLATELET ACTIVATING FACTOR RECEPTOR EXPRESSION IS UPREGULATED IN COPD

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Introduction and Aim: We recently published that Platelet Activating Factor receptor (PAFr) is upregulated on the epithelium of the proximal airways of current smokers and also in bronchial epithelial cells exposed to cigarette smoke extract. These treated cells also showed upregulation of Streptococcus pneumoniae adhesion. Bacterial wall phosphorylcholine specifically binds to PAFr expressed on airway epithelium, so facilitating adherence and tissue invasion, which may be relevant to COPD. Moreover, the use of inhaled corticosteroids (ICS) in COPD patients is associated with an increased risk of invasive respiratory pneumococcal infections. In this study we have investigated whether PAFr expression is especially upregulated in airway epithelium in COPD patients and whether this expression may be modulated by ICS therapy.

Methods: Cross-sectionally we evaluated PAFr expression in bronchial biopsies from 15 COPD patients who were current smokers (COPD-CS), 12 COPD ex-smokers (COPD-ES), compared to biopsies from 16 smokers with normal lung function (NLFS). We also used material from a previous double-blind, randomized, placebo-controlled 6 months ICS intervention study in COPD patients to explore the effect of ICS on PAFr expression. We employed computer-aided image analysis to quantify the percentage of epithelium stained for PAFr.

Results: Markedly enhanced expression of PAFr was found in both COPD-CS (p < 0.005) and COPD-ES (p < 0.002) compared to NLFS. There was little evidence that PAFr expression was affected by ICS therapy over 6 months.

Conclusion: Epithelial PAFr expression is upregulated in smokers but especially in COPD, but not obviously affected by ICS therapy.

Key words: airway epithelium, inhaled corticosteroids, platelet activating factor receptor, pneumococcal infections.

NEUTRALIZING GM-CSF SUPPRESSES LUNG INFLAMMATION IN AN EXPERIMENTAL MODEL OF COPD EXACERBATIONS

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Introduction: Exacerbations of COPD account for significant morbidity and mortality and are a major economic burden to society. Influenza virus infections are a common cause of COPD exacerbations. Current anti-inflammatory agents (i.e. corticosteroids) are often not very effective at preventing and/or treating infection-induced COPD, highlighting the need for new therapeutic strategies. We have previously shown that neutralizing GM-CSF in vivo reduces LPS- and cigarette smoke (CS)-induced lung inflammation.

Aim: To investigate the role of GM-CSF in an animal model of COPD exacerbations induced by influenza A virus.

Methods: Male Balb/C mice were exposed to CS generated from 9 cigarettes per day for 4 days. On day 5, mice were infected with influenza (flu A (Mem71, H3N1, 1 x 10^6.5 PFU). Mice were treated with 22E9 (anti-GM-CSF mAb) and isotype control antibody (100 μg/mouse, i.n.) 3 h before infection. BALF inflammation, viral titre, and whole lung cytokine, chemokine and protein expression were measured 3 and 5 days post infection. Body weight and food intake were measured daily.

Results: Compared to mice treated with flu alone, CS + flu mice had significantly more BALF total cells, macrophages, neutrophils and lymphocytes (n = 8, P < 0.05). Gene expression analysis revealed that CS + flu mice had increased levels of pro-inflammatory cytokines (TNF-α), and proteases (MMP-12), compared to flu alone mice. Treatment with 22E9 significantly reduced the enhanced BALF inflammation observed in CS + flu mice (n = 8, P < 0.05), and pro-inflammatory cytokine and protease expression. However, 22E9 was without effect on weight loss or viral clearance in CS + flu-treated mice (n = 8, P > 0.05).

Conclusion: The ability of 22E9 to markedly suppress lung inflammation in this animal model of cigarette smoke and influenza A (H3N1) infection raises the possibility that it may prove useful as a therapeutic strategy to treat and prevent exacerbations of COPD.

THERAPEUTIC MODULATION OF THE SPHINGOSINE SIGNALLING SYSTEM WITH THYMOQUINONE AS A NOVEL MACROPHAGE-TARGETED TREATMENT FOR COPD

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Background: Alveolar macrophages (AM) from subjects with COPD are defective in their ability to phagocytose apoptotic cells, associated with secondary necrosis of the uncleared material and airway inflammation. The exact mechanism for this defect is unknown. We previously identified a role for Sphingosine 1 phosphate (S1P), the product of sphingosine kinases (SPHKs), in actin cytoskeletal dynamics required for macrophage phagocytic function. We therefore hypothesized that the SPHK/S1P signalling system could play a role in the defective macrophage phagocytic function in COPD, and that a novel antioxidant, thymoquinone (TQ) could improve phagocytic function via modulation of the SPHK/S1P pathway.

Methods: SPHK/S1P system genes (SPHK 1/2, S1P receptors (S1PR1) 1–5, S1P phosphatases and S1P-lyase) were measured using Real-Time PCR in BAL-derived AM from COPD patients and controls. As cigarette smoke is a major cause of COPD, the effects of cigarette smoke extract (CSE) on SPHK/S1P-associated genes were assessed in THP-1 macrophages. We then investigated the effects of TQ ± CSE on macrophage function and SPHK/S1P-associated genes.

Results: S1PR5 and SPHK1 mRNA were significantly increased in AM from COPD patients. CSE significantly decreased phagocytosis and increased the expression of SPHK1 and S1PR5 on THP-1 macrophages, confirming the results in human AM and suggesting an effect of cigarette smoke on these mediators. TQ significantly improved phagocytosis (C: 23.16 ± 1.906; TQ: 32.20 ± 2.244 (mean ± SEM)) and reduced the gene expression of SPHK1 and S1PR5 (C: 15.76 ± 0.6524, CSE: 18.88 ± 0.216, CSE + TQ: 17.55 ± 0.4452, and C: 5.700 ± 0.3679, CSE: 8.1180 ± 0.3784, CSE + TQ: 6.128 ± 0.4305 (mean ± SEM), respectively).

Conclusions: Our results suggest a potential link between the SPHK/S1P signalling system and defective AM phagocytic function in COPD. We identify TQ as a novel adjunct macrophage-targeted therapy for COPD, with the potential to attenuate the damage by smoking in those without COPD.
MECHANISMS OF IMPAIRED IMMUNE RESPONSES IN ACUTE EXACERBATIONS OF COPD

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Chronic Obstructive Pulmonary Disease (COPD) is the most common respiratory cause of morbidity and mortality worldwide. Notably, acute exacerbations of COPD (AECOPD) are associated with a progressive decline in lung function. AECOPD is usually associated with pulmonary infections but little is known about the mechanisms causing increased susceptibility in AECOPD. Current vaccine and antibiotic trials have not prevented AECOPD; so a better understanding of the susceptibility to these events is important.

We hypothesize that chronic inflammation induces excess anti-inflammatory signals, which compromise protective T-cell responses against infection in AECOPD. Our aim was to investigate whether the expression of T-cell inhibitory molecules during AECOPD would inhibit the anti-infective immune responses thereby demonstrating a mechanism for increased infection during AECOPD.

Peripheral blood mononuclear cells (PBMC) were isolated from blood samples of AECOPD patients, stable COPD patients and healthy controls. Production of IFNγ, TNFα, IL-6 and IL-17 by PBMC was measured by ELISA post-stimulation with staphylococcus enterotoxin-B (SEB). Expression of T-cell inhibitory molecules (CTLA-4, PD-1 and CD39) was measured by flow cytometry. Plasma levels of inflammatory biomarkers were measured by ELISA.

AECOPD patients exhibited higher plasma levels of CRP and IL-6 than stable COPD patients (p = 0.018 and p = 0.087 respectively) or healthy controls (p < 0.001 for both). PBMC from AECOPD patients have lower production of IFNγ, TNFα, IL-6 and IL-17 compared to stable COPD patients and healthy controls (p = 0.001–0.072), but increased expression of PD-1 on CD4+ T-cells (p = 0.046 and p = 0.004, respectively) and CD39 on CD8+ T-cells (p = 0.008 and p = 0.016 respectively). Cytokine production was inversely related to plasma levels of CRP and IL-6 and expression of PD-1 and CD39. Blocking of CTLA-4 increased SEB-induced IFNγ and TNFα by PBMC from COPD patients.

Together, these data could account for the increased frequencies of infections in COPD patients. Blocking anti-inflammatory signals could improve anti-bacterial responses to prevent AECOPD.

MICROBIAL GROWTH DOES NOT INFLUENCE THE PHAGOCYTIC DEFECT IN ALVEOLAR MACROPHAGES IN COPD

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Background: It has been well documented that bacterial colonization of the lower airway is associated with chronic airway inflammation in stable COPD. We hypothesized that microbial growth would contribute to the defective ability of alveolar macrophages to phagocytose apoptotic cells (effrocytosis) that we have reported in COPD.

Methods: BAL was collected from 31 non-COPD controls (13 with microbial isolate from BAL) and 41 COPD patients (15 with microbial isolate). We investigated the influence of the presence of microbial growth on ability of alveolar macrophages (AM) to phagocytose apoptotic cells (effrocytosis), levels of mannose binding lectin (MBL) and inflammatory cytokines in BAL, and AM expression of effrocytosis receptor CD31 and antigen presentation molecules HLA-DR and HLA-ABC using flow cytometry, ELISA and cytometric bead array (CBA). Flow cytometry was used to determine changes in the proportion of macrophages, lymphocytes and neutrophils in the BAL and total white cell counts.

Results: As previously reported, effrocytosis, MBL, CD31, HLA-DR and HLA-ABC were significantly reduced in COPD vs controls. The presence of microbial growth had no significant effect on effrocytosis, MBL, CD31, HLA-DR and HLA-ABC (e.g., effrocytosis: control not infected 20.39% ± 1.825% vs control infected 17.49 ± 2.031%, ns; COPD not infected 12.49 ± 0.944% vs COPD infected 11.80 ± 1.192%, ns). CBA revealed that there was an increase in levels of TNF in the BAL of COPD patients; however, many TNF levels were below the lower limits of detection. In controls with microbial isolates, there was a significant increase in the percentage of neutrophils (3.71 ± 0.82% vs 17.64 ± 7.23%, p = 0.0132). However, there was no significant difference in the percentage of neutrophils in COPD patients with and without microbial isolates.

Conclusions: Although microbial colonization is associated with airway inflammation, it does not influence the AM effrocytosis defect or expression of antigen presentation molecules in COPD. The effect on phagocytosis of bacteria remains to be assessed.

BREATHEING IN CHRONIC HEART FAILURE: THE ROLE OF THE ALVEOLAR MACROPHAGE

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Introduction: Dyspnoea and exercise intolerance are cardinal manifestations of chronic heart failure (CHF), and the major cause of morbidity. Using a rat myocardial infarction model of CHF we have found fibrotic reinforcement of the extracellular matrix which results in tissue stiffening and an increase in alveolar type II cells and surfactant which provides homeostatic compensation that normalizes lung mechanics. Emerging evidence suggests that this pulmonary remodelling may be regulated by two distinct phenotypes of pulmonary macrophages.

Aim: To examine whether pulmonary remodelling in CHF is due to an increase in monocyte chemotactic protein (MCP)-1 recruited interstitially derived M2 macrophages (CD11b+2) and a relative deficit in granulocyte-macrophage colony stimulating factor (GM-CSF) regulated resident M1 alveolar macrophages (CD11b-).

Method: In this project, we utilized parallel rat and human studies to examine bronchoalveolar lavage (BAL) MCP-1 and GM-CSF macrophage activation and infiltration in the lung in CHF. Specifically, the left coronary artery ligation rat model of infarct-induced CHF was utilized, as previously, while clinical samples were derived from coronary artery bypass surgical patients (BAL) and CHF clinic attendees, Flinders Medical Centre, Adelaide.

Results: At 6 weeks following infarction in the rat we found a 4.5-fold increase in BAL MCP-1 (p = 0.001), corresponding to a 3-fold increase in recruited macrophages (p = 0.05) with no detectable GM-CSF. Data from CHF patients similarly demonstrated a 4-fold increase in BAL MCP-1 (p = 0.03) and no difference in GM-CSF (p = 0.6). In addition, we found a 3-fold increase in circulating, predominantly CD11b+ monocytes in CHF patients when compared with non-CHF patients which correlated with disease severity (p < 0.001).

Conclusion: These parallel rat and human studies demonstrate a similar increase in the M2 macrophage mediator MCP-1 suggestive of a M2 dominant alveolar macrophage prevalence in the lung in CHF.
**Induction of Epithelial to Mesenchymal Transition in a Bronchial Epithelial Cell Line**

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**Introduction:** Recent evidence suggests that epithelial to mesenchymal transition (EMT) is likely to be involved in the airway remodelling seen in COPD patients, and since EMT is also a common feature of metastatic cancer, understanding this process may additionally give further insight into the link between COPD and lung cancer. Numerous cell culture models of EMT have been described, usually involving its induction with TGFβ. The stable bronchial epithelial cell line Beas-2B is often used in such in vitro studies in asthma and COPD research; however, it is not known how closely this model mimics the EMT process in clinical COPD.

**Aim:** To induce EMT in Beas-2B cells and assess their suitability as a model of COPD, in comparison with our airway biopsy work.

**Methods:** Beas-2B cells were treated with TGFβ, cigarette smoke extract (CSE) or nicotine. Expression of EMT markers E-cadherin, N-cadherin, ZO1, Vimentin and S100A4 was assessed by qPCR and immunocytochemistry.

**Results:** TGFβ-treated cells showed induction of EMT with decreased expression of epithelial markers, E-cadherin and ZO1, and increased expression of mesenchymal markers, N-cadherin and Vimentin. However expression of the mesenchymal marker S100A4 was decreased. Both cigarette smoke extract and nicotine are able to induce changes in some of the EMT markers, with ZO1 expression being particularly affected.

**Conclusions:** These results support the idea that Beas-2B cells are able to undergo TGFβ-induced EMT. However, expression of S100A4 is down-regulated whereas it is up-regulated in the bronchial epithelium of both smokers and COPD patients. This suggests TGFβ signalling may not be involved in airway EMT in vivo, or that this cell line is not a good model.

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**The Transport of Salbutamol Sulfate through Calu-3 and Differentiated Human Bronchial Epithelial Cell**

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**Introduction:** Salbutamol is a short acting β2-adrenergic agonist commonly used to treat airway diseases.

**Aim:** The aim of this study is to investigate the transport of salbutamol sulfate through the differentiated primary human bronchial epithelial cells and Calu-3 cell line (HTB-55).

**Method:** Human primary bronchial epithelial and Calu-3 cells were cultured at an air-liquid interface for at least 21 days and 11 days respectively. Salbutamol sulfate (SS) in dry powder form was deposited on the cell layers using a twin stage impinger (TSI) at the flow rate of 60 L/min for 4 seconds. The transport of the SS was studied over 4 hours. Drug penetration across cell layers was assessed by high performance liquid chromatography (HPLC).

**Results:** The percentage of transported SS through differentiated primary human bronchial epithelial cells (n = 4) at 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180, 210 and 240 mins had a positive relationship with the amount of SS dry powder deposited on the cell layers (p < 0.05). However, this relationship was not apparent with Calu-3 cells (p > 0.05, n = 4).

**Conclusion:** To study the transport of salbutamol sulfate dry powder after deposition on the epithelial cells, differentiated primary human bronchial epithelial cells would be more representative of in vivo physiological transport rate of SS than Calu-3. Furthermore, the data could suggest that the dose of SS taken by the patients and deposited in the airways correlates with the transport of SS through the airway epithelium, which in turn would affect the concentration of the drug at airway smooth muscle level.

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**Diesel Emission Composition Mediates Cellular Responses of Primary Human Bronchial Epithelial Cells at an Air-Liquid Interface in Vitro**

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**Introduction:** In vitro studies using primary cell lines under physiological conditions may improve the current understanding of adverse health effects associated with air pollution.

**Aim:** The aim of this study was to investigate the cellular responses of primary human bronchial epithelial cells (HBECs) to neat and modified diesel emissions at an air-liquid interface (ALI).

**Method:** Primary HBECs, established at the UQ Thoracic Research Centre, were cultured and differentiated at ALI for 28 days. The functional characteristics of the cell layer were determined with a series of stains assessing cilia growth and mucus production. Primary HBECs were exposed to diesel emissions generated at the International Laboratory for Air Quality and Health. HBE responses to diesel emissions were measured as cell viability and cytokine secretion (IL-8 and IL-6).

**Results:** The HBECs demonstrated a mucociliary phenotype after 28 days of differentiation at ALI. Neat diesel emissions caused a reduction in cell viability and increase in cytokine secretion. This was attenuated by the removal of the organic content from particles. Results are summarized in the table below. N = 3, ±SEM, *indicates a significant difference (P < 0.05).

| Cell Line | Challenge | Viable Cells (%) | IL-6 Secretion (pg/mL) | IL-8 Secretion (pg/mL) |
|-----------|-----------|------------------|------------------------|------------------------|
| HB1103 No challenge | 100 ± 0 | 1357 ± 81 | 23474 ± 1878 |
| Neat diesel | 41 ± 4.4* | 1798 ± 113 | 33022 ± 1955 |
| Gas phase | 63 ± 4.2* | 3377 ± 533* | 24077 ± 943 |
| Diesel with no organics | 96 ± 1.8 | 1618 ± 372 | 19465 ± 1183 |

**Conclusion:** Primary HBE responses to diesel emissions are sensitive to composition and organic content may be a strong mediator of the adverse health effects associated with diesel emission exposure.
**Methods:**

Cyclic adenosine monophosphate (cAMP), ultimately leading to muscle relaxation.

**Conclusion:**

Increased epithelial cell apoptosis and fibroblast proliferation are thought to be central processes. The BRCA1-associated protein BARD1 has tumour suppressor functions with BRCA1 and act as an inducer of p53-dependent apoptosis. In breast, ovarian and lung cancers, differentially spliced BARD1 isoforms lacking tumour suppressor activity are upregulated and have pro-proliferative functions. We wanted to elucidate the role of BARD1 and its isoforms in lung fibrosis initiation and progression.

**Methods:**

We have previously shown that BARD1 expression is induced by hypoxia and in response to TGF-β. As hypoxia and TGF-β are key factors driving lung fibrosis, we investigated BARD1 expression profiles in tissues from patients with pulmonary fibrosis and in a bleomycin model of lung fibrosis. We established a potential pathway from TGF-β signalling to epithelial cells and fibroblasts in *in vitro* cultures.

**Results:**

While in healthy lung tissue BARD1 expression is low, it was markedly increased in areas of active fibrosis in humans and in bleomycin-induced fibrosis in the mouse. Furthermore, BARD1 immunostaining co-localized with apoptosis markers. Protein and RNA expression data, suggested that with progression of fibrosis, alternatively spliced isoforms of BARD1 were expressed in fibrotic tissues, and expression of full length (FL) BARD1 was lost. Importantly, mice expressing a BARD1 transgene reacted stronger and developed more fibrosis after belomycin treatment. In vitro studies, using epithelial cells and fibroblasts, confirmed the distinct changes in BARD1 expression patterns in response to TGF-β signalling.

**Conclusions:**

Our data demonstrate that BARD1 is involved in the pathogenesis and progression of pulmonary fibrosis and the switch from FL BARD1 to BARD1 isoform expression might provide one possible pathway for the TGF-β signalling towards apoptosis of epithelial cells and proliferation of fibroblasts.

**Conflict of Interest:**

None.

**Support by:**

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**THE EFFECT OF FATTY ACIDS ON β2-AGONIST RESPONSE IN HUMAN AIRWAY SMOOTH MUSCLE CELLS**

**Aim:** To investigate the effect of different fatty acids on β2-agonist-induced cAMP in human ASM.

**Methods:** ASM were isolated from lung tissue obtained with written informed consent. ASM were treated with either the saturated fatty acid (SFA), palmitic acid (PA); the omega-6 polyunsaturated fatty acids (n-6 PUFA), arachidonic acid (AA) and linoleic acid (LA); or the omega-3 (n-3) PUFA, docosahexaenoic acids (DHA) and eicosapentaenoic acid (EPA). These fatty acids were tested at 30, 60 or 100 μM in cell medium (final [ethanol] 0.1%). ASM were subsequently stimulated with the β2-agonist salbutamol sulphate for 10 minutes. Cell lysates were then collected and levels of cAMP were measured by ELISA.

**Results:** Pre-incubating the ASM in 100 μM AA, LA, DHA and EPA all caused a decrease in salbutamol sulphate induced cAMP compared to those pre-incubated at 30 and 60 μM (n = 5, p < 0.05). PA had no effect on salbutamol cAMP production at all concentrations tested (n = 5).

**Conclusion:** This study has shown that long chain fatty acids of both the n-3 and n-6 PUFA class caused decreased cAMP production in response to salbutamol sulphate. This may explain the clinical observation of a decreased response to β2-agonists following a high fat meal.

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A RETROSPECTIVE AUDIT OF A SPECIALIST REFERRAL CLINIC FOR SUSPECTED OR PROVEN THORACIC MALIGNANCIES

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Background: St Vincent’s Hospital Melbourne offers a specialist referral clinic for patients with suspected or proven thoracic malignancy, providing a multidisciplinary diagnostic and management approach. This service is a major tertiary referral centre for regional and metropolitan patients in Victoria. A number of patients referred to the service are found not to have malignant disease. The spectrum of benign diagnoses and tumour characteristics of those patients with malignant diagnoses has not been examined previously.

Aim: To evaluate the demographics, final diagnoses (both benign and malignant), tumour characteristics and investigations performed on patients referred to this specialist service for suspected or proven thoracic malignancy.

Method: A retrospective audit of the St Vincent’s Hospital Combined Lung Clinic database was conducted from January 2009 to January 2013 inclusive. All referrals obtained were reviewed from the initial workup to diagnosis.

Results: There were 1236 referrals to the Combined Lung Clinic of which 813 were primary lung cancers, 56 mesotheliomas, 138 metastatic thoracic lesions, 4 malignant lesions with an unidentified primary site and 225 benign lesions. The benign lesions included a wide spectrum of pathology and were diagnosed using combination of modalities including surgical intervention, interventional radiology, bronchial endoscopy and surveillance imaging.

Conclusion: A multidisciplinary clinic for the investigation and management of known or suspected thoracic malignancy requires access to a wide range of diagnostic tools and specialty services as well as knowledge of the management of a wide range of benign conditions and malignant disease other than primary lung cancer. Diagnostic and management decisions are complex and require the involvement of multiple specialties. While a thoracic surgical service is an important component of this clinic, there are many patients who have advanced primary lung cancer, benign disease or a secondary malignancy who benefit from the involvement of other specialist services.
RELATIONSHIP OF PLEURAL FLUID PH AND GLUCOSE: A MULTI-CENTRE STUDY OF 2971 CASES

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Introduction: Pleural fluid pH and glucose reflect the metabolic activity in the pleura and can aid diagnosis and clinical management of pleural effusions. International guidelines recommend the use of either/both tests in the workup of undiagnosed effusions. The relationship, if any, between pleural pH and glucose, and the need to perform both tests has not been defined.

Aim: To investigate the relationship between pleural fluid pH and glucose in unselected pleural effusions of different causes.

Methods: Paired pleural fluid pH (measured by blood gas analyser) and glucose were determined from unselected samples prospectively collected from three specialist pleural centres in Spain, UK and Western Australia. Causes of the effusion were further subdivided into malignant, infection (parapneumonic effusion or empyema), TB or benign (encompassing all other benign aetiologies).

Results: 2971 samples were analysed (35.17% malignant, 18.04% infection, 8.38% TB and 38.04% from other benign causes). The mean age was 65.6 years and sex:male:female ratio 3:2. The median pH was 7.43 and glucose was 5.99 mmol/L. Pleural fluid pH and glucose were concordant (ie both above or below the commonly used clinical cut-offs of pH 7.2 and glucose = 3.3 mmol/L) in 92% of the entire cohort. The degrees of concordance were relatively consistent in diagnostic subgroups: malignant 90%, infection 86%, TB 81% and benign 98%. However, the predictive curves of pH against glucose was highly variable with large prediction errors (using the overall cohort, or as diagnostic subgroups) in regression analyses.

Conclusions: Pleural fluid pH and glucose were concordant if analysed as dichotomous variables. In such clinical scenarios (eg determination of pleural infection and chest drain insertion), performing either test appears adequate. However, the magnitude of change in each variable cannot be accurately predicted from the other. Further analyses on the factor causing the discordance are underway.

Grant Support: Prof Lee is a NHMRC Career Development Fellow and receives project grant support from NHMRC, West Care, NSW Dust Disease Board, Cancer Council WA and Sir Charles Gairdner Research Advisory Council.

EXERCISE TRAINING FOR PEOPLE FOLLOWING LUNG RESECTION FOR NON- SMALL CELL LUNG CANCER (NSCLC)—A COCHRANE SYSTEMATIC REVIEW

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Aim: To determine the effects of exercise training on exercise capacity, health-related quality of life (HRQoL) and lung function (forced expiratory volume in one second [FEV1]) in people who have had a recent lung resection for NSCLC.

Method: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, SciELO and PEDRO up to February 2013. Randomized controlled trials (RCTs) in which study participants with NSCLC, who had undergone lung resection, were allocated to receive either exercise training or no exercise training were included. Two review authors screened and identified the studies for inclusion. Meta-analyses were performed using post-intervention data for studies in which no differences were reported between the exercise and control group either (i) prior to lung resection or (ii) following lung resection, but prior to the commencement of any exercise training.

Results: Three RCTs involving 178 participants were identified. On completion of the intervention period, exercise capacity, as measured by the six-minute walk distance, was significantly greater in the intervention group compared to the control group (mean difference [MD] 50 m; 95% confidence interval [CI] 15 to 85 m). No between-group differences were observed in HRQoL (standardized mean difference [SMD] 0.17; 95% CI –0.16 to 0.49) or FEV1 (MD –0.13 L; 95% CI –0.36 to 0.11 L).

Conclusion: Exercise training appears to increase the exercise capacity of people following lung resection for NSCLC. The findings of this review should be interpreted with caution due to disparities between the studies, methodological limitations, risk of bias and small sample sizes. This systematic review emphasizes the need for larger RCTs.

TIME SPENT IN MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY FOLLOWING LUNG RESECTION FOR NON-SMALL CELL LUNG CANCER—A COMPARISON OF ABSOLUTE AND RELATIVE CUT-OFF VALUES

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Aim: To quantify the proportion of waking time spent in moderate-to-vigorous physical activity (MVPA) by applying and comparing absolute and relative cut-off values, both expressed as Metabolic Equivalent of Tasks (METS).

Method: Fourteen participants (10 females; median [interquartile range] age 69 [62 to 73] years and body mass index 24 [22 to 30] kg·m−2) between 6 to 10 weeks following lobectomy for primary non-small cell lung cancer (NSCLC) were instructed to wear a physical activity monitor (SenseWear Armband) during waking hours, for 7 days. Two different MET cut-off values were used to classify MVPA: (i) ≥3 METs (absolute) and (ii) 50% of the participant’s measured peak oxygen uptake (50%VO2peak) (relative). Total time in MVPA as well as MVPA performed in uninterrupted bouts of ≥10 minutes were analysed.

Results: Time per day wearing the monitor was 14 [12 to 15] hours. The proportion of total waking hours spent in MVPA was significantly different when comparing absolute and relative MET cut-offs (6 [3 to 16]% versus 21 [13 to 29]%, respectively, p < 0.001). The proportion of waking hours spent in MVPA in uninterrupted bouts ≥10 minutes was also significantly different when comparing absolute and relative MET cut-offs (1.2 [0.8 to 2.7]% and 7.1 [3 to 12]%, respectively, p < 0.001). Ten of the 14 (71%) participants spent ≥10 minutes per day in MVPA in bouts ≥10 minutes when the relative cut-off was applied.

Conclusions: The majority of people following lobectomy for NSCLC met the recommendations of the American College of Sports Medicine for MVPA (≥30 minutes per day in MVPA in bouts ≥10 minutes) only when the cut-off based on the 50%VO2peak was applied. Caution is needed when interpreting time spent in MVPA based on absolute compared to relative cut-off values as the estimates may vary up to 6-fold.

Nominated: Physiotherapy Prize.

Supported by: Curtin Strategic International Research Scholarship (CSIRS).

Conflict of Interest: No.

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IMPROVEMENTS IN LUNG CANCER MANAGEMENT DUE TO STREAMLINED CARE—THE ROYAL ADELAIDE HOSPITAL EXPERIENCE

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Introduction: A previous audit at the Royal Adelaide Hospital (RAH) found delays in treatment initiation when compared to the United Kingdom (UK) National Cancer Plan targets. As a result, measures were introduced to streamline the care of lung cancer patients, including upgrading the triaging systems, pre-booking investigations and establishing streamlined lung cancer clinics with a dedicated rural pathway.

Aim: To review our performance in 2012–13 after the introduction of these innovations, and re-compare our outcomes against the UK targets.

Methods: Using a pathology database, we retrospectively identified patients managed by the Department of Thoracic Medicine, RAH with histologically confirmed lung cancer from June 2012 to June 2013. We identified patient characteristics including patient location, treatment intent and key dates in diagnosis and treatment before calculating median time intervals.

Results: 191 patients (47% rural) were analysed. There was a 49% increase in cases managed by the unit (128 vs 191) compared with 2011. Fewer patients required inpatient admission (35% vs 18%) despite a higher proportion of stage IV lung cancers (32% vs 40%). The median time intervals were referral to first appointment: 6 days; referral to first treatment: 45 days (rural: 44 days, urban: 46 days, 2011 41 days); surgical patients: 55 days (rural: 55 days, urban: 49 days); curative non-surgical treatment: 43 days (rural: 40 days, urban: 49 days, 2011 41 days); 46 days, 2011 41 days); surgical patients: 55 days (rural: 55 days, urban: 49 days); curative non-surgical treatment: 43 days (rural: 40 days, urban: 49 days).

Conclusions: For 2012–13, the RAH met the first target and maintained similar timely care compared to 2011 despite an increasing number of cases and no increased resource. However, the second UK target set for referral to commencing treatment was not met. Hospital bed days were saved and rural patients achieved equitable timeliness of care. This data show the ability of effective streamlining measures to improve outcomes.

S100A8, A9 AND A12 EXPRESSION BY MYELOID-DERIVED SUPPRESSOR CELLS (MDSC) IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Introduction: Smoking is known to cause chronic obstructive pulmonary disease and NSCLC. MDSC are involved in immune tolerance which allows cancer progression and S100A8 and A9 have been identified as markers of MDSC in NSCLC while the role of A12 remains unclear.

Aim: This study investigated the expression of S100A8, A9 and A12 monocytes and granulocytes in smokers and non-smokers to identify the role of these S-100 calcium-binding protein calgranulins in the development of NSCLC.

Methods: Subjects with NSCLC, COPD, healthy smokers, ex-smokers and never-smokers were recruited. S100A8, A9 and A12 levels in whole blood monocytes and granulocytes in smokers and non-smokers were measured using median fluorescence intensity (MFI) assessed by flow cytometry.

Results: S100A8, A9 and A12 levels in monocytic and granulocytic MDSC did not differ between groups. Smokers and ex-smokers tended to have higher levels of calgranulins but this did not reach statistical significance, potentially due to the inter-individual variability.

Conclusion: Our results differ from previous studies suggesting up-regulation of S100A8 and A9 as potential markers of monocytic and granulocytic MDSC in NSCLC. The high inter-individual variability may explain the lack of differences between groups and longitudinal follow up is needed to assess the role of the calgranulins in NSCLC development.
SERUM AND EXHALED BREATH CONDENSATE (EBC) LEVELS OF S100A9, NITRITE/NITRATE (NOx) AND INTERLEUKIN-10 (IL-10) IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Introduction: MDSC are a heterogeneous population of myeloid progenitors, precursors of macrophages, granulocytes and dendritic cells with T-cell immunosuppressive activity, suggested to be characterized by S100A9 expression. MDSC numbers increase in NSCLC and are implicated in response to therapy, potentially reducing immunity through production of interleukin-10 (IL-10) and by increasing L-arginine conversion to nitric oxide and nitrite/nitrate (NOx).

Aim: This study aimed to assess NOx generation, and IL-10 and S100A9 levels in serum and EBC from patients with NSCLC. Controls included smokers and those with chronic obstructive pulmonary disease (COPD) as smoking is known to cause NSCLC and many individuals with NSCLC also have COPD. Asthma acted as a benign control inflammatory disorder.

Methods: Samples from subjects with NSCLC were compared with those from COPD, asthma, healthy smokers, ex-smokers and never-smokers. S100A9 and IL-10 levels in serum and EBC were assessed using enzyme-linked immunosorbent assays (ELISAs) and NOx using a modified fluorometric adaptation of the Griess method.

Results: NOx production was increased in serum of subjects with NSCLC (NSCLC 9.80 ± 1.49 μM vs non-smokers 6.86 ± 0.78 μM, p = 0.002) but not in EBC. S100A9 also tended to be elevated in serum of smokers and subjects with NSCLC but this did not reach significance. Serum IL-10, on the other hand, was only detected in one subject with asthma and another with NSCLC. EBC S100A9 and IL-10 levels were mostly below the levels of detection.

Conclusion: NOx production is increased in NSCLC but larger studies are needed to confirm these observations.

PLEURAL FLUID PROTEIN AND PH SIGNIFICANTLY DECREASES ON LONGITUDINAL ANALYSIS IN MALIGNANT PLEURAL EFFUSION

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Introduction: Malignant pleural effusions (MPE) are incurable and often recurrent. Patients with indwelling pleural catheter (IPC) for MPE offer a unique opportunity, not possible before, for longitudinal pleural fluid (PF) sampling.

Aim: This observational study describes for the first time the longitudinal changes in PF biochemistry in MPEs.

Methods: All patients who had IPC inserted for MPE in our pleural service were entered prospectively into a database over a 44-month period from Jul 2009. PF samples were prospectively collected during IPC drainage and supernatant stored. PF samples were routinely tested for pH, protein, LDH and glucose. PF and corresponding blood biochemistry results were analysed using linear mixed models, specifically a straight-line model with varying intercepts and varying slopes for each individual. Results reported are for the population parameters of this model.

Results: 107 patients (77% male; 60% had mesothelioma) underwent a total of 110 IPC insertions. PF protein (mean, 40.97 g/L; n = 638) and pH (mean, 7.34; n = 570) decreased significantly by 0.08 g/L/day (SE, 0.00; p-value <0.001) and by >0.001/day (SE, 0.002; p-value, 0.02) respectively. Serum protein (mean, 70.58; SE, 0.75; n = 378) compared to PF protein did not demonstrate a parallel decrease (0.01 g/L/day; SE, 0.005; p-value, 0.08). PF:serum protein ratio (mean, 0.56; SE, 0.02; n = 364) decreased by 0.001/day (SE, 0.0001; p-value, 0.04) indicating greater PF protein decrease than serum protein. PF LDH (mean log, 6.29 U/L; n = 624) increased by 0.0008 U/L/day (SE, 0.001) and PF glucose (mean 3.84 mmol/L; n = 627) decreased by 0.001 mmol/L/day (SE, 0.001) but did not reach statistical significance. Serum albumin (mean, 38.35; n = 384) decreased by 0.03 g/L/day (SE, 0.005; p-value <0.001).

Conclusions: This study demonstrates for the first time the longitudinal changes in PF biochemistry in MPEs, in particular the significant longitudinal decrease in PF pH and protein. Further analyses using cytokines and other biomarkers are underway.
BREATH ANALYSIS USING FIELD ASYMMETRIC ION MOBILITY SPECTROMETRY (FAIMS)

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Aim: Human breath contains volatile biomarkers that could be used to diagnose lung diseases, which may be achieved by FAIMS technology. This method separates gas-phase ions at atmospheric pressure and ambient temperature. Compounds are ionized and passed through an asymmetric charged field. Ions are separated by their mobility under this varying electric field. A compensation voltage (CV) is used to filter the ions through the electrode channel to the detector. Using the range of the dispersion field (DF), different ionizable entities in the breath can be detected. The aim was to adapt FAIMS to first analyse breath from normal subjects intending to later map diagnostic ion patterns in lung diseases.

Methods: Breath from normal healthy subjects was cooled on ice. The exhaled breath condensate (EBC) was retained, while the gaseous phase was mixed with dry clean air and drawn into the FAIMS analyser under negative pressure. In a separate experiment, the EBC collected previously was vapourized by negative pressure and analysed in a similar manner.

Results: Breath water vapour generates a dominant, overwhelming signal when the humidity of the sample is higher than 10%. At <10% humidity, accomplished by condensing breath water and mixing with dry air, FAIMS showed similar spectra in healthy subjects. Food or beverages consumed by the subjects prior to breath analysis added additional peaks to the spectra, indicating that these will need to be assessed in breathprint analysis.

| Sample                          | Dispersion field | Positive spectrum | Negative spectrum |
|---------------------------------|------------------|-------------------|-------------------|
| Breath                          | 110 V            | 1.75, -0.3        | -1.2, -0.5, 0.1   |
| Vapourized EBC                  | 110 V            | 1.9, -1.05, 0.4   | -1.7, -0.9, 0.5, 0.1 |
| Breath after consumption of alcohol| 143 V           | -0.5, 0.95        | 1 and 0.8        |
| Breath after consumption of mint chewing gum | 110 V     | -1, 0.3           | -1, -0.8, 0.2    |
|                                 | at 0.6 V         |                   |                   |

Conclusion: Water vapour in the breath lowers the separation efficiency of the FAIMS significantly but consistency in peaks within and between healthy subjects was observed. Recent consumption of food substances is likely to alter the analysis.

THE LUNG CANCER JOURNEY: A PROSPECTIVE STUDY COMPARING THE EXPERIENCE OF NON-URBAN AND URBAN PATIENTS REFERRED TO A SPECIALIST THORACIC CENTRE IN QUEENSLAND

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Aim: Non-urban cancer populations in Australia have poorer health outcomes and reduced access to specialist services compared to their urban counterparts. This study aimed to determine if there is a difference between the journey of non-urban and urban patients with suspected lung cancer referred to a tertiary hospital in Queensland.

Method: A prospective cohort study of consecutive patients referred to a tertiary hospital in Queensland for suspected lung cancer between 01 February and 01 August 2013. The main outcome was the patient journey from symptom onset to diagnosis. Type of referrer, journey times and diagnosis were extracted from hospital electronic records for all patients referred. Investigation patterns, out-of-pocket expenses, patient-perceptions of care, and travel and accommodation needs were obtained from self-reported questionnaires mailed to consenting patients at the time of referral and one-month following.

Results: Of 107 eligible patients identified, 45 (42.1%) returned questionnaires. Times to referral and first specialist appointment; patterns of referral, investigations and diagnosis; and patient perceptions of care were similar for non-urban and urban patients. Total out-of-pocket expenses were significantly greater for non-urban patients (median, $133 non-urban and $40 urban, p = 0.03) and distance from residential address to the hospital correlated strongly with days off paid work (r = 0.90, p < 0.001).

Conclusion: Non-urban patients with suspected lung cancer incurred higher out-of-pocket expenses and more days off paid work, but were otherwise not significantly disadvantaged during their journey to diagnosis compared to urban patients.

Conflict of Interest: No

Acknowledgements: NHMRC Practitioner Fellowship (KF).

EVALUATION OF THE IMPLEMENTATION OF A TRACHEOSTOMY REVIEW SERVICE (TRS) AT WESTERN HOSPITAL, FOOTSCRAY (WHF), AN ADULT GENERAL TEACHING HOSPITAL

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Introduction: There is an increasing trend in literature suggesting that multidisciplinary tracheostomy teams may improve safety, enhance outcomes and promote excellence.

Aim: To evaluate the effect of introduction of a TRS on patient outcomes and staff attitudes.

Method: A multidisciplinary TRS commenced in March 2012 reviewing all patients with tracheostomies on general wards, excluding ENT patients. Data were collected via medical record audit. Two years of retrospective data of pre-TRS patients (n = 39) were compared with 12 months of prospective post-TRS patients (n = 28) for: Canulation time (LOC), length of stay (total and ICU LOS), adverse events and speaking valve (PMV) usage. Medical, nursing and allied health staff were surveyed regarding knowledge and confidence in tracheostomy management.

Results: Analysis of the data demonstrated a mean (SD) APACHE score of 22.0 in the post-TRS group and 27.3 in the pre-TRS group (p = 0.01). There was a significant increase in frequency of PMV use (p = 0.01) post-TRS. No statistical difference was demonstrated in: LOC, LOS (total and ICU), time to trial PMV and adverse events. Results from staff surveys show improvement in staff (median years experience 3.0, IQR 1–6) self-reported knowledge and confidence in basic care and complex areas of tracheostomy management post-TRS (p < 0.05). 78% of staff surveyed reported a desire for the TRS to continue.

Conclusion: Although contributing to improvements in some aspects of staff knowledge and confidence, our results suggest that a multidisciplinary TRS had a limited effect on patient outcomes at our centre. Limitations of this study include small sample size and extreme heterogeneity of patient characteristics. Better understanding of our patient group may help to identify patients who may benefit from multidisciplinary team management to formulate a referral guide.

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AUSTRALASIAN MALIGNANT PLEURAL EFFUSION (AMPLE) STUDY: A MULTICENTRE RANDOMIZED TRIAL COMPARING INDWELLING PLEURAL CATHETER (IPC) VS TALC PLEURODESIS: PROGRESS UPDATE

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Introduction: Malignant pleural effusions (MPE) are common. IPCs and talc pleurodesis are approved treatments for MPE and were equally efficacious in providing symptom relief as shown in a recent (TIME-2) randomized study. Our recent patient-choice study showed that MPE patients who chose to have IPC treatment spent significantly (∼12) fewer days in hospital and required fewer additional pleural procedures compared to those who chose talc pleurodesis.

Aim: AMPLEx is designed to verify the benefits of IPC over pleurodesis in reducing inpatient care days.

Primary Endpoint: The total number of days in hospital for any cause for admission from the trial intervention to death or end of study period.

Design: Patients (n = 146) with symptomatic MPE will be randomized 1:1 to IPC or talc slurry pleurodesis. Randomization will be stratified for mesothelioma (vs other cancers) and the presence (vs absence) of trapped lung. Self-reported quality-of-life and breathlessness scores, adverse events, and healthcare costs will be recorded. Participants will be followed up for a minimum of 6 months after recruitment (or until death).

Progress to Date: From commencement of recruitment in July 2013, 72 participants have been enrolled from five centres (and their feeding hospitals) in Western Australia, New South Wales, Queensland, and Wellington. Several additional centres will join the study upon local ethics approval.

Conclusion: This study will help determine if IPC treatment can reduce inpatient care days. The data will have a direct impact on patient care and inform health policy decisions. Given the large number of patients who develop MPE every year, the implications on healthcare cost can also be substantial.

THE ROLE OF BRONCHOSCOPY IN ASSESSMENT OF PULMONARY CAVITARY LESIONS

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Aim: Pulmonary cavities are thick-walled (greater than 2–5 mm) cystic parenchymal masses and they may be filled with air, fluid or both. Their underlying aetiology may be due to a variety of processes including infection, neoplasms and vasculitides. Moreover, a diagnosis of infection or abscess often requires the exclusion of other processes. A number of investigations are used to identify the cause including bronchoscopy and biopsy. Therefore, the process of achieving a final diagnosis (aetiology of the cavity) can be prolonged and challenging. We sought to determine the aetiology of the lesions diagnosed in our region over the last three years and the clinical utility of diagnostic procedures.

Methods: All of the patients (n = 1426) whom underwent bronchoscopy at Flinders Medical Centre from 31/05/2010 to 31/05/2013 were assessed for the radiological evidence of pulmonary cavitary lesion(s). 24 patients were identified and case notes were reviewed.

Results: 83.8% of twenty four cases (n = 20) were identified to have infectious aetiology. The total duration to achieve final diagnosis varied from 3 to 139 days however 41.7% were diagnosed in less than 10 days. In 17 out of 24 cases (70.8%), bronchoscopy enabled a diagnosis. CRP and wall thickness were not predictive of, or associated with final diagnosis. Tuberculosis was not identified in this cohort.

Conclusion: Bronchoscopy remains a useful tool for diagnosis. Considerable delays in achieving the final diagnosis were observed in a minority of cases. A diagnostic algorithm may reduce the delays in diagnosis.

Funding Source: None

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ENDOBRONCHIAL ULTRASOUND-GUIDED TRANBONCHIAL NEEDLE ASPIRATION (EBUS-TBNA): EXPERIENCE OF A REGIONAL CENTRE IN AUSTRALIA

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Aim: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become widely adopted by major tertiary centres as an effective, minimally invasive diagnostic tool for the evaluation of lesions adjacent to the respiratory tract. However, the performance of EBUS-TBNA has not been well studied in regional centres. EBUS was first introduced in our centre servicing Northern Tasmania in November 2012. Here, we report our single-operator experience with EBUS-TBNA compared with the existing practice of conventional TBNA with regard to its clinical utility, diagnostic accuracy and safety.

Method: Data were collected prospectively on consecutive EBUS-TBNA (December 2012–June 2013) and conventional TBNA (May 2012–November 2012) performed at the Launceston General Hospital. Patient demographics and the operating characteristics were recorded. Final diagnosis was based on a composite standard: histological evidence at surgery, or non-equivocal cytology on FNA and follow-up serial imaging. Inclusion and calculation of diagnostic performance were based on this composite standard.

Results: 34 EBUS-TBNA (24 men, mean age 69.5 years, range 47–87) and 26 conventional TBNA (15 men, mean age 67.7 years, range 42–83) were performed during the study period. For EBUS-TBNA, 29 and 5 patients were evaluated for malignancy and sarcoidosis, respectively. While for conventional TBNA, 25 and 1 patients were evaluated for malignancy and sarcoidosis, respectively.

EBUS-TBNA was superior to conventional TBNA in evaluating for malignancy, with higher sensitivity (89.47% vs. 88.42%) and higher negative predictive value (83.3% vs. 50%). The diagnostic yield of EBUS-TBNA for sarcoidosis was not statistically different from conventional TBNA.

Conclusion: Our experience suggests that EBUS-TBNA can be performed safely and effectively in a regional centre while maintaining high diagnostic accuracy comparable to major tertiary centres. Therefore, we conclude that it is feasible to perform EBUS-TBNA in regional centres. No major complications were observed during the study period.

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PLEUROSCOPIC CRYOPROBE BIOPSIES OF THE PLEURA: A PILOT STUDY

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Introduction: Flexible-rigid pleuroscopy is a useful tool in the workup of pleural effusions but the small biopsy channel often limits the size of tissue obtained especially in patients with thickened pleura. This pilot study evaluated the usefulness and safety of using a cryoprobe to obtain parietal pleural biopsies during flexi-rigid pleuroscopy.

Method: Single centre prospective pilot study. Diagnostic pleuroscopy was performed in patients with suspected pleural malignancies using a flexi-rigid pleuroscoope by one of two experienced operators. Additional cryoprobe biopsies were obtained when the operator has completed the standard pleuroscopic examination and biopsies using flexible forceps (FFB) ± rigid forceps (RFB) via a second entry port. A flexible autoclavable cryoprobe (2.4 mm diameter) was activated for 3 seconds to obtain cryobiopsies. All biopsy sites were assessed for bleeding. Histological samples were reviewed in random order by a specialist respiratory pathologist blinded to patient identity and biopsy technique.

Results: 20 patients were included: all had cryobiopsies and FFB, 4 had additional RFB. A malignant diagnosis was established in 11 patients (82% mesothelioma). Patients with benign pleuritis were followed up for a median of 8 months with no signs of cancer. An accurate diagnosis was made in 19 of 20 patients from cryobiopsies which was comparable with FFB (19 of 20 patients) and 4 of the 4 patients who had RFB. The size of cryobiopsies was significantly larger than FFBs: mean 8.15 vs 3.19 mm², p = 0.0001. Crush artefact was significantly less common from (2 of 20) cryobiopsies: vs FFB (19 of 20, p = 0.0001) or RFB (4 of 4, p = 0.014). Most (90%) cryobiopsies were graded as easily interpretable by a blinded pathologist (vs 90% of FFB and 100% RFB). No significant bleed occurred in any patient.

Conclusion: This pilot study showed that cryobiopsies during flexi-rigid pleuroscopy was safe and could provide larger pieces of parietal tissue samples than FFB. Cryobiopsies minimize crush artefact and better preserve the histological architecture for pathological examination. Cryobiopsies may have a role in selected cases though its routine use may not be necessary for experienced pleuroscopists.

A CASE OF A WOMAN WHO DEFIED THE LAWS OF PHYSICS: PLATYPOINEA-ORTHODEOXIA

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Introduction: Platypnoea-Orthodeoxia is a rare phenomenon in which dyspnoea and arterial oxygen desaturation are accentuated by upright posture and improved by recumbency. It requires a high index of suspicion for diagnosis.

Case Report: An 80-year-old Chinese woman presented with a fractured neck of humerus after a fall for conservative management, on a background of 5-pack-year smoking history. While in the emergency department, she developed acute arterial oxygen desaturation to 80% on 10 L via Hudson mask, improving to 91% on 100% FiO2 via high-flow mask. She, interestingly, had a previous presentation 3 years prior with dyspnoea. Follow-up CXR, CTPA, V/Q scan, Lung function test and Echocardiogram then only revealed mild left ventricular hypertrophy and a 4.7 cm thoracic aorta aneurysm. There has since been a 12-month history of progressive dyspnoea and dizziness with recurrent falls. Admission CXR and CT chest this time revealed no other additional information, apart from confirming the thoracic aorta aneurysm. She was admitted to Intensive Care Unit and continued to exhibit fluctuating arterial oxygenation levels while changing position. She avoided intubation as she developed no respiratory distress during observation. All other biochemistries were also unremarkable. She underwent a repeat Echocardiogram with contrast bubble study confirming the presence of an interatrial septal aneurysm communicating with the left atrium in the upright position.

Conclusion: Platypnoea-Orthodeoxia in this case was most likely caused by an anatomical distortion of the fenestrated septal aneurysm during upright posture. One needs to exercise a high degree of suspicion when encountering such patients, as invasive ventilation can be avoided and definitive treatment can now be offered.

PHASE 2 STUDY OF METHOXYFLURANE AS AN ANAESTHETIC AGENT IN AVERSIVE PLEURAL PROCEDURES

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Introduction: Adequate analgesia in pleural procedures remains a challenge in interventional pulmonology. Methoxyflurane has an established profile in managing severe pain in trauma medicine, and has the advantage of being a patient-controlled analgesia with minimal risks of respiratory depression.

Aim: To assess the efficacy and tolerance of methoxyflurane during pleural procedures.

Method: This was a prospective study of consecutive consenting patients undergoing invasive pleural procedures at Concord Hospital, from February to August 2013. Patients inhaled methoxyflurane prior to standard local anaesthetic infiltration at the procedural site. IV access was available for supplemental opiate analgesia as needed. Patient and operator questionnaires regarding efficacy and tolerance of methoxyflurane were conducted after pleural procedures and the dose of opiates required was recorded.

Results: Eighteen invasive pleural procedures were performed during this time period, with mean age of 74 years (range 43–94). Pleural procedures included 12 intercostal catheter insertion (14 Fr, Seldinger technique), one pleural aspiration, two tunneled intercostal catheters, two medical pleuroscopies and one tunneled intercostal catheter removal. Underlying pathology was malignant in seven cases. Average pain score was 2.9/10 during and 1.7/10 post-procedure, which correlated well with operator reported pain scores of 2.2/10. Average anxiety levels were 4.4/10. Cough was the most commonly reported side effect occurring in 22%. No patient required additional opiate analgesia during the procedure. Methoxyflurane was well tolerated, and 77% of patients would be happy to use it in future procedures.

Conclusion: Methoxyflurane provides effective analgesia and is well tolerated with minimal side effects. Future randomized control studies will further elucidate the use of methoxyflurane in this setting compared to current standard practice.
CLINICAL EXAMINATION DOES NOT RELIABLY DETERMINE SAFE SITE FOR THORACENTESIS

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Introduction: Several well-recognized adverse complications are associated with ‘blind’ procedures (i.e. based on clinical examination and CXR) including mortality related to drain misplacement.

Aim: To determine the accuracy of clinical examination in selecting safe sites for thoracentesis in a busy thoracic ward.

Methods: The study was performed prospectively on inpatients admitted to a tertiary teaching hospital with pleural effusion. For each patient, up to five clinicians of varying levels of experience were asked to determine a safe site for thoracentesis. Clinician experience was defined based on the number of procedures performed within the last 12 months (level 1 least experienced; level 4 most experienced). After viewing the radiology, each clinician examined the patient (blinded to the previous examiner) and identified a safe site for pleural drainage. A small group of trained physicians, who had successfully completed an accredited thoracic ultrasound course, immediately examined the selected site with ultrasound to determine its safety based on the pre-defined criterion of the presence of fluid >1 cm perpendicular to the chosen site.

Result: A total of 59 examinations were performed on 19 patients. 50 sites were selected based on clinical examination as being safe for thoracentesis. In 9 examinations, no site was identified as being safe. Among the selected sites, 15 errors (30%) were noted. These were identified on ultrasound as reflecting underlying spleen (n = 5), fluid <1 cm (n = 5), liver (n = 4) or diaphragm (n = 1). Clinical errors were made by physicians of all levels of experience (40% level 1, 27% level 2, 17% level 3 and 29% level 4) (p > 0.7 for comparison of error rates according to experience). Effusion size did not influence the safety of site selection.

Conclusion: A significant number of clinical errors are made by clinicians using clinical examination alone regardless of the clinical experience or the magnitude of pleural effusion.

AURID OF COMPLIANCE & POTENTIAL COMPLICATIONS OF EMPERIAL ANTICOAGULATION IN PATIENTS WITH HIGH PROBABILITY OF PULMONARY EMBOLISM

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Background: The benefits and safety of empirical anticoagulation (EA) before imaging confirmation for suspected pulmonary embolism (PE) is unclear. Despite being common practice in most healthcare centres, there appears to be a lack of standardization with regards to this. No high level studies have been performed to evaluate the efficacy as well as the outcomes of this practice. The American College of Chest Physicians (ACCP) recommends EA in patients with a high clinical suspicion of acute PE while awaiting the results of diagnostic tests. Evidence clearly supports that early initiation of anticoagulation results in better outcomes, particularly within the first 24 hours of presentation. However, the consequences or outcome of empirical anticoagulation, especially bleeding, has not been clearly studied.

Aim: To study the impact of early or empirical anticoagulation at Flinders Medical Centre (FMC) in high risk patients. The primary outcome studied is bleeding complications (major and minor) as well as compliance of empirical anticoagulation use within FMC. We would also like to monitor the incidence of PE in this cohort.

Methods: Clinical audit based on electronic database of high probability (Well’s score) patients requiring imaging confirmation for PE. From this, case notes were reviewed to ascertain the outcomes of interest.

Results: Only 45% of patients with high probability score were given EA. Risk of bleeding in the EA group was (4/25) 16% with a number needed to harm of 7. None of the patients without EA had any significant bleeding. However, of the three patients with bleeding and no PE (EA+/PE−), one patient had a metastatic malignancy with a previously undiagnosed cerebral lesion, one most likely presented subarachnoid haemorrhage and another one patient was already on anticoagulation for DVT despite not having PE. Only 21% (12/56) of patients had PE despite being labelled with a high pre-test probability.

|       | EA+/PE+ | EA+/PE− | EA−/PE+ | EA−/PE− | Total |
|-------|---------|---------|---------|---------|-------|
| Bleeding+ | 1       | 3       | 0       | 0       | 4     |
| Bleeding− | 7       | 14      | 4       | 27      | 52    |
| Total    | 8       | 17      | 4       | 27      | 56    |

Conclusion: Despite evidence and a specific algorithm at FMC for EA in high risk patients, EA remains underused. However, EA may be associated with an increased bleeding risk in this cohort. Further studies using a larger sample size is needed.
SMOKING DURING PREGNANCY AND TOBACCO ABUSE PREVENTION IN ABORIGINAL AND TORRES STRAIT ISLANDER YOUTH: A QUALITATIVE ANALYSIS

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Aim: To explore factors contributing to the high prevalence of tobacco use in Aboriginal and Torres Strait Islander pregnant women and youth and to identify potential strategies to reduce tobacco abuse amongst this population.

Method: Semi-structured interviews developed in consultation with Aboriginal Elders, researchers and healthcare workers were conducted with respiratory consultants, key community stakeholders and Aboriginal Elders between March and October 2013. Quantitative data on demographics, perceptions, knowledge and attitude surrounding tobacco use were also collected. Data were analysed 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. Explanations for the high prevalence of tobacco use during pregnancy in Indigenous communities are similar to those reported by the non-Indigenous population, with addiction being an important factor. Limited knowledge about the health effects of tobacco use in utero are amplified by health consequences not being immediately perceived. Indigenous youth are heavily influenced by their peers, Elders and broader community. Cultural acceptance of tobacco use and other social and environmental factors make smoking cessation and prevention particularly difficult. Community-owned initiatives are important strategies to improving the success of anti-tobacco programmes. These may include smoke-free community events, stricter policies restricting smoking indoors and around children, and firm governance of cigarette sales to minors. Utilizing sporting role models with regular tobacco abuse prevention programmes in schools highlighting the health effects of tobacco use and second-hand smoke exposure may facilitate reductions in smoking prevalence long-term.

Conclusion: It is difficult to quit smoking during pregnancy regardless of ethnicity and it is therefore even more important to encourage smoking cessation in young Aboriginal women before they become pregnant. Preventing the uptake of tobacco use among youth is fundamental to reducing tobacco prevalence.

LUNG SICKNESS IN MURRI KIDS: A COHORT STUDY IN URBAN INDIGENOUS CHILDREN

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Introduction: Respiratory illnesses with cough as a symptom are predominant causes of morbidity in young Australian Indigenous children. With the exception of ear disease, there are limited studies that have addressed burden and outcome. Also, there are no studies that are specific to urban Indigenous children.

Aim: We aim to comprehensively investigate the incidence, aetiology, risk factors for and outcomes of acute respiratory illnesses (ARIs) in this population.

Methods: A cohort study of Indigenous children aged less than 5 years registered with an urban Indigenous primary health care service. Comprehensive baseline data are collected and children are followed monthly for 12 months to capture ARI events. ARI events are subsequently followed weekly for 4 weeks to determine cough outcomes, with review by a paediatric respiratory physician if cough has not resolved within 28 days.

Results: To date, 58 children (57% female) have been enrolled and 46 ARIs have been captured over 907 child weeks of observation (5.1 events per 100 child weeks, 95%CI 3.7–6.8). 13 ARIs (28.3%) have resulted in persistent cough for >28 days following onset.

Conclusion: Our early findings suggest an excess incidence of ARI in this population. The proportion of ARIs resulting in persistent cough for more than 4 weeks is the highest yet reported.

Key Words: Indigenous, acute respiratory illness, paediatric.
SAFETY OF VENTILATION—DOES IT GET TO WHERE WE WANT IT?

INTRODUCTION: Salbutamol is commonly used to treat perioperative bronchospasm. In awake children, salbutamol is usually administered via a pressurized metered dose inhaler (pMDI) connected to a spacer. Intra-operatively, the 3 main administration techniques are: 1) pMDI via inline adapter, 2) pMDI in 50 ml Luer-lock syringe attached to angle-piece of ventilator 3) actuator directly attached to endotracheal tube (ETT). This pilot study aims at comparing the efficiency of these 3 techniques with that of the pMDI connected to a spacer.

METHODS: Delivery efficiency of the 3 intraoperative techniques was assessed in-vitro under spontaneous ventilation conditions against the efficiency of the ‘awake technique’, considered as the gold standard. 3.0 and 7.0 mm ETT and 2 different brands of salbutamol, Ventolin and ProAir were used. The amount of drug recovered was recovered from each component of the set-up used, was assayed and particle size distribution calculated using a Copley Next Generation Pharmaceutical impactor.

RESULTS:

Table 1 summarizes the preliminary results.

| 7 mm ETT | Actuator | Ventolin Adapter | Syringe | Actuator | ProAir Adapter | Syringe |
|----------|----------|------------------|---------|----------|----------------|---------|
| Total exiting ETT (% of label claim) | 21.3 | 10.7 | 8.4 | 7.48 | 2.72 | 1.30 |
| Exiting ETT < 3.99 μm (% of label claim/puff) | 9.6 | 5.2 | 1.7 | 4.71 | 0.87 | 0.07 |

| 3 mm ETT | Actuator | Ventolin Adapter | Syringe | Actuator | ProAir Adapter | Syringe |
|----------|----------|------------------|---------|----------|----------------|---------|
| Total exiting ETT (% of label claim) | 40.9 | 26.6 | 14.9 | 30.8 | 26.9 | 13.4 |
| Exiting ETT < 5.39 μm (% of label claim/puff) | 4.3 | 0.2 | 0.6 | 9.2 | 0.7 | 0.0 |

Figure 1: Percentage of drug delivered within the 2–6 μm range by each technique and compared against the spacer technique in an awake-child simulation.

CONCLUSIONS: Inter-technique differences were significant; the syringe was the least efficient with only 1.9% of drug in the respirable fraction. The active drug delivered has major implications on the dosing regime, particularly in the event of a bronchospasm in intubated children and the significant differences of delivery between the techniques have to be considered.

HIGH-FLOW NASAL PRONG (HFNP) THERAPY FOR INFANTS IN THE HOME SETTING

INTRODUCTION: Heated humidified high-flow air via nasal prong (HFNP) with added oxygen (O₂) can be used to provide O₂ and continuous positive pressure (CPAP) to infants needing inpatient respiratory support. HFNP therapy may be used for the same indications as traditional CPAP delivered via nasopharyngeal tube or face-mask. The technology to deliver HFNP in the outpatient setting has recently become commercially available. Outpatient HFNP therapy may be better tolerated than standard mask CPAP. HFNP also offers more convenient delivery interface, and nasal cannulae may avoid the side effects associated with long term facemask use.

AIM: To describe our experience using HFNP therapy for infants in the outpatient setting.

METHODS: A retrospective chart review of infants <24 months of age discharged home on HFNP therapy between 2012–13 from a tertiary paediatric hospital.

RESULTS: 4 infants (3 M/1 F) 24–39 weeks gestation were identified. All required prolonged ventilation and developed chronic lung disease. Co-morbidities included pulmonary interstitial glycosgenosis, pulmonary hypertension, craniofacial and airway abnormalities (laryngomalacia, tracheobronchomalacia) and genetic conditions (Noonan’s, chromosome 9 deletion). All were commenced on HFNP therapy as inpatients (aged 5–15 months) following unsuccessful wean from CPAP to low flow oxygen prior to discharge. Indications for outpatient HFNP therapy included an inability to tolerate face-mask CPAP (2), CPAP unsuccessful due to inappropriate mask fit and parental refusal for tracheostomy, CPAP dependent but care-givers assessed as unable to manage CPAP at tracheostomy. Duration of outpatient HFNP therapy: 1 day (just discharged) to 2 years. No complications secondary to HFNP therapy recorded.

CONCLUSION: HFNP O₂ therapy has been used successfully to support the discharge of patients who were unable to wean from standard CPAP to low flow oxygen.

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ITEM REDUCTION AND VALIDATION OF A CHILDREN'S ACUTE COUGH SPECIFIC QUALITY OF LIFE QUESTIONNAIRE (PAC-QoL)

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Introduction: Patient-relevant outcome measures are essential for high-quality clinical research, and quality of life (QoL) tools are the current standard. Currently there is no validated children’s acute cough specific QoL measure. The objective of this study was to develop and validate a parent-proxy acute cough specific QoL questionnaire (PAC-QoL). Here we present our data on item reduction and validation.

Methods: Parents of children with a current acute cough (<2 weeks duration) at enrolment completed 4 questionnaires (state trait anxiety inventory (STAI); 24-hour recall short form health survey (SF-8); depression, anxiety and stress 21-item scale (DASS21); and our preliminary 48-item parent acute cough specific QoL (PAC-QoL48) questionnaire), in addition to two cough score measures. All measures were repeated at Days 3, 7 and 14.

Results: Median age of the 155 children enrolled was 2.17 years (IQR 1.25, 4.58); 86 were boys. Median length of cough at enrolment was 3 (IQR 2, 5) days. Utilizing the clinical impact method of item reduction, an arbitrary cut off at a natural break in impact resulted in a 16-item scale with high internal consistency (Cronbach α = 0.94). Evidence for repeatability and criterion validity was examined with significant correlations found between the domains and total PAC-QoL16 scores and the SF-8, STAI and DASS21 scales. The PAC-QoL16 questionnaire was sensitive to change over time with changes relating to changes in cough score measures (PAC-QoL16 with: verbal category descriptors, Spearman r = -0.463, p = 0.01; visual analogue scale, r = -0.633, p = 0.01).

Conclusions: The 16-item QoL questionnaire derived from the clinical impact method is a reliable and valid outcome measure that assesses parental QoL related to their child’s acute cough at a given time point and reflects changes in QoL over time.

Supported by: QCMRI.

Conflict of Interest: No.

RECOVERY FROM ACUTE ASTHMA EXACERBATIONS IN CHILDREN: INFLUENCE OF VIRUSES, ECZEMA AND ATOPY

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Background: Acute asthma, one of the most common causes of childhood emergencies, is associated with viral infections. Although eczema and atopy are recognized as risk factors for severe asthma, the factors associated with recovery following exacerbations are not well understood.

Aims: In children with hospitalized and non-hospitalized asthma exacerbations, to (a) describe the point prevalence of respiratory viruses/atypical bacteria using polymerase chain reaction (PCR) and (b) evaluate the impact of respiratory viruses/atypical bacteria, eczema and atopy on acute severity and clinical recovery.

Methods: 244 children aged 2–16 years presenting with acute asthma to the Emergency Departments of 2 hospitals were recruited. A nasopharyngeal aspirate and allergen skin prick test were performed. Asthma quality of life questionnaires for parents (PACQLQ) and validated daily diary scores for asthma were recorded for 21 and 14 days, respectively.

Results: PCR for viruses/atypical bacteria was positive in 81.7% of children (75.1% human rhinovirus, co-detection in 14.2%). M. pneumoniae and C. pneumoniae were rarely detected. The presence of micro-organisms had little impact on acute asthma or recovery outcomes. Children with eczema had significantly slower asthma recovery, i.e. higher asthma diary scores on days 7, 10 and 14 (β = 0.47, 95%CI 0.09,0.85, p = 0.015; β = 0.49, 95%CI 0.10,0.88, p = 0.015; β = 0.40, 95%CI 0.02,0.78, p = 0.041 respectively) whereas children with atopy were significantly more likely to relapse and re-present for medical care by day 14 (OR 1.11, 95%CI 1.00,1.23, p = 0.042).

Conclusions: Viruses are associated with asthma exacerbations but do not appear to influence asthma recovery. In contrast, eczema is associated with delayed recovery from acute asthma while atopy is associated with asthma relapse.
INTERLEUKIN-1β IS RELATED TO CLINICAL OUTCOMES IN PROTRACTER BACTERIAL BRONCHITIS

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Introduction: Protracted bacterial bronchitis (PBB) is a common and treatable cause of chronic wet cough in children in which the mechanisms are not understood.

Aim: To investigate the interleukin (IL)-1 pathway and a neutrophil gene expression signature in PBB.

Method: Bronchoalveolar lavage (BAL) was collected from children in an experimental cohort (n = 21 PBB, n = 33 controls), and a second validation cohort (n = 38 PBB; n = 11 controls). Interleukin (IL)-1β and IL-1 receptor antagonist (IL-1RA) were assayed by ELISA, western blot and qPCR, together with selected IL-1 pathway members and neutrophil related molecules.

Results: Children with symptomatic PBB had significantly higher levels of IL-1β protein and mRNA. IL-1RA was also higher; however, the IL-1RA/IL-1β ratio was lower in PBB than controls. IL-1β levels lowered when PBB was treated and resolved. In children with recurrent PBB, gene expression of the IL-1β signalling molecules pellino-1 and IL-1 receptor associated kinase 2 was significantly higher. IL-1β correlated with BAL neutrophilia, and the duration and severity of cough symptoms. Neutrophil mediators including α-defensins 1–5 and chemokine receptor CXCR2 were also higher in PBB.

Conclusion: PBB is characterized by increased IL-1β pathway activation. IL-1β and related mediators were associated with BAL neutrophils, cough symptoms and disease recurrence, providing insight into PBB pathogenesis.

COMBINATION INHALED CORTICOSTEROIDS AND LONG-ACTING β2-AGONISTS FOR CHILDREN AND ADULTS WITH BRONCHIECTASIS

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Aim: Bronchiectasis is a major contributor to chronic respiratory morbidity and mortality worldwide. Wheeze and other asthma-like symptoms and airway hyper-responsiveness may occur in people with bronchiectasis. Physicians often use asthma treatments in patients with bronchiectasis.

Method: The Cochrane Airways Group performed a literature search, in accordance with Cochrane methodology. This included the Cochrane Central Register of Controlled Trials and clinical trial registers. Inclusion criteria were all randomized controlled trials (RCTs) of combined ICS and LABA compared to a control (placebo, no treatment, ICS alone). Data assessed the efficacy of combined ICS-LABA compared to monotherapy. Data were assessed for the presence or absence of co-existing airway hyper-responsiveness and consideration of adverse events associated with combined ICS-LABA.

Results: 51 abstracts were reviewed. We included one RCT that compared combined ICS and LABA with high dose ICS in 40 adults with non-CF bronchiectasis. There was no significant difference between groups in quality of life, number of people with one or more exacerbation or lung function.

Conclusion: There is insufficient evidence in the current literature to make reasonable conclusions about the efficacy of combined ICS-LABA in adults or children with bronchiectasis. Until further evidence is available, we recommend that therapy be individualized based on the presence or absence of co-existing airway hyper-responsiveness and consideration of adverse events associated with combined ICS-LABA.

THE PERSISTENCE OF RESPIRATORY MORBIDITY IN 9–11 YEAR OLD CHILDREN BORN VERY PRETERM AND THE INFLUENCE OF NEONATAL FACTORS

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Introduction: Recent improvements in neonatal care have resulted in viability of infants at lower gestational ages, and increased numbers of very preterm survivors (<32 weeks gestation), including many with bronchopulmonary dysplasia (BPD). Little is known about whether this generation of very preterm survivors experience increased persistence of respiratory symptoms compared to their full-term peers.

Aim: We aimed to compare persistence of symptoms between preterm and full-term children, and investigate whether there are early life factors that can predict those children likely experience persistent symptoms.

Methods: Pearson’s chi squared tests were used to compare persistence of symptoms between 400 full-term children and 194 very preterm children, 123 with and 71 without BPD. Retrospectively collected neonatal information and respiratory symptom data including incidence of cough and wheeze at 1, 5 and 8–11 years of age were collated from previously collected research databases. Persistence was defined as presence of the symptom at any two or more time points. Logistic regression was used to investigate early life predictors for persistent cough and wheeze in preterm children. 

Results: Preterm children were more likely to experience persistent cough (OR: 4.6, 95% CI 3.1–6.9) and wheeze (OR: 2.6, 95% CI 1.6–4.2) compared to full-term children. There was no difference in persistence of cough and wheeze between very preterm children with and without BPD. Very preterm children who experienced higher incidence of upper and lower respiratory tract infections during the first year of life were more likely to have persistent cough and wheeze.

Conclusions: Very preterm children are more likely to have persistent symptoms compared to their full-term peers, and those who experience respiratory tract infections during the first year of life are most at risk. This highlights the importance of protecting these infants from respiratory infections, which may help to reduce persistent symptoms later in life.

RECURRENT, THERAPY-RESISTANT ALVEOLAR INFILTRATES IN A YOUNG CHILD: APPROACHES TO DIAGNOSIS AND CHALLENGES IN MANAGEMENT

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We report a young girl who presented with recurrent episodes of cough, wheeze and dyspnoea in early childhood. She was trialled on asthma medication but continued to suffer from frequent lower respiratory tract infections and at 5 years of age was admitted to ICU with bilateral patchy lung consolidations, fever, cough, and severe respiratory distress. She was noted to have melena, iron deficiency anaemia, and needed a blood transfusion and a Salmonella-positive stool sample was detected. Over the next 6 months she continued to have frequent chest infections and small amounts of haemoptysis for which she was further investigated. Her chest x-ray (CXR) during an acute episode showed bilateral diffuse pulmonary infiltrates and bilateral consolidation with ground glass opacities. A CT chest showed bronchiectatic changes in right lower lobe. Bronchoalveolar lavage fluid was blood stained and lung biopsy confirmed haemosiderin-laden macrophages. After exclusion of infective, cardiac, immunological and glomerular causes, she was diagnosed with idiopathic pulmonary haemosiderosis.

Initial inpatient treatment was with IV methylprednisolone and antibiotics and she was discharged home on prednisolone and hydroxychloroquine but this failed to control her symptoms. A steroid-sparing agent – azathioprine – was introduced and needed to be increased to its maximum tolerable dose of 6 mg/kg/day. To gain effective control and stop haemoptysis she required several courses of high-dose methylprednisolone intravenously. Her management has been complicated by significant steroid side effects. Recently immunoglobulin therapy has been added to her treatment.

We will discuss approaches towards diagnosis and the challenges in managing idiopathic pulmonary haemosiderosis.
MATERNAL CHRONIC HYPOXIA INCREASES THE EXPRESSION OF GENES REGULATING FOETAL LNG REABSORPTION AND THE MATURATION OF THE SURFACTANT SYSTEM

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Introduction: Exposure to intrauterine hypoxia occurs due to a variety of maternal, foetal and/or placental factors. Respiratory outcome of the infant following birth depends on the duration and/or severity of the hypoxic insult.

Aim: Here, we determine the effect of maternal chronic hypoxia during late gestation in sheep on the expression of genes regulating foetal lung liquid reabsorption and maturation of the surfactant system. These are vital processes that aid the successful transition to air-breathing at birth.

Methods: Chronically catheterized pregnant sheep were exposed to normoxia (n = 8) or hypoxia (n = 7; 10% O2) from 105–138 d (term, ~145 d). At 138 d, foetuses were delivered, measured and their tissues collected. qRT-PCR was used to quantify lung mRNA expression of genes regulating sodium and water reabsorption, as well as the surfactant proteins (SP). These included amiloride-sensitive epithelial sodium channel (ENAC)-α, -β and -γ subunits, sodium potassium active transport pump (ATPase)-α1 & -β1 subunits, aquaporin (AQP)-1, -4, -5 and SP-A, -B, -C & -D. Data were analysed using the Student’s unpaired t-test.

Results: Exposure to hypoxia reduced the maternal PaO2 (106 ± 2 vs. 47 ± 1 mmHg). Maternal hypoxia reduced foetal body weight (4.0 ± 0.1 vs. 3.2 ± 0.3 kg) and increased the ratio of bi-parietal diameter to hind limb lower length (3.7 ± 0.1 vs. 6.5 ± 0.6). Lungs of foetuses from hypoxic pregnancies showed increased mRNA expression of ENAC-γ, ATPase-α1 & -β1, AQP-1 & -4, SP-B, -C & -D.

Conclusion: Maternal chronic hypoxia in late gestation stimulates processes mediating lung liquid reabsorption and surfactant system maturation in the foetus. This may be an adaptive response in preparation for possible preterm delivery.

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SMALL AIRWAYS FUNCTION IN CHILDREN POST BONE MARROW TRANSPLANT (BMT)

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Background: Small airways disease plays an important role in the pathology of pulmonary complications that occur post BMT. However conventional pulmonary function testing performed in clinical practice does not adequately assess the function of small airways. Newer measures of small airway function such as Multiple Breath Washout (MBW) and Forced Oscillation Technique (FOT) may facilitate a better understanding of the pathogenesis and evolution of small airway disease in children post BMT.

Aim: To assess the feasibility of measuring small airway function in children post BMT using MBW and FOT.

Methods: A cross sectional study of children over three years of age at a large BMT clinic, at varying times post BMT will be performed. The primary diagnosis of patients recruited are limited to Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Leukaemia (AML) and Myelodysplasia which all share similar conditioning regimes pre BMT.

Results: To date, five patients, 3 male, age ranging 4 to 18 years have been recruited and tested. The median age at BMT was 9.0 years (range 3–10) and the median time post BMT was 2.0 years (range 1–9 years). All five patients had allogeneic transplants (4 unrelated donor, 1 fully matched sibling), all patients performed MBW and FOT and 3/5 patients had evidence of peripheral airway abnormalities. Median LCI was 9.2 (range 6.15–12.75). Median Sac in 0.13 (range 0.080–0.46) and median Scond was 0.073 (range 0.02–0.09). At 6 Hz median resistance was 6.73 (range 3.05–8) and median reactance was -2.10 (range -1.13–2.71).

Conclusion: It is feasible for children post BMT to perform MBW and FOT tests. Small airways involvement as assessed by MBW and FOT can be seen in post BMT patients. The ability to make sensitive small airway measurements in these patients will allow the relationships with clinical parameters and longitudinal changes to be examined.

ASTHMA AND ALLERGY SIG 1 POSTER PRESENTATION

PATTERNS OF ASTHMA CONTROL AND INHALED CORTICOSTEROID (ICS) USE IN AUSTRALIANS LIVING WITH ASTHMA

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Introduction: Australia has had a comprehensive public health approach to asthma for over two decades. While asthma mortality and hospitalizations have fallen, there are fewer data about broader measures of asthma control.

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. Using the Asthma Control Test (ACT), asthma control was categorized as well-controlled (WC; 20–25), not well controlled (NWC; 16–19) or very poorly controlled (VPC; <16). Current control was compared to patterns of ICS use and acute care episodes.

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

| Level of asthma control | VPC | NWC | WC |
|-------------------------|-----|-----|----|
| Full population         | 1461 (54.4%) | 615 (22.9%) | 609 (22.7%) |
| ICS >= 5 days per week  | 275 (44.7%) | 247 (41.0%) | 388 (26.8%) |
| ICS 1–4 days per week   | 63 (10.2%)  | 63 (10.4%)  | 77 (5.3%)  |
| ICS < weekly            | 32 (5.3%)   | 47 (7.9%)   | 123 (8.5%) |
| ICS a few times a year  | 17 (2.8%)   | 45 (7.4%)   | 207 (14.3%)|
| No ICS use in last year | 228 (37.0%) | 201 (33.3%) | 655 (45.2%)|

Of subjects with VPC asthma 45% had an urgent GP visit for asthma vs 13% with WC asthma (OR 5.4 (4.4–6.9)) and 18% an ED/hospital visit compared to 7% with WC asthma (OR 3.1 (2.3–4.1)).

Conclusions: Many in this cohort did not report WC asthma. 40% of non-users of ICS (17% study population) had poor control (NWC or VPC). Guidelines suggest this group should use ICS. Poor control is associated with greater use of acute care.

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Background: Asthma is not controlled in some patients, despite using medium-dose ICS.

Methods: Two identical Phase III, randomized, double-blind, double-dummy, placebo (pbo)-controlled, parallel-group trials (NCT01172808/821) assessed tiotropium (tio) efficacy/safety. Patients with symptomatic asthma and prebronchodilator FEV1 60–90% predicted and ACQ score ≥1.5. A pre-specified co-primary end points included peak FEV1(0–3 h) and trough FEV1 response at 24 wks.

Results: Baseline characteristics were similar between trials/treatment groups in 2103 randomized patients (2100 treated); mean post-bronchodilator FEV1 88.8% predicted. Both tio doses showed significant improvements vs pbo: mean change from baseline in peak FEV1(0–3 h) at 24 wks: 236 mL (tio 2.5 μg)/198 mL (tio 5 μg) greater than pbo in trial 1 (sal 213 mL); 211 mL (tio 2.5 μg) or 169 mL (tio 5 μg) greater in trial 2 (all p < 0.0001) (sal 176 mL), FEV1 trough response at 24 wks: 185 mL (tio 2.5 μg)/152 mL (tio 5 μg) greater in trial 1 (sal 123 mL); 176 mL (tio 2.5 μg)/133 mL (tio 5 μg) greater in trial 2 (all p < 0.0001) (sal 106 mL). Discontinuation due to adverse events (AEs): pbo, 2.5%; tio 2.5 μg, 1.2%; to 5 μg, 1.9%, sal, 1.6%. No fatal events. AEs balanced across treatment groups.

Conclusion: In patients with symptomatic asthma and airflow limitation despite medium-dose ICS, addition of once-daily tiotropium provides sustained bronchodilation (efficacy comparable to sal) and is well tolerated.

Background: Despite current medications, there remains an unmet need for asthma control in patients with moderate asthma receiving at least ICS. We analysed ACQ data in patients treated with once-daily long-acting anticholinergic bronchodilator tiotropium who had symptomatic asthma despite treatment with medium-dose ICS (400–800 μg budesonide equivalent).

Methods: 2103 patients were randomized in 2 identical Phase III, double-blind, double-dummy, parallel-group studies (NCT01172808 and NCT01172821). Patients received tiotropium 2.5 μg or 5 μg or placebo (all doses via Respimat® Soft Mist™ Inhaler). A salmeterol arm (active comparator) was included with no inferential analysis. Key inclusion criteria included a prebronchodilator FEV1 60–90% of predicted and ACQ score ≥1.5. A pre-planned pooled analysis was performed for ACQ responder rate, a co-primary end point; responders were defined as ACQ improvement >0.5 at 24 weeks.

Results: Baseline characteristics in patients were similar across both trials and all treatment groups. Mean baseline ACQ total score was 2.18 (SD 0.49). Both doses of tiotropium significantly improved the ACQ responder rate at 24 weeks compared with placebo (299/518 responders; 57.7%): tiotropium 2.5 μg, 332/515 (64.5%; p = 0.03); tiotropium 5 μg, 330/513 (64.3%; p = 0.03); salmeterol 356/535 (66.5%; p = 0.004).

Conclusion: In patients with symptomatic asthma despite ICS therapy, the addition of once-daily tiotropium provided a statistically significant and clinically relevant improvement in asthma control. A similar ACQ responder rate was observed with tiotropium (2.5 μg and 5 μg) and the active comparator salmeterol.
FOLLOWING HOSPITAL PRESENTATION WITH A WHEEZING EXACERBATION, CHILDREN WITH A PARENTAL HISTORY OF ASTHMA OR ALLERGIES HAVE INCREASED RECURRENCE OF HUMAN RHINOVIRUS (HRV)

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Introduction: Human rhinovirus (HRV), and particularly HRV species C, is the most common cause of acute wheezing episodes in children presenting to hospital. It is unclear whether children wheezing with HRV are more susceptible to respiratory viruses.

Aim: To determine whether children presenting to hospital with a wheezing exacerbation and HRV, HRV-A or HRV-C have an increased rate of recurrent viral detections, particularly with HRV, and whether familial respiratory history plays a role.

Methods: Children presenting to hospital with acute wheeze were prospectively recruited and tested for respiratory viruses. Further data on viruses detected in respiratory samples assessed longitudinally from May 1997 through to December 2012 were obtained from hospital microbiology records. This was supplemented with HRV testing on hospital respiratory samples retrieved from September 2009 to December 2012. Parental respiratory history was defined as either parent with reported asthma and/or allergic disease.

Results: Children with an acute wheezing episode (n = 373, 0–16 years) had HRV detected in 69.2% of samples at recruitment and HRV-C was the most common of the HRV species (65.5%). Children with a parental history and an HRV-associated wheezing exacerbation at recruitment, had a 14-fold increased incidence rate ratio (IRR) of later HRV detection (IRR 14.0, 95%CI 1.1–5.1, p = 0.010) compared with those that did not have HRV at recruitment. Acute wheezing with HRV-A at recruitment was also associated with an increased rate of recurrent HRV detections (IRR 2.4, 95%CI 1.1–5.1, p = 0.028) in children predisposed to asthma or allergies.

Conclusion: Children with an asthmatic or atopic predisposition and an HRV-related wheezing exacerbation that warranted presentation to hospital were more likely to have subsequent HRV detection in a hospital setting, and thus may be inherently more susceptible to HRV-related respiratory illnesses.

THE ROLE OF MATERNAL OBESITY IN SUSCEPTIBILITY TO RESPIRATORY VIRAL INFECTION AND EXACERBATION RATE IN PREGNANT WOMEN WITH ASTHMA

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Introduction: Obesity may be a risk factor for exacerbations of asthma, but the mechanisms of this effect in pregnancy are unknown.

Aim: To determine the influence of maternal body mass index (BMI) on the risk of asthma exacerbations during pregnancy, and investigate the role of respiratory viral infection.

Method: Women with asthma (n = 164) participated in a prospective cohort study of viral infection and asthma exacerbations during pregnancy. BMI was recorded at baseline (17 weeks gestation) and categorized as healthy weight (18.5–24.9), overweight (25–29.9) or obese (>30). Exacerbations requiring medical intervention were recorded prospectively. Asthma control (ACQ7), inhaled corticosteroid (ICS) use, exhaled nitric oxide (FENO), lung function and common colds were assessed at monthly visits, and additional visits were attended during colds and asthma exacerbations. Nasal and throat swabs were collected during suspected viral infections and viruses determined by PCR.

Results: Women who were overweight or obese had a higher prevalence of exacerbations during pregnancy (49.5%) than healthy weight women (25%, P = 0.007). ACQ during exacerbation was higher in overweight/obese women (median 2.14) than in healthy weight women (1.69, P = 0.025). FENO during first exacerbation was a median of 13.4 (IQR 8.2, 39.2) in the healthy weight group (n = 8), 19.9 (9.5, 34.1) in the overweight group (n = 22) and 8.8 (6, 20) in the obese group (n = 27, P = 0.1083). Overweight/obese women were more likely to have exacerbations associated with PCR positive respiratory viral infections (24.7%) than healthy weight women (8.3%, P = 0.284). Excess weight gain was not associated with exacerbation risk.

Conclusion: Being overweight/obese confers a greater risk of asthma exacerbation during pregnancy, and may be due to increased susceptibility to viral infection. Further studies are required to confirm these findings and determine the mechanisms involved.
EXHALED NITRIC OXIDE MEASUREMENT: INTER-INSTRUMENT VARIABILITY AND IMPLICATIONS ON TESTS INTERPRETATION

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Introduction: Differences in measurement of fractional exhaled nitric oxide (FeNO) between instruments is well documented. However the clinical implications of these differences using the 2011 ATS FeNO interpretation guidelines has not been described.1

Aims: To document inter-instrument variability in FeNO measurements from 3 devices. Secondly, to investigate the implications of this variability on how test results are interpreted in an adult clinical cohort.

Method: Paired FeNO measurement comparisons between NIOX MINO instruments and both Ecomedics model CLD88 (comparison A) and Sievers NOA 280 (B) systems were performed. ATS cut-point criteria of 25 ppb and 50 ppb for FeNO interpretation were applied to test results.1 The diagnostic performance of the MINO in correctly identifying abnormal FeNO results was calculated using the Ecomedics and Sievers systems as the standard. Results are expressed as mean (SD). Results: Ninety-four adults (18 M:76 F) with MINO FeNO range of 5–98 ppb were assessed for comparison A and average difference was small at 0.2 (8.8)ppb. MINO interpretation agreement between systems was 94.7% using both cut-points. Comparison B comprised 73 adults (33 M:40 F) with MINO FeNO range of 5–131 ppb and the MINO tended to have lower FeNO values with difference of 8.8 (9.6) ppb. Interpretation agreement for this comparison was 87.7% using both cut-points. For both comparisons there was strong co-linearity across the FeNO ranges with simple linear correction (A: Y = 1.16x–3.81. R² = 0.89, p < 0.01. B: Y = 1.25x–0.733. R² = 0.97, p < 0.01) enabling precise correction to inter-instrument differences.

Conclusions: FeNO measurements from the hand-held MINO device compare favourably with more expensive chemi-luminescence analysers. Inter-instrument differences resulted in 7% (12 of 167 subjects) misclassification rate for clinical interpretation. Simple corrections can be reliably applied to make comparable instrument readings.

Key words: nitric oxide, FeNO, airway inflammation, asthma, eosinophils.

Reference:
1. American Thoracic Society, AJRCCM, 2011; 184:602–15.

ENVIRONMENTAL TOBACCO SMOKE EXPOSURE INCREASES SUSCEPTIBILITY FOR HUMAN RHINOVIRUS SPECIES A INFECTION IN ACUTE ASTHMATIC CHILDREN

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Introduction: Respiratory viral infection (RVI), particularly by human rhinovirus (HRV), and environmental tobacco smoke exposure (ETS) are common causes of asthma exacerbation. It is essential that inhaled toxic substances associated with ETS are detoxified to minimize their potential harmful effects. The glutathione defence system is crucial in this regard. We hypothesized that variations in the glutathione genes may influence an individual’s ability to detoxify pollutants leading to susceptibility to RVI, such as HRV, and subsequently to asthma exacerbation.

Aim: Variants in the glutathione genes, GSTT1 and GSTM1, in combination with ETS exposure are examined to determine their effect on respiratory viral infection.

Method: Children with acute asthma (n = 476, 60.3% male, age 0–16 years), presenting to Emergency Department were studied. The presence/absence of the genes were determined by PCR. ETS exposure was determined by questionnaire, which was validated by measuring urinary cotinine levels in a subset of children. RVI to 6 common respiratory pathogens was determined and HRV species were typed using molecular methods.

Results: In total, 88.4% (n = 342) of the tested children had a RVI and 35.7% (n = 133) were exposed to smoke. Of these children, 26.1% and 50% were infected by HRV-A and HRV-C, respectively. Children with the GSTT1 or and GSTM1 genes and exposed to ETS were more likely to be infected by HRV-A (OR = 2.44, 95%CI 1.14–5.23, p = 0.022; OR = 5.00, 95%CI 1.67–14.92, p = 0.004, respectively, and combined OR = 5.54, 95%CI 1.63–18.90, p = 0.006) than by HRV-C. This pattern remained consistent when examining smoke exposure by mother and father separately.

Conclusion: The presence of GSTT1 and GSTM1 genes may lead to increased susceptibility to HRV-A in ETS-exposed asthmatic children.

INFLAMMATORY PHENOTYPES AND AIRWAY NARROWING IN ASTHMA

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Background: Airway wall remodelling and mechanisms of airway narrowing may differ between different inflammatory phenotypes of asthma.

Aim: To compare airway wall dimensions, airway smooth muscle (ASM) cell size and number, percent muscle shortening (PMS), mucus occupying ratio (MOR) and mucus gland area in cases of asthma (fatal and nonfatal) with paucigranulocytic inflammation (PG, n = 37), eosinophilic (Eos, n = 12), neutrophilic (Neu, n = 7) mixed eosinophilic and neutrophilic (Mixed, n = 18) and control subjects (Co, n = 48).

Methods: On sections of airway (H&E, 5 µm) taken from post-mortem lungs, airway wall dimensions, PMS, MOR and the area densities of eosinophils and neutrophils within the inner airway wall were estimated. Cut-offs of mean eosinophil and/or neutrophil density of more/less than 5 cells/mm² were used to categorize cases of asthma as above. On contiguous 30 µm sections stained with haematoxylin, ASM cell size and number were determined using stereological techniques.

Results: There were no significant differences in duration, age of onset of asthma or smoking history between case groups, however PG had less numbers of fatal asthma cases (p < 0.05) than other asthma groups. The reticular basement membrane thickness was significantly increased in Eos, Neu and Mixed groups compared with Co (p < 0.05). The thickness of the ASM layer was significantly increased in large airways from all asthma groups compared with Co (p < 0.05). ASM cell number per mm of airway was increased in Eos and Mixed compared with Co (p < 0.05). MOR was increased in Eos and Mixed compared with Co and PG cases. PG cases had increased gland area compared with Co (p < 0.05). These finding were similar when fatal asthma cases were analysed separately.

Conclusion: ASM hyperplasia and increased luminal mucus may contribute to airway narrowing in asthma and appear to be related to eosinophilic airway inflammation.

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THE EFFECT OF ASThma ON THE PERIMETER OF THE AIRWAY BASEMENT MEMBRANE

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Background: When comparing airways cut in cross-section, the perimeter of the basement membrane (Pbm) is used as a marker of airway size as it is constant despite airway smooth muscle shortening or airway collapse. The extent to which remodelling of the basement membrane perimeter occurs in asthma is thought to be small but has not been quantified.

Aim: To compare the Pbm from post-mortem lungs from asthma cases (n = 57) and control subjects (n = 31) from the same anatomical site within the lung.

Methods: A stratified technique was used to sample the axial airways from the apical segment of the left upper lobe and the anterior and basal segments of the left lower lobe. Nine equidistant sections (‘generations’) of airways were taken from each lobe ranging from cartilaginous bronchi to terminal bronchioles. The Pbm (mm) was measured on cross-sections of airway stained with haematoxylin and eosin. Multiple linear regression analysis used Pbm as the dependent variable and gender, age, height, lobe, airway generation and history of asthma were included as independent variables with subject entered as a random effect.

Results: Pbm was not significantly related to Pbm and was removed from subsequent analysis. The final model showed that Pbm was related to height (0.037/cm), airway generation (2.98/generation), subject (0.013) gender (-0.835 for female) (all p < 0.001), and age (0.020/year, p < 0.05). The coefficient for having asthma was -0.49, that is, in the airways of asthma cases the Pbm would be approximately 0.5 mm shorter than similar airways in control subjects.

Conclusion: Asthma is associated with remodelling of the Pbm. This could contribute to an over-estimation of wall thickness in asthma when comparing airways of similar Pbm in control cases. However the effect is small and would not account for published differences in wall area observed in cases of asthma.

GALECTIN 3 AND GALECTIN 3 BINDING PROTEIN IN ASTHMA INFLAMMATORY SUBTYPES

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Introduction: Galectin-3 (Gal-3) is a member of the galectin family of β-galactoside-binding animal lectins which function in a variety of biological processes including inflammation. It is unclear if Gal-3 has anti- or pro-inflammatory roles in asthma. The aim of this study was to examine the expression of Gal-3 and Gal-3 binding protein (BP) in adults with difficult asthma, in relation to their inflammatory subtype.

Methods: Participants (n = 80) with uncontrolled (ACQ > 0.7), treated asthma underwent clinical assessment and sputum induction. Sputum was dispersed using dithiotreitol and cytospin slides were prepared. Cell viability and differential cell counts were recorded. Gal-3 and Gal-3BP were measured in sputum supernatant by ELISA and assessed in sputum cells using immunocytochemistry. Eosinophilic asthma was defined as sputum eosinophils ≥3%, Neutrophilic asthma as sputum neutrophils ≥61% and Paucigranulocytic asthma as sputum eosinophils <3% and neutrophils <61%.

Results: Sputum Gal-3 (median, quartile1, quartile3) was significantly reduced in neutrophilic asthma (183 ng/mL (91, 287)) compared with eosinophilic (293 ng/mL (188, 471)) P = 0.021 and paucigranulocytic asthma (399 ng/mL (213, 514)) P = 0.004 while Gal-3BP was significantly elevated in neutrophilic asthma (103 ng/mL (74, 164)) compared with eosinophilic (53 ng/mL (17, 117)) P = 0.007 and paucigranulocytic asthma (58 ng/mL (19, 158)) P = 0.093. Gal-3 and Gal-3BP expression was present in airway macrophages. Gal-3BP was significantly associated with airway neutrophil, macrophage and lymphocyte proportions (r = 0.371 P = 0.001, r = 0.368 P < 0.001 and r = 0.254 P = 0.025, respectively).

Conclusions: Increased Gal-3BP and reduced Gal-3 suggest that Gal-3 activity may be reduced in neutrophilic asthma. Loss of Gal-3 anti-inflammatory function in neutrophilic asthma may contribute to the inflammatory imbalance occurring in this asthma phenotype.

REDUCED ANTI-VIRAL INNATE IMMUNITY IN PATIENTS WITH SEVERE ASTHMA IS ASSOCIATED WITH NEUTROPHILIC INFLAMMATION AND HIGH DOSE INHALED STEROIDS

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Rationale: People with asthma are prone to viral respiratory infections and this has been linked to immune dysfunction. Though phenotypic heterogeneity is increasingly recognized in asthma, it is not clear whether impaired anti-viral immunity is present in all asthmatics, or only a subset. This study examined the hypothesis that immune dysfunction in asthma varies across different inflammatory phenotypes.

Methods: Inmate immune responses to human rhinoviruses were examined in 85 adults with poorly controlled asthma (mean age 59 years, 63% female, mean Asthma Control Questionnaire (ACQ)-6 score = 1.7 ± 0.8). Blood mononuclear cells were cultured with two strains of HRV and cytokines measured by ELISA. Inflammatory phenotypes were characterized using induced sputum as eosinophilic (sputum eosinophils ≥3%), neutrophilic (sputum neutrophils >61%), paucigranulocytic (sputum eosinophils <3% and sputum neutrophils <61%) and mixed granulocytic (sputum eosinophils ≥3% and sputum neutrophils >61%).

Results: Human rhinovirus stimulated IFNγ release (n; median (q1, q3) pg/ml; P value) at 24 h was significantly lower in those with neutrophilic asthma (n = 12; 55.2 (22.4, 265) pg/ml), than in those with either eosinophilic (n = 35; 606 (281,111) pg/ml; P < 0.01) or paucigranulocytic asthma (n = 35; 437 (212,1000) pg/ml; P < 0.01) and not different to those with mixed granulocytic asthma (n = 4; 61.4 (36,0,84) pg/ml; P = 0.804). HRV-stimulated IL-1β, IL-6 and IL-8 synthesis did not vary across asthma phenotypes. Basal (unstimulated) release of IL-1β and IL-8 was correlated with ACQ scores across all patients. Multivariate analysis demonstrated HRV stimulated IFNγ release was independently correlated with sputum neutrophil proportion and inhaled corticosteroid dose but not age, gender, smoking status, FEV1% predicted or ACQ-6.

Conclusions: In asthma anti-viral innate immune dysfunction is evident in responses from patients with neutrophilic asthma. The ability of inhaled corticosteroids to impair important innate immune responses requires further attention and study. The extent to which this predicts subsequent risk of infections and asthma exacerbations remains to be determined.
A MATRIKINE ABSENT IN ASTHMATIC AIRWAYS ALTERS THE ECM DEPOSITED BY AIRWAY SMOOTH MUSCLE CELLS, REDUCING THE ANGIGENIC POTENTIAL OF THE MICROENVIRONMENT

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Introduction: The altered composition of the extracellular matrix (ECM) in the asthmatic airway may result from an imbalance in the levels of matrixkines, endogenous proteases and their inhibitors. There is also uncontrolled vascular remodelling, with an increased number, size and density of blood vessels within the asthmatic airway wall. Tumstatin is a matricine derived from collagen IV, previously reported to be significantly reduced in the asthmatic airway tissue. Tumstatin possesses anti-angiogenic activity by interfering with the integrin signalling of endothelial cells.

Aim: To investigate additional indirect angioregulatory roles of tumstatin in the asthmatic airway.

Method: Primary human airway smooth muscle cells (ASMCs) from people without asthma were stimulated for 24 hr with 50 μg/mL recombinant human tumstatin and gene expression was assessed using a RT-PCR ECM array. The activity of human umbilical vascular endothelial cells (HUVECs) when seeded on the ASMC-derived ECM was examined using toluidine blue staining to quantify adhesion; transwell migration through boyden chambers; and metabolic activity by MTT.

Results: Following 24 hr treatment with tumstatin, ASMCs showed an increase in matrix metalloproteinase 1 (MMP1; N = 7, P < 0.05), and MMP10 (N = 8, P < 0.05) gene expression. The ECM deposited by tumstatin-treated ASMCs induced greater adhesion of HUVECs after 30 min (N = 3, P < 0.05) and inhibited HUVEC migration after 4 hr (N = 3, P < 0.05), but had no effect on the metabolic activity of HUVECs seeded onto this matrix for 72 hr (N = 3, P > 0.05).

Conclusion: Tumstatin alters the angiogenic functional patterning of the ECM via enhanced proteolytic activity with ASMCs. An alteration in tumstatin expression or activity in the airway may contribute to changes in composition and arrangement of the ECM, and increased vasculature seen in the airways of people with asthma.

Funding: Asthma Foundation NSW, NH&MRC.

OBESITY IS ASSOCIATED WITH BRONCHIAL HYPER-RESPONSIVENESS BUT THE ASSOCIATION IS INFLUENCED BY HOW OBESITY IS ASSESSED

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Aim: Bronchial hyper-responsiveness (BHR) and obesity are asthma risk factors but studies of obesity-BHR relationships have produced conflicting results. We hypothesized that the method of assessing obesity might influence such findings. Using Tasmanian Longitudinal Health Study (TAHS) data, we examined obesity and BHR in middle-age using three obesity measures.

Method: TAHS began in 1968 when 99% (n = 8,583) of all 7-year old Tasmanian school-children were enrolled. In 2010, a stratified sub-sample (n = 836) was re-surveyed by questionnaire and clinical study. A standard protocol methacholine bronchial challenge test was conducted. BHR was defined as a PDE20 < 2 mg methacholine, BMI, waist circumference (WC), and waist-to-hip ratio (WHR) assessed obesity. Logistic regression computed odds ratios for BHR, adjusting for sex, smoking, atopy, and childhood BMI. To avoid potential confounding by asthma, analysis was restricted to asthma-free participants (n = 303). For interactions with a p-value <0.1, stratum-specific estimates were computed.

Results: BHR prevalence (weighted) was 9.7% (95% CI 5.1–14.4%) with no sex difference. For females, each kg/m² increase in BMI was associated with BHR (OR = 1.22; 95% CI 1.09–1.37, p < 0.001) but not for males (OR = 1.05; 0.90–1.21, p = 0.536). BMI > 30 kg/m² was associated with BHR (OR = 7.83; 1.70–36.0, p = 0.008) in females but not males (OR = 1.16; 0.21–6.26, p = 0.867). Overweight (25 < BMI < 30 kg/m²) in women was weakly associated with BHR (OR = 3.82; 0.92–15.9, p = 0.066) but not associated in men (OR = 0.60; 0.12–2.87, p = 0.52). Greatly increased WC was associated with BHR in women (OR = 4.05; 1.03–15.96, p = 0.046) but not in men (OR = 2.35; 0.48–11.51, p = 0.292). WHR was not associated with BHR (OR = 1.04; 0.98–1.11, p = 0.219).

Conclusion: BMI and WC were associated with BHR in non-asthmatic middle-aged women but not men. No association was found between WHR and BHR suggesting that obesity measurement could influence findings in association studies.

Grant Support: NHMRC, Clifford Craig Medical Research Trust, Royal Hobart Hospital Research Foundation, Victorian, Queensland & Tasmanian Asthma Foundations.

Conflict of Interest: None.
**TP 079**

**SELF-IDENTIFIED WELL CONTROLLED ASTHMA AND SUB-OPTIMAL ASTHMA CONTROL TEST**

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**Introduction:** Several surveys have identified patients who self-identify their asthma control as well controlled however score poorly on the Asthma Control Test (ACT).

**Aim:** To characterize this group of asthma sufferers with disparate measurements of asthma control.

**Methods:** An online survey was conducted of people aged >15 with health-professional diagnosed asthma and symptoms or asthma treatment in the past year. The sample was weighted to the New Zealand asthma population by age, gender and region. Using the ACT, asthma control was categorized as well controlled (WC) (20–25), not well controlled (16–19) or very poorly controlled <16. That was correlated to the participants’ self-estimated level of control.

**Results:** A total of 537 asthma sufferers participated in the survey. Respondents who had self-perceived ‘well’ or ‘completely controlled’ asthma but ‘not well controlled’ or ‘very poorly controlled’ asthma on ACT were the index group (n = 114/537; 21%). Compared to all other participants, more identified as Maori (24.5% vs 14.9%), fewer had post-graduate education (3.7% vs 11.1%), less had private insurance (19.6% vs 31.4%) and more were current smokers (28.4% vs 17.0%). This group reported higher reliever use (97.4% vs 91.0%), preventer use (56.3% vs 48.0%), combination medication (38.6% vs 28.2%) and symptom controller use (20.9% vs 7.0%). They were more likely to have discussed asthma with a health professional in the last 12 months, follow a written asthma action plan (37.0% vs 15.5%) and always use a spacer (54.1% vs 25.0%).

**Conclusions:** Participants who felt that their asthma was well controlled despite being not well controlled according to the Asthma Control Test were prescribed more medication and more had management plans. This may suggest that health care providers have identified this asthma group and managed them according to the current guidelines.

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**TP 080**

**WHO DECIDES WHOSE ASTHMA IS CONTROLLED—IS GINA TOO STRICT?**

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Canterbury District Health Board

**Introduction:** Several surveys have identified patients with asthma who self-identify their asthma as well controlled, however score poorly on the Asthma Control Test (ACT).

**Aim:** To identify this group of asthma sufferers who have disparate measures of asthma control. This group perceives their asthma as well controlled despite a low ACT score suggesting not well controlled asthma. We explore this group investigating other markers of quality of life.

**Methods:** An online survey was conducted of people aged >15 with health professional diagnosed asthma and symptoms or asthma treatment in the past year. The sample was weighted to the New Zealand asthma population by age, gender and region. Using the ACT, asthma control was categorized as well controlled (WC) (20–25), not well controlled (16–19) or very poorly controlled <16. The participants self estimated level of asthma control and other measures of quality of life were explored in this group and correlated to the ACT measurements.

**Results:** A total of 537 asthma sufferers participated in the survey. Respondents who had self-perceived ‘well’ or ‘completely controlled’ asthma but ‘not well controlled’ or ‘very poorly controlled’ asthma on ACT were the index group (n = 114/537; 21%). Compared to all other participants there was no significant difference between this group and the rest of the participants in terms of feeling healthy, having enough energy, wanting to be healthy and do things that were best for their health and having health consistent with their life goals.

**Conclusion:** This survey opens the discussion on who determines what is well controlled asthma—the patient or the health care professional. What are we treating if participants score well in measurements of quality of life? Are we ‘creating illness’ by applying the ACT and following strict guidelines?

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**TP 081**

**MAIN RESULTS FROM THE THIRD ECRHS IN MELBOURNE**

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**Introduction:** The European Community Respiratory Health Survey (ECRHS) is the largest international study of lung health in young and middle aged adults.

**Aim:** To describe changes in chronic respiratory diseases and symptom prevalence in adults as they age.

**Methods:** 876 young adults participated in ECRHS in Melbourne in 1992. Of 722 eligible surviving subjects, 550 (76.2%) completed postal or telephone screening questionnaires in 2012. 451 were invited for clinical testing including an interviewer-administered questionnaire (main questionnaire), asking about symptoms, treatment, and health service utilization for respiratory disease. 271 main questionnaires (MQs) were analysed.

**Results:** Of the 271 subjects, 139 (51.3%) were female. The mean (SD) age was 56 (6.0) years. The most common respiratory symptoms reported were shortness of breath after exertion 114 (42.1%), wheezing 75 (27.7%), nocturnal cough 80 (29.5%), chest tightness 41 (15.1%), nocturnal shortness of breath 27 (10.0%), daytime cough 46 (17.0%), productive cough 23 (8.5%), shortness of breath at rest 27 (10.0%) and morning cough 23 (8.5%). There were no significant differences in respiratory symptoms between sexes. Doctor diagnosed asthma was reported by 80 (29.5 %); 28 (10.3%) reported an attack within the last 12 months and 29 (10.7%) were taking medication for asthma. Chronic bronchitis was reported by 31 (11.4%), three reported emphysema and two COPD. Short acting beta agonists (SABA) were used by 45 (16.6%) and combination (LABA/steroid) inhalers by 27 (10.0%).

**Conclusions:** The cohort remains symptomatic, although most have not been diagnosed or treated. Longitudinal analysis of the complete data will be conducted to determine whether there have been changes in the prevalence of respiratory symptoms or diseases over 20 years.

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**TP 082**

**AN AUDIT OF SERIAL SPIROMETRY IN A COHORT OF FABRY’S DISEASE PATIENTS WITH OR WITHOUT ENZYME REPLACEMENT THERAPY**

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**Introduction:** Fabry’s Disease or Anderson-Fabry Disease is a rare X-linked inherited lysosomal storage disease. It is a result of deficiency of alpha galactosidase A, which results in the accumulation of globotriaosylceramide. It predominantly results in small vessel disease within the heart, kidney and nerve tissues. It is thought that globotriaosylceramide accumulates in airway smooth muscle resulting in airflow obstruction. Previous studies have shown worsening obstruction over time without treatment, and the stabilization of spirometric obstruction with enzyme replacement.

**Aim:** To assess if there is worsening of airflow obstruction with time in patients with Fabry’s Disease. To assess if there is a reduction in progression of airflow obstruction with enzyme replacement.

**Method:** We obtained serial spirometry results for 24 patients under regular review within our institute. 19 of those patients were on enzyme replacement therapy, 5 were not. Changes in spirometry were analysed statistically.

**Results:** There was no significant difference in FEV1 and FVC over time between the treated and untreated groups. This is likely accounted for by the small number of patients within the non-treatment group. There was a significant difference in decline in FEV1 when comparing age, those below the age of 35 versus those above 35. In one case, there was improvement from severe airflow obstruction back to within normal limits with initiation of enzyme replacement.

**Conclusions:** Within this cohort, it appears that there is worsening of airflow obstruction with age. There appears to be some reduction in the rate of obstruction progression with enzyme replacement, however this was not significant. Enzyme replacement at a younger age appears to be more effective at stabilizing airflow obstruction and in some cases can improve spirometric values.

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Indoor allergens and built environment factors have been associated with an increased risk of child asthma hospital admissions but their relevance to repeat admissions has been investigated seldomly. We conducted a case control study to explore the role of indoor and outdoor factors of the built environment and lifestyle characteristics on child asthma repeat admissions.

### Method

Our study included 29 children who had one admission only and 25 children who had a repeat admission within 13 weeks of their index admission to hospital for asthma. We measured indoor allergen, fungal levels and air quality in the bedrooms and living areas of the participants. We also surveyed home and school indoor and outdoor characteristics. To assess the factors that increased risk of re-admission we calculated odds ratios (OR) and 95% confidence intervals (CI) while adjusting (aOR) for each other and for gender, age and virus infection at index admission.

### Results

- Increased odds of readmission were associated with higher levels of airborne yeast in the child's bedroom $aOR \text{1.65 (1.02, 2.68, } p = 0.041)$, higher levels of airborne Cladosporium in the child's bedroom $aOR \text{1.57 (0.90, 2.74, } p = 0.11)$; and increased vacuuming frequency in the child's home $aOR \text{12.16 (2.58, 57.42, } p = 0.002)$, particularly for vacuums with a bag dust collector.

### Conclusion

The indoor environment, particularly factors in children's bedrooms, plays an important role in increasing the risk of repeat hospital admission for asthma. Further investigation is warranted.

### Key words:

- asthma, hospital, child, indoor air quality, fungi, vacuum.

### Grant Support:

L.E.W. Carty Charitable Fund.

### Conflict of Interest:

All the authors report that they have no conflict of interest.

### Introduction and Aim

Research indicates that Indian parents of children with asthma lack clear understanding of asthma and have low self-management competence. The aim of the study was to design and evaluate an asthma education programme for Indian children and parents based on asthma education and self-management.

### Methods

A parallel group repeated measures pilot study was conducted with tertiary hospital outpatient clinic's paediatric patients in New Delhi, India. The participants were randomized into two groups (usual care and test group). In the test group, an audio-visual education session was conducted with the parent/child pair and a child-friendly workbook was provided to the child (Hindi/English). Goal setting and action plan provision followed. In the usual care group, parents and children were given a standard information pack and asked to obtain an action plan as they moved on to see their doctor for a 'usual visit'. Baseline measures were repeated at 1 and 6 months for a within group and between groups statistical comparison in key outcomes PACQLQ, 1st outcome, ACQ 0, knowledge, action plan ownership, goal achievement and medication use.

### Results

- 20 parent-child pairs were recruited in each group, with 100% retention at study completion. Positive outcomes were obtained for the test group as compared to the control group in terms of improved: PACQLQ scores, ($\Delta 1.13 \text{ vs } 0.44, p = < 0.001$), asthma control ($\Delta 21.92 \text{ vs } 0, p = < 0.001$), and asthma knowledge ($\Delta 2.92 \text{ vs } 0, p = < 0.001$). The test group had 100% action plan ownership. 70 goals were set and achieved by test group children by the end of the study.

### Discussion

Asthma education programmes designed with a sound pedagogical approach, that include the parent in the session together with the child, and which offer self-management skills are effective in improving asthma management and patient outcomes.

### Conflict of Interest:

None.
THE ROLE OF T-BET IN THE PERIPHERAL BLOOD OF SARCOIDOSIS PATIENTS

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Introduction: Sarcoidosis is a multi-systemic granulomatous disease of unknown aetiology. It is often termed an immune paradox as there is peripheral anergy with a reduced delayed-type hypersensitivity to common antigens, despite exaggerated inflammation at disease sites. The inflammation at these sites is TH1 dominated, which is characterized by IFNγ despite exaggerated inflammation at disease sites. The inflammation at these anergy with a reduced delayed-type hypersensitivity to common antigens, which may help explain part of the phenomenon of peripheral anergy associated with sarcoidosis.

Methods: PBMCs were isolated from patients with sarcoidosis and controls by Ficoll separation. Total RNA and total protein was extracted from PBMCs using TRIzol and a cell lysis buffer respectively. IFNγ and T-bet mRNA were measured using quantitative real-time PCR. IFNγ protein was measured by ELISA while T-bet was quantitated by western blotting.

Results: See table. Parametric results are presented as mean ± SD while non-parametric results are presented as median (range).

|                          | Controls | Patients | p-value |
|--------------------------|----------|----------|---------|
| IFNγ mRNA expression relative to HPRT | 0.22 (0.10,0.99), n = 18 | 0.24 (0.067,0.66), n = 16 | p = 0.68 |
| IFNγ protein expression | 0.43 ± 0.075, n = 15 | 0.40 ± 0.059 n = 15 | p = 0.74 |
| T-bet mRNA expression relative to HPRT | 6.6 ± 0.84, n = 18 | 3.9 ± 0.45, n = 15 | p = 0.010 (<0.05) |
| T-bet protein expression | 1.3 ± 0.075, n = 17 | 0.93 ± 0.093, n = 17 | p = 0.0043 (<0.05) |

Conclusion: Decreased expression of T-bet in PBMCs of patients compared to healthy controls may be maintaining the peripheral IFNγ expression levels at normal levels. Depressed T-bet expression levels in PBMC of sarcoidosis patients may help explain part of the phenomenon of peripheral anergy associated with sarcoidosis.

Conflict of Interest: No.

IL-27 MRNA AND PROTEIN EXPRESSION IN THE PERIPHERAL BLOOD OF SARCOIDOSIS PATIENTS

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Introduction: Sarcoidosis is a systemic non-caseating granulomatous disease characterized by peripheral anergy to common recall antigens but exaggerated CD4+ TH1 responses at sites of disease. This local disease is largely mediated by cytokines which play a crucial role in initiating and perpetuating inflammation. IL-27 is a heterodimeric cytokine structurally related to IL-12 and has been shown to direct naïve CD4+ T-cells into the TH1 subset by inducing IL12βR. IL-12 then acts on IL12βR to produce IFNγ, the canonical TH1 cytokine. Recently, IL-27 has been increasingly considered as an attenuator of inflammatory responses, repressing cytokine production from activated T lymphocytes. This study aimed to investigate the expression of IL-27 mRNA and protein in PBMCs and plasma of sarcoidosis patients.

Methods: PBMCs were isolated from whole blood by Ficoll density gradient centrifugation. Total RNA was extracted from PBMCs of sarcoidosis patients and healthy controls using TRIzol and IL-27 mRNA expression measured using quantitative real-time PCR with HPRT as a reference control. Plasma IL-27 protein was measured by ELISA in 100 µl aliquots in sarcoidosis patients and healthy controls.

Results: See table. Results are presented as median (range).

|                          | Controls | Patients | p-value |
|--------------------------|----------|----------|---------|
| IL-27 mRNA expression relative to HPRT | 0.029 (0.0020–0.10) | 0.1125 (0.012–0.60) | 0.0019 (0.0020–0.10) |
| IL-27 protein expression (pg/ml) | 631 (113–12142) | 579 (16–12660) | 0.94 |

Conclusion: The inconsistency between the IL-27 mRNA and protein expression levels in sarcoidosis could be due to the short in vivo half-life of IL-27. Nevertheless, increased expression of IL-27 mRNA in PBMCs of patients compared to healthy controls suggests that IL-27 may have a role in the sarcoidosis immunopathogenesis and may be implicated in sarcoid-associated peripheral anergy.

Conflict of Interest: No.
THE ROLE OF MIR-29A IN THE PERIPHERAL ANERGY OF SARCOIDOSIS PATIENTS
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Introduction: Sarcoidosis is a systemic granulomatous disease usually affecting the lungs. It has also been described as an immune paradox with peripheral anergy to common antigens despite exaggerated inflammation at sites of disease. The inflammation at these sites is considered to be T helper-1 (Th1) in nature, characterized by IFNγ production. MicroRNAs are non-coding RNAs that inhibit gene translation. microRNA-29a (miR-29a) has been shown to be down-regulated in IFNγ-producing T cells. This study aimed to investigate the immune paradox by examining the miR-29a expression levels in peripheral blood mononuclear cells (PBMC), juxtaposing these with the miR-29a expression levels in exhaled breath condensate (EBC) of sarcoidosis patients.

Methods: PBMCs were isolated from patients with sarcoidosis and controls by Ficoll separation. Total RNA was extracted using TRIzol and expression of miR-29a was measured using quantitative real-time PCR. Sample input and processing were highly standardized especially when investigating miR-29a expression levels in EBC.

Results: See table. Parametric results were presented as mean ± SD non-parametric results were presented as median (range).

|         | Controls | Patients | p-value |
|---------|----------|----------|---------|
| miR-29a | 16.1     | 16.1     | 0.592   |
| in PBMC | (11.2, 21.6), n = 18 | (10.9, 30.7), n = 17 |         |
| miR-29a | 1.40 ± 0.12 n = 19 | 0.86 ± 0.092 n = 17 | 0.0012  |
| in EBC  | (0.05)    | (0.05)   |         |

Conclusion: miR-29a expression levels were lower in EBC from sarcoidosis patients compared to healthy controls but in PBMCs expression levels were similar. This indicates that the expression of miR-29a at physiological levels may be sufficient to limit the expression of IFNγ. Exaggerated inflammation at disease sites could be explained by a down-regulation of miR-29a. These data suggest that miR-29a expression is a possible mechanism underpinning the peripheral anergy observed in sarcoidosis.

Conflict of Interest: No.

REDUCED MACROPHAGE PHAGOCYTIC HOST RESPONSE TO NTHI IN CHILDREN WITH BRONCHIECTASIS
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Background: Bronchiectasis is prevalent in Northern Territory children (1 in every 68 Indigenous children) and occurs very early in life. Poor or inadequate treatment leads to loss of lung function and subsequent reduction in life expectancy. The disease is associated with ongoing infection, colonization of the lower airway with NTHi and neutrophilic inflammation. We hypothesized that a reduced macrophage host response to infection may contribute to the development of bronchiectasis. We investigated the ability of alveolar macrophages (AM) to phagocytose NTHi. As we have previously found defective AM clearance of apoptotic cells (efferocytosis) in other chronic lung diseases that may contribute to tissue damage and ongoing inflammation, we also assessed efferocytosis and expression of scavenger receptors involved in phagocytosis/efferocytosis.

Methods: 8 controls (mean age 7.8 months) and 35 children with bronchiectasis (mean age 43.5 months) were recruited. Efferocytosis, phagocytosis of NTHi, and expression of mannose receptor, colec12 and scavenger receptor A were assessed by flow cytometry.

Results: A small but significant decrease in the ability of AM to phagocytose either NTHi or apoptotic cells was found in children with bronchiectasis vs control children (NTHi 19% vs 15%; apoptotic cells 20% vs 15%). Reduced expression of MR and SRA was noted in the bronchiectasis group vs controls. There were no significant correlations between % phagocytosis/efferocytosis and age, blood or BAL neutrophilia, CRP, or Indigenous status among children with bronchiectasis.

Conclusions: Ineffective clearance of NTHi or apoptotic cells in children with bronchiectasis may contribute to colonization of the lower airway with NTHi, chronic inflammation and progressive lung damage.

SERUM IL-10 IN PATIENTS WITH SARCOIDOSIS SUPRESSED BY HIGH LEVELS OF FUNGAL EXPOSURE
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Background: Sarcoidosis in an inflammatory disease with increased levels of inflammatory cytokines. Previous studies have shown a relation between the degree of granuloma infiltration and serum cytokine levels, except for interleukin (IL)-10.

Aims: The aim of the study was to further investigate the serum levels of IL-10 in sarcoidosis and relate them to fungal exposure indicators in terms of β-glucan in broncho-alveolar lavage (BAL) fluid and the domestic exposure to fungi. Furthermore the secretion of IL-10 from PBMC stimulated with lipopolysaccharide (LPS) or LPS + chitin was measured.

Methods: Patients with sarcoidosis (n = 60) were enrolled. IL-10 was determined in serum. BAL was performed and the amount of β-glucan was measured. Domestic exposure to fungi was determined by measuring airborne β-N-acetylhexosaminidase (NAHA) in the bedrooms. Blood samples were taken for the isolation of peripheral blood mononuclear cells (PBMC). The cells were challenged with LPS and LPS + chitin and the secretion of TNFα, IL-2R, IL-6, IL-10, and IL-12 was measured.

Results: At high levels of fungal exposure (β-glucan in BAL and domestic fungal exposure), serum IL-10 values were lower than at intermediate exposure levels. The addition of chitin to LPS reduced the secretion of cytokines from PBMC, with the highest depression for IL-10.

Conclusion: The low serum IL-10 values at high fungal exposure and the blocking effect of chitin on the IL10 secretion induced by LPS suggest that fungal cell wall agents play a role in granuloma formation in sarcoidosis by inhibiting the secretion of the anti-inflammatory cytokine IL-10.

Funding: Internal hospital funds only.

Key words: interleukin-10, sarcoidosis, β-glucan, chitin.
INCREASED PERIPHERAL BLOOD PRO-INFLAMMATORY/CYTOTOXIC T AND NKT-LIKE CELLS IN INDIGENOUS CHILDREN WITH BRONCHIECTASIS

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Background: Like chronic obstructive lung disease (COPD) in adults, bronchiectasis (BE) is also a chronic inflammatory lung disease. Thus, systemic inflammation that is present in COPD may also be present in children with BE, especially in Indigenous children where BE is generally more severe and diagnosed later. Co-morbidities such as cardiovascular disease (CVD) that are prevalent in COPD are also the largest cause of death in Indigenous adults and may stem from childhood. We have previously shown increased pro-inflammatory cytokines and granzyme B by CD8+ T cells, NKT-like and NK cells in the peripheral blood and bronchoalveolar lavage (BAL) of adults with COPD and we hypothesized that Indigenous children with BE may show similar findings.

Methods: Intracellular cytotoxic mediators perforin and granzyme B and pro-inflammatory cytokines IFNγ and TNFα were measured in T cell subsets, NKT-like and NK cells from blood and BAL samples from a group of Indigenous children with BE and aged-matched control children using flow cytometry.

Results: There was a significant increase in the percentage of CD8+ T cells and T and NKT-like subsets expressing perforin and granzyme in blood in BE compared with controls (eg, perforin and granzyme B positive CD8+ T-cells (mean ± SEM BE 34 ± 3.5(9 ± 1.7) vs Control 20 ± 4.7(5 ± 1.8)). There was a significant increase in the percentage of T and NKT-like subsets (trend for NK cells) producing IFNγ and TNFα in BE compared with controls (eg, % T cells producing IFNγ and TNFα (mean ± SEM BE 35 ± 4.9(11 ± 2.5) vs Control 39 ± 4.2(21 ± 3.2)) There was no change in any of these mediators in BAL.

Conclusions: Bronchiectasis in Indigenous Australian children is associated with increased systemic pro-inflammatory/cytotoxic T and NKT-like cells in the peripheral blood. Strategies that target these pro-inflammatory/cytotoxic cells could reduce potential future co-morbidities in these patients that may be linked to systemic inflammation.

HUMAN NEUTROPHIL ELASTASE ACTIVITY AND MATRIX METALLOPROTEINASE ACTIVITY ARE MARKERS OF DISEASE SEVERITY IN NON-CF BRONCHIECTASIS

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Aim: Bronchiectasis is an airway condition characterized by irreversible airway dilatation thought to be the end result of airway mucosal damage resulting from a range of potential insults. While the underlying aetiology and the cellular and molecular mechanisms that drive disease progression are unclear, host-derived proteases could be important contributors. This project aimed to characterize the link between protease activities and clinical markers of disease severity in non-CF bronchiectasis subjects enrolled in the BLESS study of low-dose erythromycin.

Method: Induced sputum samples were collected from subjects with non-CF bronchiectasis (n = 100) and normal healthy controls (n = 20). All control subjects and a subset of non-smoking, idiopathic bronchiectasis subjects (n = 34) underwent bronchoscopy with endobronchial biopsy. Protease activities and gene expression were determined. A subgroup of patients with non-CF bronchiectasis (n = 37) was re-sampled after 48 weeks to monitor changes in protease activities.

Results: Human neutrophil elastase activity (NE) and matrix metalloproteinase activity (MMP) were elevated in induced sputum from bronchiectasis vs healthy individuals by >200-fold and ~140-fold, respectively (p < 0.001). Significant correlations were seen between protease activity and culture of pathogenic organisms in sputum, serum CRP, lower lung function, and IL-1β and IL-8 concentration in sputum (r 0.64–0.85, all p < 0.001). Airway biopsies from bronchiectasis subjects showed significantly higher expression of genes encoding MMP7 (~5-fold, p < 0.001), but not MMP9 or MMP10. The incidence of pulmonary exacerbations in the 12 months following sampling was not predicted by baseline levels of NE or MMP. Levels of protease activities remained similar after 48 weeks (r = 0.74 and r = 0.68 for NE and MMP, respectively (p < 0.001).

Conclusion: Adult subjects with non-CF bronchiectasis have substantial elevations of activity levels of the potent proteases MMP and NE. These were correlated with markers of disease activity and severity, and were reproducible over 48 weeks. However, neither protease was predictive of subsequent 12 month exacerbation outcomes.

Key words: bronchiectasis, neutrophil elastase, matrix metalloproteinase, MMP, disease severity, pathogenic microbe.

Grant Support: Mater Adult Respiratory Research Trust Fund.
**CLINICAL BENEFITS OF LONG-TERM, LOW-DOSE ERYTHROMYCIN IN BRONCHIECTASIS ARE NOT DUE TO MODULATION OF SPUTUM MUCIN CONTENT**

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**Aim**: Macrolide antibiotics have demonstrated clinical efficacy in inflammatory airway diseases, notably bronchiectasis, cystic fibrosis (CF) and diffuse panbronchiolitis. As part of the recent Bronchiectasis and Low-dose Erythromycin Study (BLESS) study, we hypothesized that low-dose erythromycin would significantly reduce production of airway mucins.

**Method**: BLESS randomized 117 subjects to either low-dose erythromycin (n = 59) or placebo (n = 58) for 48 weeks. All subjects underwent sputum induction with 4.5% hypertonic saline at weeks 0, 4, 24 and 48. In a linked study, 20 healthy controls also underwent a single sputum induction. Mucin protein concentrations were determined.

**Results**: Erythromycin significantly reduced protocol defined pulmonary exacerbations (event rate 1.29 vs 1.97, IRR 0.57, 95% CI 0.42 to 0.77, p = 0.003) and 24-hour sputum volume. Total mucin and individual key airway gel-forming mucins, MUC5AC and the low charge isoform of MUC5B, were elevated in induced sputum of bronchiectasis vs healthy controls. However, there was no significant change in mucin concentrations in induced sputum of erythromycin-treated subjects after 4 or 48 weeks, indicating that long-term low-dose erythromycin treatment does not have a direct effect on the relative abundance of mucins in sputum. Furthermore, there was no significant effect of erythromycin upon airway mucin concentration within subjects with more than 45% reduction in 24-hour sputum volume at end of the trial, or subgroups demonstrating particular clinical benefits (Pseudomonas aeruginosa positive subjects and subjects reporting ≥4 pulmonary exacerbations in the 12 months preceding enrolment).

**Conclusion**: In spite of significant clinical improvements with erythromycin in non-CF bronchiectasis, the current comprehensive, double-blind, placebo-controlled analysis of sputum failed to show any suppression of mucin production. These data suggest that the mechanism by which macrolides achieve clinical benefit in bronchiectasis relates to an alternate mechanism.

**Key words**: bronchiectasis, erythromycin, macrolide, mucin, MUC5AC, MUC5B.

**Grant Support**: Mater Adult Respiratory Research Trust Fund.

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**PROFILING INTEGRIN EXPRESSION ON ASTHMATIC AND NON-ASTHMATIC AIRWAY EPITHELIAL CELLS**

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**Introduction**: Epithelial cell migration represents a significant component of the wound repair process that involves both cell-to-cell interactions, as well as, cell interactions with the extracellular matrix (ECM). We have previously shown that primary airway epithelial cells (pAECs) from asthmatic children have a defective cell migration capacity and are unable to produce sufficient amounts of cellular fibronectin (FN). Known receptors for cellular FN include integrins; however, which subtype predominates in pAECs derived from children remains unknown.

**Aims**: To investigate the expression of FN-binding integrins in paediatric pAECs and to determine whether these proteins are differentially expressed in asthmatic pAECs compared to non-asthmatic pAECs.

**Methods**: pAECs were obtained from asthmatic and non-asthmatic children who were undergoing elective surgery for non-respiratory conditions. RNA was extracted and qPCR used to determine the expression of FN-binding integrins. Protein expression of integrins was also used to confirm gene expression via immunocytochemistry.

**Results**: pAECs were found to express all of the alpha (α1, α3, α5) and beta (β1, β3, β6) subunits known to bind to FN by epithelial cells. Of these, α5 and β1 were the most predominantly expressed integrin subunits by all pAECs. In addition, these specific subunits were significantly down-regulated in asthmatic pAECs (α5, 4-fold down-regulation [p = 0.034]; β1, 2-fold down-regulation [p = 0.044]). Immunocytochemical staining of pAECs confirmed gene expression results and revealed α5 and β1 integrin to be localized to the cell membrane. Furthermore, asthmatic pAECs had markedly lower staining for both subunits compared to non-asthmatic pAECs.

**Conclusion**: This study has demonstrated that pAECs express all of the known alpha and beta FN-binding integrin subunits. There was, a reduced down-regulation of α5β1 expression in asthmatic pAECs. This, reduced expression may contribute to the defective cell migration and repair seen in asthmatic airway epithelium.
DIFFERENCES IN FIBRONECTIN PRODUCTION BETWEEN ASTHMATIC AND NONASTHMATIC AIRWAY EPITHELIAL CELLS

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Introduction: Airway remodelling is a key feature of asthma, with altered extracellular matrix (ECM) protein deposition in the airway wall. Fibronecin (Fn) is an ECM protein that is increased in asthmatic airways which affects cell adhesion, proliferation and differentiation. Human airway epithelial cells (HAECs) contribute to airway remodelling by secreting ECM proteins. TGF-β1 is a profibrotic growth factor known to be elevated in asthmatic airways which controls ECM production.

Aims: To investigate in HAECs: (1) constitutive or TGF-β1-induced Fn levels by asthmatic (A) or nonasthmatic (NA) cells; (2) whether ECM Fn regulates HAEC proliferation and cytokine release.

Methods: Soluble and matrix bound ECM proteins were harvested at day 0 or 3 with or without TGF-β1 stimulation and levels of Fn were determined using ELISA. To test the effects of Fn, HBECs were either grown on human Fn coated plates (ECM form) or treated with soluble Fn. Supernatants were collected at day 1 and IL-6 and IL-8 levels were measured by ELISA. Cells were counted after 3 days of Fn treatment.

Results: A HAECs deposited higher levels of Fn than NA cells, while the two types of cells expressed similar levels of soluble Fn and mRNA. TGF-β1 increased Fn in both ECM and soluble forms in both cells (P < 0.05, n = 4–7). Inhibition of Smad2/3 completely prevented TGF-β1-induced Fn deposition. In NA cells, ECM Fn increased HAECs proliferation (n = 9, P < 0.05) and IL-6 release (P < 0.01, n = 5), but had no effect on IL-8. Soluble Fn didn’t affect cell proliferation and IL-6 and IL-8 release.

Conclusion: Asthmatic HAECs are intrinsically primed to produce more ECM Fn, and Fn is capable of driving remodelling and inflammation. The increased airway Fn, which is insensitive to current therapeutics, may be one of the key driving factors in the persistence of asthma and represent a novel therapeutic target.

IDENTIFICATION OF A NOVEL INTERLEUKIN-13 SIGNALLING PATHWAY

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Introduction: Interleukin (IL)-13 is pivotal in the pathogenesis of asthma and eosinophilic oesophagitis (EoE). Administration of recombinant IL-13 protein to mice induces mucous production, eosinophilic inflammation and airways hyperresponsiveness (AHR).

Aim: To characterize the downstream molecular signalling pathway involved in IL-13 driven AHR as well as lung and oesophageal inflammation.

Method: Mice were treated with recombinant murine IL-13 (rIL-13) after receiving Midline -1 (MID-1) targeting siRNA or nonsense control siRNA. AHR was assessed as total lung resistance and dynamic compliance in response to inhaled methacholine, expressed as percentage increase over baseline (PBS). Molecular markers of inflammation were assessed by qRT-PCR and ELISA.

Results: Treatment with rIL-13 induced AHR and upregulation of Muc-5Ac. TRAIL and MID-1 expression was increased after rIL-13 treatment and associated with decreased PP2A activity. TRAIL and MID-1 induction was strongly attenuated in STAT6-/- mice. MID-1 siRNA treatment restored PP2A activity, attenuated AHR and inflammatory markers induced by rIL-13 in both the lung and oesophagus.

Conclusion: IL-13 signals through the newly discovered TRAIL/MID-1/PP2A axis to induce AHR and inflammation. Restoring PP2A activity with MID-1 targeting siRNAs protects against IL-13 driven pathogenesis in the lung and oesophagus.

LUNG CANCER IS ASSOCIATED WITH DECREASED EXPRESSION OF PERFORIN, GRANZYME B AND IFN BY INFILTRATING T CELLS, NKT-LIKE AND NK CELLS

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Background: Cytotoxic CD8+ T cells mount immune responses to cancer via pro-inflammatory and cytotoxic pathways including IFNγ and perforin/granzyme B. We have previously shown reduced granzyme B expression by CD8+ T cells in lung cancer tissue resected from lung cancer patients. We hypothesized that lung cancer may also be associated with deficiency of perforin and IFNγ by T cells and other lymphocyte subsets including NKT-like and NK cells.

Methods: Lung cancer and normal tissue was identified by experienced pathologists and tissue disaggregated into single cells. Following adherence and removal of macrophages, intracellular pro-inflammatory cytokines and expression of the cytotoxic mediators granzyme B and perforin were measured in CD4 and CD8+ T cells using flow cytometry.

Results: There was a significant inverse correlation in the percentage of CD3+ T cells in cancer tissue (Ca: 92 ± 14 and N: 71 ± 14 (mean ± SD) p < 0.05) and a decrease in the percentage of T, NKT-like subsets and NK cells expressing perforin and IFNγ compared with normal tissue (Ca: 0.4 ± 0.6, 8 ± 7, 6 ± 5 and N: 22 ± 8, 36 ± 23, 93 ± 39 perforin+ T, NKT-like and NK cells). There was also a decrease in the percentage of CD8+ T cells and CD56+ NKT-like cells expressing granzyme B compared with normal tissue (Ca: 6 ± 5 and N: 30 ± 15 CD8+NKT-like GB+ cells).

Conclusions: Lung cancer is associated with decreased expression of perforin, granzyme B and IFNγ by infiltrating T cells, NKT-like and NK cells that may be an important immune evasion mechanism.

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Inhibition of Fibroblast Growth Factor-9 Significantly Retards Tumour Growth in Two Murine Models of Malignant Mesothelioma

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Introduction: Identifying key molecules in the pathology of malignant mesothelioma (MM) is needed to develop new therapies. Fibroblast Growth Factor-9 (FGF-9) is an exciting and novel target uncovered from our global profiling of human MM samples.

Aim: To demonstrate that inhibition of FGF-9 reduces tumour growth in vivo.

Methods and Results: We transfected the mouse AB1 MM cell line with shRNA directed against FGF-9 (or scrambled vector). Heterotopic model: Murine AB1-FGF-9 knockdown cells (or controls) were injected (5 × 10⁵ cells) subcutaneously into the flank of Balb/c mice. Tumour dimensions were measured thrice weekly and animals sacrificed when tumours reached 100 mm².

Results: BMPR2 upregulation led to a decrease in several FGF-9-induced upregulation effects, including phosphorylation of Smad2, AKT, Erk 1/2 and Smc. BMPR2 reversed the FGF-9-induced decrease in Smad 1/5/8 phosphorylation. FGF-9-induced upregulation of nNOX4 mRNA was also reduced. NOD2 was identified as a factor mediating hypoxia induced proliferation of PASM.

Conclusions: These findings suggest that the PAH-modulating effect of BMPR2 gene delivery is in part related to downregulation of ’pro-proliferative’ FGF-9 signalling.

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Adenovirus Delivered BMPR2 Mediates TGF-9 Signalling in Human Pulmonary Hypertension Related Cells: Relevance to PAH?

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Introduction: Idiopathic Pulmonary Arterial Hypertension (IPAH) is a fatal disease characterized by pulmonary microvascular remodelling. Recent studies show that PAH is associated with reduced BMPR2 and increased TGF-9, and can be ameliorated by BMPR2 gene delivery.

Aims and Objectives: To investigate the impact of BMPR2 gene delivery on TGF-9 signalling.

Methods: BMPR2 was delivered to human pulmonary artery smooth muscle cells (hPASMC, Passage 4) using Adenovirus vector expressing human BMPR2, then cells were stimulated with TGF-9 and downstream signalling assessed with western blots and quantitative RT PCR.

Results: BMPR2 upregulation led to a decrease in several TGF-9-induced upregulation effects, including phosphorylation of Smad2, AKT, Erk 1/2 and Smc. BMPR2 reversed the TGF-9-induced decrease in Smad 1/5/8 phosphorylation. BMPR2 was delivered to human pulmonary artery smooth muscle cells (hPASMC, Passage 4) using Adenovirus vector expressing human BMPR2 gene, and the expression was confirmed by Western Blot.

Conclusions: Our data suggest that BMPR2 can be a potential therapeutic target for the treatment of PAH.

Supported by: National Health and Medical Research Council, APP1010743.

Identification of Novel Potential Candidate Biomarkers in Lymphangioleiomyomatosis (LAM)

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Introduction: Lymphangioleiomyomatosis (LAM) is a rare and progressive cystic lung condition affecting approx. 3.4–7.5 million women, with an average lag time between symptom onset and diagnosis of approx. 4 years. Currently no reliable biomarker exists for LAM.

Aim: Identification of altered proteins in LAM serum which may be potential candidate biomarkers.

Methods: From LAM patient volunteers (n = 3, n = 5) and healthy aged matched control volunteers (n = 5, n = 5) were pooled and analysis was carried out using iTRAQ technology (AB Sciex). Differentially expressed proteins were validated using ELISAs in a wider cohort (LAM n = 18, age matched control n = 12). Pathway analysis was carried out using Ingenuity Pathways Analysis™.

Results: Fourteen proteins were differentially expressed in LAM compared to age-matched control serum (p < 0.05). Further screening validated the observed differences in the extracellular matrix remodelling proteins fibronectin (decreased expression of 50% in LAM sera, p = 0.03), von Willebrand Factor (40% reduction in LAM, p = 0.03) and the serum protease Kallikrein III (25% increase in LAM, p = 0.03). Pathway networks elucidated the relationships and feedback loops between the ECM and cell trafficking in LAM.

Conclusion: This study highlighted a substantial imbalance in protein network important for remodelling in LAM, providing a set of novel candidate biomarkers. These may be useful in the development of a feasible approach to diagnosis, potentially leading to new effective treatment for LAM.

Key words: lymphangioleiomyomatosis, biomarkers, extracellular matrix.

Grant Support: Philanthropic Funds, NH&MRC, LARA.

Hypertraemia Reduces Acute Lung Injury, Independent of Fluid or Sodium Load

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Background: Hypertraemia, which is often associated with abnormalities in fluid or sodium balance, is associated with adverse outcomes in critically ill patients. However hyperosmolarity, a secondary effect of hypertraemia, is lung protective in both cell culture and animal models. Induced hypertraemia (leading to hyperosmolarity) has not been studied in lung injury.

Aim: To investigate whether hypertonic saline is protective in an intratracheal lipopolysaccharide (LPS) induced lung injury rat model.

Methods: Immediately following induction of acute lung injury male Sprague Dawley rats received either hypertonic 20% saline (i.v.) or resuscitation fluids at dosages designed to control for either or both sodium or water load (0.9% saline, 4% albumin, 20 % albumin or 5% dextrose). Following 2 hours of no-injurious mechanical ventilation blood gases, lung oedema, respiratory mechanics and histological lung injury score were assessed. Results were analysed with 2-way ANOVA and Tukey’s post-hoc analysis.

Results: Administration of hypertonic saline resulted in hypertraemia (serum [Na+] 168 mmol/l and 162 mmol/l) by 30 min, maintained to 2 hours, after initiation of lung injury. Administration of hypertonic saline was associated with reduced lung injury evident as decreased lung oedema (p < 0.001), myeloperoxidase activity (p < 0.0001), bronchoalveolar lavage cell count (p < 0.0001), protein (p < 0.001), TNFα (p < 0.001), IL-8 (p < 0.001) and lung histology injury score compared with positive fluid control animals. Similarly, lung physiology was improved with higher PaO₂ (p < 0.0001) and lower lung elastance (p < 0.0001), which was associated with preservation of surfactant activity as assessed by small to large aggregate ratio of surfactant phospholipids (p < 0.0001).

Conclusion: Hypertraemia is lung protective in LPS induced acute lung injury, independent of fluid or sodium load.
IMPAIRED FORMATION OF ANTIVIRAL STRESS GRANULE AND INTERFERON-BETA ENHANCEOSOME LEADS TO REDUCED ANTIVIRAL RESPONSES TO INFLUENZA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction: People with chronic obstructive pulmonary disease (COPD) have impaired antiviral interferon (IFN)-β responses to influenza infection. The mechanisms underlying the reduced IFN-β induction in COPD however are unknown. Antiviral stress granule (AvSG) and IFN-β enhanceosome formation is important in the induction of IFN-β production.

Aim: We hypothesize that the formations of AvSG and IFN-β enhanceosome are impaired in COPD primary bronchial epithelial cells (pBECs) to influenza infection, leading to reduced IFN-β induction and enhanced viral replication.

Methods: pBECs from healthy non-smoking volunteers and subjects with COPD were infected with human influenza A/H1N1 at MOI of 5. AvSG proteins PKR, TIAR, G3BP were detected by immunofluorescence/confocal microscopy, and by western blotting. IFN-β enhanceosome proteins pIRF3, pATF2, and p300 were also measured. IFN-β protein was measured by western blotting. Viral replication was measured by plaque assay. PKR was silenced by specific siRNA 24 before infection. Co-localization test was performed using ImageJ according to instructions.

Results: Influenza infection resulted in reduced AvSG component PKR, TIAR, and G3BP expression and decreased formation of AvSG in COPD pBECs. The formation of IFN-β enhanceosome was also significantly decreased in COPD pBECs with reduced expression of enhanceosome components pIRF3, pATF2, and p300. We then determined that PKR was important in the formation of AvSG, as PKR inhibition by siRNA led to impaired AvSG formation and also IFN-β enhanceosome. This then led to reduced IFN-β induction and increased influenza viral replication in COPD pBECs.

Conclusion: COPD pBECs have impaired formation of AvSGs and IFN-β enhanceosome to influenza infection. This was the result of reduced PKR protein expression, leading to reduced IFN-β protein production and increased viral titre.

FIELWALKING TESTS ARE RELIABLE AND RESPONSIVE TO EXERCISE TRAINING IN INDIVIDUALS WITH NON-CYSTIC FIBROSIS BRONCHIECTASIS

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Introduction: The 6-minute walk test (6MWT) and incremental shuttle walk test (ISWT) are often used to assess exercise capacity, but the reliability and responsiveness of these tests in individuals with non-cystic fibrosis (CF) bronchiectasis, has not been determined.

Aim: To describe the test-retest reliability of the 6MWT and the ISWT in individuals with non-CF bronchiectasis and to determine which test is more responsive to exercise training.

Method: Eighty-five participants, mean(SD) age 64(13) years, FEV1 73(22)% predicted with non-CF bronchiectasis, completed two 6MWTS and two ISWTs in random order according to a standardized protocol. Testing was repeated after conclusion of an eight-week exercise training programme in 42 of the participants.

Results: Both tests demonstrated high test-retest reliability (intraclass correlation coefficients = 0.95 for both tests). The mean(95% CI) increase in the 6-minute walk distance (6MWD) on repeat testing was 20 m (13 to 26 m); 3%(0 to 5%) change, with 79% participants improving on the 2nd test. The mean(95% CI) increase in the incremental shuttle walk distance (ISWD) was 15 m (4 to 25 m); 4%(2 to 6%) change, with 55% improving on the 2nd test. The effect size (ES) and standardized response mean (SRM) following exercise training were moderate for the 6MWT (ES = 0.32, SRM = 0.68) and the ISWT (ES = 0.42, SRM = 0.71).

Conclusion: The 6MWT and ISWT are reliable tests for the assessment of exercise capacity in patients with non-CF bronchiectasis, with a large proportion of participants demonstrating a learning effect in both measures. Both field walking tests are responsive to exercise training and can be used as an outcome measure of this intervention.

EFFECTS OF THE EVERGO PORTABLE OXYGEN CONCENTRATOR ON EXERTIONAL DESATURATION IN PEOPLE WITH INTERSTITIAL LUNG DISEASE

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Aim: Portable oxygen concentrators (POC) are lighter and easier to manoeuvre than portable oxygen cylinders, however their ability to meet the oxygen requirements of people with interstitial lung disease (ILD) during exercise has not been evaluated. The aim of this study was to compare the effects of ambulatory oxygen delivered during exercise using the EverGo POC to ambulatory oxygen delivered with a portable cylinder in people with ILD.

Methods: People with ILD who desaturated to less than 90% during a 6-minute walk test (6MWT) on room air were recruited. Following two practice tests, participants undertook a 6MWT using a portable oxygen cylinder and a 6MWT using the EverGo POC, in random order. The Evergo POC delivered pulsed flow on its maximum setting of 6, whilst the portable cylinder was set on 5 L/minute with continuous flow. Participants pulled their own oxygen devices which were matched for weight. The primary outcome was nadir SpO2 during the 6MWT.

Results: Participants were 7 people with ILD (6 IPF, mean age 68(SD 6) years, TLCO 50(13)% predicted). The 6MWT distance on room air was 377(243)m with nadir SpO2 80(8)%. At rest PaO2 was significantly higher using the cylinder (cylinder 139(34)mmHg vs POC 112(27)mmHg, p = 0.02) but there was no difference in PaCO2 or pH. During the 6MWTS on oxygen, nadir SpO2 did not differ according to the device used (cylinder 84(7)% vs POC 84(8)%, p = 0.74). There was no difference between 6MWTS for dyspnoea, fatigue or maximum heart rate, although distance walked tended to be slightly higher with the cylinder (461(175)m vs POC 446(179)m, p = 0.06). Two participants preferred the cylinder, three preferred the POC and two had no preference.

Conclusion: The EverGo POC has similar effects on exertional desaturation to a portable oxygen cylinder in people with ILD.
PULMONARY ALVEOLAR PROTEINOSIS IN TWO TEACHING HOSPITALS IN QUEENSLAND

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Introduction: Pulmonary Alveolar Proteinosis (PAP) is characterized by abnormal intra-alveolar accumulation of pulmonary surfactant. PAP is very rare with an estimated annual incidence and prevalence of 0.36 and 3.70 cases per million population, respectively.

Aim: To describe the clinical, epidemiologic, laboratory features and treatment of PAP in a cohort of patients with PAP in two teaching hospitals in South-East Queensland.

Method: This was a retrospective review of patients diagnosed with PAP between July 1997 to July 2013, by searching the medical records data base of The Prince Charles Hospital and Gold Coast Hospital. Data was collected by interviewing physicians, reviewing medical records, pathology results and radiology.

Results: 12 cases of PAP comprised nine males. The mean age at diagnosis was 43 years. One half of them were current or previous smokers. Occupational dust or fume exposure occurred in 58% of the cases. The mean forced vital capacity was 3.2 litres (SD 0.98) and oxygen saturation at presentation was 92.1% (SD 5.4). The diagnosis was confirmed following bronchoalveolar lavage (50%), transbronchial lung biopsy (17%) or surgical lung biopsy (33%).

Conclusion: PAP is a rare disease underlining the importance of a dedicated team managing these patients. WLL is currently the gold standard treatment and is safe and effective. Toxic particle inhalation may be more frequently associated with PAP in this group.

RELIABILITY OF THE HAND HELD DYNAMOMETER IN MEASURING MUSCULAR STRENGTH IN PEOPLE WITH INTERSTITIAL LUNG DISEASE

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Aim: Skeletal muscle weakness is a common feature of interstitial lung disease (ILD) and correlates strongly with reduced exercise tolerance. Given the potential impact of skeletal muscle function on exercise tolerance, skeletal muscle strength is an important component of assessment in patients with ILD. Our aim was to evaluate the inter-rater and intra-rater reliability of the hand held dynamometer in measuring muscular strength in people with ILD.

Methods: Biceps and quadriceps strength was measured using a Jtech Commander Powertrack II hand held dynamometer. Participants completed three consecutive maximal isometric contractions of each muscle separated by 10–30 seconds rest (within session intra-rater reliability). Participants were tested twice on the same day by two independent assessors in random order, 30 minutes apart (inter-rater reliability). Participants returned a week later to repeat the strength testing procedure (between-session intra-rater reliability). Relative reliability for peak and mean muscle strength (kg) for each muscle was estimated using the intraclass correlation coefficient (ICC).

Results: Thirty participants with ILD of varying aetiology (13 IPF, mean age 70 (SD 10) years) were included. Twenty participants completed the inter-rater and within session intra-rater reliability protocol (11 male and 9 female, FVC 74 (17)%predicted, TLO 43 (12)%predicted) and twenty one participants completed the between session intra-rater reliability protocol (11 male and 10 female, FVC 78 (15)%predicted, TLO 51 (17)%predicted). Within session intra-rater, inter-rater and between session intra-rater reliability was very high for biceps with ICC scores of 0.99, 0.91 and 0.96 for peak strength and 0.99, 0.95 and 0.98 for mean strength respectively. Within session intra-rater, inter-rater and between session intra-rater reliability was very high for biceps with ICC scores of 0.99, 0.92 and 0.93 for peak strength and 0.99, 0.95 and 0.97 for mean strength respectively.

Conclusion: Hand-held dynamometry is reliable in measuring biceps and quadriceps strength in people with ILD.

RETROSPECTIVE AUDIT ON PATIENTS WITH PULMONARY EMBOLISM (PE) PRESENTING TO THE PRINCE CHARLES HOSPITAL (TPCH): SUMMARY OF THE EXPERIENCE AT TERTIARY HOSPITAL AT BRISBANE

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Aim: To retrospectively gather data on patients presenting to TPCH with diagnosis of PE to provide perspective on the current clinical practice of follow-up at a tertiary hospital.

Methods: While PE is a common clinical problem, there are several controversial areas with regards to the management and the follow-up. We performed a retrospective audit on patients who presented to TPCH from August 2011 to September 2012 with diagnosis of PE. In particular, we gathered data on patients with myocardial injury (Troponin leak) and right ventricular dysfunction (on imaging or elevated Beta-Natriuretic Peptide), follow-up imaging, follow-up echocardiograms and formal malignancy screening.

Results: Data was collected from 62 patients. Overall, 34% of patients received follow-up imaging and 27% received a follow-up echocardiogram. 19.5% of the 41 patients tested for troponin were positive. The rate of chronic PE and pulmonary hypertension was 12.5% each for this positive group compared to 24% and 9% respectively for the negative group. 36% of the 55 patients tested had RV dysfunction. 35% of the RV dysfunction group developed chronic PE and 25% developed pulmonary hypertension (compared with 14% and 7% respectively for those without RV dysfunction). Only 5 patients (11%) had a formal malignancy screen.

Conclusions: This study shows that while the majority of patients who present with PE were tested for myocardial injury or dysfunction, only a minority of patients received formal follow-up imaging and echocardiogram to assess for long-term sequelae. While RV dysfunction appeared to predict the risk of chronic PE and pulmonary hypertension, myocardial injury did not. Further research on the optimal follow-up strategy of patients with PE is required.
CLINICAL PRACTICE OF THROMBOPHILIA TESTING ON PATIENTS WITH VENOUS THROMBOEMBOLISM AT THE PRINCE CHARLES HOSPITAL

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Background: Testing for thrombophilia in patients with VTE is controversial, as major guidelines differ on their recommendations. Consequently, clinical practice of thrombophilia testing in hospital settings is variable and sometimes illogical.

Aim: To retrospectively assess the clinical practice of thrombophilia testing on patients presenting to TPCH with venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE).

Methods: We performed a retrospective audit on patients who presented to TPCH between August 2011 to September 2012 with DVT or PE. Data was collected on demographics, patient with recurrent episodes of VTE, patients with idiopathic VTE, yield of the test, and whether the result of the test changed duration of anticoagulation.

Results: Data was collected from 83 patients: PE (55), DVT (21) and both (7). 42 out of 83 (51%) were tested for thrombophilia with 13 out of 42 (31%) returning a positive result. The most common result was Heterozygous Factor 5 Leiden Mutation (4 patients). No patient fulfilled criteria for Antiphospholipid Syndrome. The yield of the test was 48% in Idiopathic VTE compared with 14% in Provoked VTE and 50% in those with recurrent VTE compared with 21% in those with 1st episode of VTE. No patient’s duration of anticoagulation was altered as a result of their Thrombophilia result.

Conclusions: Thrombophilia testing in our patients with VTE are sometimes performed indiscriminately without sound and consistent clinical reasoning. While the yield of the test was higher in patients who presented with Idiopathic VTE and those with recurrent episodes of VTE, no cases of thrombophilia testing resulted in a change of duration of anticoagulation therapy. While thrombophilia testing is useful in patients with VTE, it needs to be done in selective cases backed-up by good clinical reasoning.

DIAGNOSTIC VALUE OF SERUM PRECIPITINS FOR DISTINGUISHING HYPERSENSITIVITY PNEUMONITIS IS IMPROVED WHEN APPLIED TO PATIENTS WITH A HISTORY OF EXPOSURE TO KNOW KNOWN ANTIGENS

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 Aim: To investigate the role of serum precipitins in distinguishing hypersensitivity pneumonitis (HP) from other interstitial lung diseases (ILD) and identify optimal thresholds of specific antibody levels for diagnosing HP.

Method: Consecutive patients attending Royal Prince Alfred Hospital ILD clinic (Sept 2010 -Jan 2013) with results for serum precipitins were analysed. Diagnoses from multidisciplinary review were recorded. Clinical data, including HP antigen exposure, and serum precipitins were collected by an investigator blinded to the ILD diagnosis. Results for budgerigar (Ge90), pigeon (Ge91) (Jul 2011 -Jan 2013) and farmer’s lung (GMX7) (Jan 2012-Jan 2013) specific IgG measured on the ImmunoCAP250 (Phadia™), and FSX4 (pigeon, budgerigar and poultry) and FSX3 (farmer’s lung) serum precipitins identified using immunoprecipitation (Sept 2010-Dec 2011) were analysed.

Results: 144 ILD patients (mean age 63 ± 13 yrs; 74 male) had serum precipitins analysis. Diagnoses included: idiopathic interstitial pneumonia (n = 48); connective tissue disease related ILD (n = 45); HP (n = 24); sarcoidosis (n = 10), other ILD (n = 14) and non-ILD (n = 3). Mean FVC = 77.5 ± 22.4% and DLCo = 53.7 ± 20.5%. A relationship between positive serum precipitins and HP diagnosis was demonstrated (OR 2.58; 95%CI 1.03, 6.48; p = 0.04). ROC curve analysis revealed optimal threshold levels of 20.7, 11.0 and 12.5 mg/L to pigeon, budgerigar and farmer’s lung antigens respectively, with sensitivities of 42.9, 35.7, 50% and specificities of 78.5, 87.2, 73.1% respectively. ROC analysis within the exposed study population determined optimal levels of 34.2, 11 and 12.5 mg/L to pigeon, budgerigar and farmer’s lung antigens respectively, with improved sensitivities of 80, 80, 66.7% and specificities of 100, 84.6, 77.8% respectively.

Conclusion: Serum precipitins are predictive of HP diagnosis, although limited by poor sensitivity within unstratified ILD patients. Their diagnostic value is improved in exposed individuals with suspected ILD.

VITAMIN D INSUFFICIENCY IS COMMON IN INTERSTITIAL LUNG DISEASE BUT NOT ASSOCIATED WITH OSTEOPENIA AT BONE DENSITY SCANNING

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Introduction: In interstitial lung disease (ILD), vitamin D (VitD) deficiency is thought to be common, and associated with connective tissue disease (CTD) and with poorer pulmonary function.1 It is not clear whether VitD deficiency in this setting has an impact on bone density.

Aim: To describe the prevalence of VitD deficiency in our ILD cohort, and the relationship between VitD levels and osteopenia on bone density scan.

Method: Consecutive patients referred to the RPAH ILD clinic (Mar 2011 – Nov 2012) were consented for serum storage (n = 79, 45 male; mean age 64 ± 13 yrs). Serum was analysed for 25-OH VitD levels using the Liaison immunoassay. All patients also had concurrent pulmonary function and 54 had bone density scans within 28 months. VitD insufficiency was defined as 30–60 nmol/L, and VitD deficiency as <30 nmol/L.

Results: ILD diagnoses included CTD-ILD (n = 22) and granulomatous disease (n = 19), idiopathic interstitial pneumonia (IIP, n = 30) and other ILD (n = 5), 25 (32%) were using VitD supplements, 39 (49%) corticosteroids, and 8 (10%) bisphosphonates. Mean FVC was 78 ± 23%. DLco was 52 ± 21%. 25-OH VitD levels were 62.5 ± 21.7 nmol/L. 33 (42%) were VitD insufficient and 6 (8%) were VitD deficient. VitD insufficiency was not associated with underlying ILD diagnosis. VitD levels were higher in those taking Vit D supplements, and were weakly negatively correlated with lung function: TLC% (R = −0.23, p = 0.04); DLco% (R = −0.29, p = 0.01). 28 (32%) had osteopenia, and 8 (15%) had osteoporosis. VitD levels of osteoporotic patients (52.5 ± 30.6) did not significantly differ from those with osteopenia (61.3 ± 25.7) or normal bone density (67.2 ± 20.6; p = 0.42).

Conclusion: Vitamin D insufficiency and osteopenia are common in ILD patients. Further studies assessing the importance of VitD insufficiency for the bone density of ILD patients are needed.

Conflict of Interest: None.

Reference: 1. Hagaman JT, Panos RJ, McCormack FX, et al. Vitamin D deficiency and reduced lung function in connective tissue-associated interstitial lung diseases. Chest; 139:353–60.

ANTI-FUNGAL TREATMENT IN SARCOIDOSIS—A COMPARISON WITH CORTICOSTEROIDS

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Background: There are limited clinical and case studies showing that short-term treatment with anti-fungal medication improved the clinical status of the disease. To further explore this, a study was undertaken where treated patients were followed till healing of the disease.

Method: Newly diagnosed cases of sarcoidosis were given corticosteroids (n = 21) or anti-fungal medication (n = 20). Seven patients were given both drugs in view of the severity of their disease. The patients were followed with x-ray, determining the degree of granuloma infiltration and chitotriosidase (CTO) and angiotensin converting enzyme (ACE) in serum. The time till clinical healing of the disease was recorded as well as the number of recurrences.

Results: The time till healing was 11.9 months for those with anti-fungal treatment and 13.7 months for corticosteroid (NS). Regarding x-ray scores, there was no difference between the groups at diagnosis. At six months after initiation of treatment and at healing, the granulomatous infiltration was significantly less severe among those with anti-fungal medication (p = 0.025 and 0.003 respectively). The number of recurrences was also lower in the anti-fungal group (1 vs 7, p = 0.006).

Conclusion: There were no differences in the studied parameters, comparing treatment with corticosteroid and anti-fungal medication. The presence of subjects with more severe disease, who were given both medications, suggests that the efficiency of anti-fungal treatment may be limited to the less severe forms of the disease. It may also reflect the cautionary attitude of the clinician administering the medication.

Funding: Internal hospital funding only.

Key words: sarcoidosis, fungi, granuloma, inflammation.

Nomination: Young Investigator Award.
THE NATURAL HISTORY OF IDIOPATHIC PULMONARY FIBROSIS (IPF) IN AUSTRALIA: INFORMATION FROM THE AUSTRALIAN IPF REGISTRY

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Introduction: Despite the increasing incidence of Idiopathic Pulmonary Fibrosis (IPF) worldwide, there are many unanswered questions with regard to its pathogenesis, natural history and management. In Australia IPF research is now facilitated by a collaborative national initiative, the Australian IPF Registry.

Methods: The Australian IPF Registry, an initiative of the Lung Foundation Australia, encourages physicians to identify their IPF patients and State Registry Coordinators obtains consent and collate data every six-months. We describe the natural history of IPF patients, over the first fifteen-month period of data collection.

Results: 268 IPF patients have consented (174 male; mean age 70.8 ± 8.2 yrs). Baseline pulmonary function included: FVC 2.6 ± 0.8 (80.3 ± 20.7%), FEV1 2.2 ± 0.6 (84.9 ± 20.6%), DLco 45.7 ± 15.0%. Six-minute walk test distance (6MWT) was 429 (48, 640)m, with resting SpO2 94.4 ± 7.6%. 89 (64.0%) of 139 participants with a pulmonary function test have more than one recorded on the Registry while 30 (21.8%) of participants have more than one six minute walk test. Follow-up up data is available in 92 patients (including 8 deaths) of these 139 participants. Pulmonary function tests and 6MWT, although correlation with HADS A and D was weak and end-exercise 85.9 ± 8.0%. 232 patients have completed QOL questionnaires: Total UCSD 42.3 ± 28.0; HADS A Score 5 (2–8), 21.1% > 8, HADS D Score 4 (2, 8), 19.3% > 8; SGRQ scores: Symptom score 50.4 ± 21.8; Activity score 22.6; Total score 47.8 ± 21.8. The UCSD had the strongest relationship overall with markers of severity of IPF (FEV1: R = −0.37, p < 0.05; FVC: R = −0.38; p < 0.05; DLco: R = −0.48, p < 0.05; 6MWD: R = −0.54, p < 0.05). Nearly all QOL scores correlated with pulmonary function tests and 6MWT, although correlation with HADS A and D was weak or absent.

Conclusions: The Australian IPF Registry is a unique resource and a platform for epidemiological and clinical research. Serial physiological testing reveals the natural history of IPF across Australia.

QUALITY OF LIFE OF PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF)—WHAT CAN THE AUSTRALIAN IPF REGISTRY TELL US?

GLASPOLE I1, GOH N1, HOPKINS P2, MOODLEY Y2, REYNOLDS P2, WALTERS H2, WOOD-BAKER R2, ZAPPALA C3, CHAPMAN S2, COOPER W1, DARBISHIRE W1, ELLIS S1, MAHAR A1, SMITH S4, CHAPLIN H5, FULLER J5, MACANSH S5, MCALISTER M4, STEVENS E2, SYMONS K2, WEBSTER S2
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Introduction: Idiopathic Pulmonary Fibrosis (IPF) is a progressive, fibrosing lung disease with poor survival. A variety of contributors result in diminished health related quality of life (HRQOL). We sort to determine the contribution made by physiological impairment.

Methods: The Australian IPF Registry is a national collaboration involving all states of Australia. IPF patients identified by their physician are reported to State Registry Coordinators. Longitudinal data is collated, including 6-monthly questionnaires and investigations. HRQOL measures include the UCSD Shortness of Breath Questionnaire, St George Respiratory Questionnaire (SGRQ) and Hospital Anxiety and Depression (HAD) scale. We compared these QOL measures with traditional physiological measures.

Results: To date, 310 IPF patients have consented (199 male; mean age 71.1 ± 8.1 yrs). Baseline pulmonary function included: FVC 2.6 ± 0.8 (81.6 ± 23.1%), FEV1 2.1 ± 0.6 (84.6 ± 21.8%), DLco 46.4 ± 17.0%. Six-minute walk test distance (6MWT) 434 (48,640)m, with resting SpO2 94.8 ± 7.6%. 89 (64.0%) of 139 participants with a pulmonary function test have more than one recorded on the Registry while 30 (21.8%) of 139 participants. Pulmonary function tests and 6MWT, although correlation with HADS A and D was weak and end-exercise 85.9 ± 8.0%. 232 patients have completed QOL questionnaires: Total UCSD 42.3 ± 28.0; HADS A Score 5 (2–8), 21.1% > 8, HADS D Score 4 (2, 8), 19.3% > 8; SGRQ scores: Symptom score 50.4 ± 21.8; Activity score 22.6; Total score 47.8 ± 21.8. The UCSD had the strongest relationship overall with markers of severity of IPF (FEV1: R = −0.37, p < 0.05; FVC: R = −0.38; p < 0.05; DLco: R = −0.48, p < 0.05; 6MWD: R = −0.54, p < 0.05). Nearly all QOL scores correlated with pulmonary function tests and 6MWT, although correlation with HADS A and D was weak or absent.

Conclusions: The Australian IPF Registry is a unique resource for epidemiological and clinical research. Our data shows the relationship between QOL and physiological measures is moderate and further study to establish other determinants of HRQOL in IPF is needed. This may be relevant in the day to day management of IPF patients, as well as in the choice of clinical trial endpoints.
DOES SUPPLEMENTAL OXYGEN INCREASE EXERCISE ENDURANCE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS?

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Background: In idiopathic pulmonary fibrosis (IPF), exercise oxygen desaturation is associated with poorer outcomes independent of disease severity. The role of supplemental oxygen in patients without resting hypoxia is not clear.

Aim: To study the effect of supplemental oxygen (compared to air) during exercise on endurance distance and other exercise parameters in IPF patients without resting hypoxia but with six minute walk test (6MWT) oxygen desaturation.

Methods: IPF subjects displaying oxygen desaturation at 6MWT but without resting hypoxia were studied. Subjects performed two cardiopulmonary exercise tests (CPET) using stationary cycle ergometry, randomized to 60% oxygen or medical air in a cross-over double-blinded fashion. Subjects also completed two endurance shuttle walk tests (ESWT) randomized to 3 L/min oxygen or medical air in a cross-over double-blinded fashion. We studied the difference between endurance distance and other variables between oxygen and medical air using Student’s paired t-test.

Results: Six subjects (mean age 64.5 ± 6.0 yrs; five males) were studied, with mean FVC 79.5 ± 19.5%, DLco 46.2 ± 10.2%, resting SpO2 95.2 ± 2.5% and 6MWT nadir SpO2 63.9 ± 3.8%. Two subjects had pulmonary hypertension at echocardiography. At CPET, subjects had a non-significant increase in endurance time with supplemental oxygen compared to air (oxygen: 488 ± 68 sec; air: 408 ± 93 sec; p = 0.07). Oxygen was associated with increased peak exercise SpO2 (99.4 ± 0.7%; 89.5 ± 4.8%; p = 0.004), maximal workload (142 ± 58 W; 124 ± 62 W; p = 0.07), peak VO2 (1.6 ± 0.5 L/min; 2.4 ± 0.8 L/min; p < 0.05), oxygen pulse (19.0 ± 6.9 mL/beat; 13.6 ± 2.8 mL/beat; p = 0.08) and end tidal CO2 (41.9 ± 7.4 L/min; 35.8 ± 3.9 L/min; p < 0.05). At ESWT, oxygen was associated with a non-significant rise in endurance distance compared to air (oxygen: 1120 ± 544 m; air: 855 ± 446 m; p = 0.14). There was no difference between nadir SpO2, peak HR and Borg dyspnoea score whether subjects received oxygen or air.

Conclusion: In IPF patients with exercise-induced hypoxia, supplemental oxygen is associated with a trend towards increased endurance and other measures of exercise performance, compared to medical air, on both CPET and ESWT.

THE WAY FORWARD—EXERCISE CARDIAC MAGNETIC RESONANCE IMAGING IN PULMONARY HYPERTENSION

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Aim: Right ventricular dysfunction (RVD) associated with pulmonary hypertension (PHT) is characterized by significant exercise limitation and portends a poorer prognosis. Whilst exercise training is recommended for a number of severe heart and lung disease populations, exercise training in PHT was only recently endorsed at the World Pulmonary Hypertension Symposium. However the impact of exercise training on right ventricular (RV) function in PHT remains unknown, due to the difficulty of accurately assessing RV function during exercise. We aim to present the first case report of exercise cardiac MR (CMR) imaging (Siemens: Aera.1.5 Tesla) in a PHT patient correlated with metabolic data from a modified cardiopulmonary exercise test (CPET).

Method: 23 year old female with severe PHT (NYHA II) related CTEPH on combination PHT therapy prospectively performed resting and exercise CMR at 0, 25 and 50 W workload. On a separate day the subject performed a modified CPET (Cortex, Metamax, Germany) using the same protocol i.e. 0, 25 and 50 W workload. Data presented as mean.

Results: Oxygen uptake (VO2), arterio-venous difference (a-vDO2) and heart rate (HR) all increased from rest to 50 W (VO2: 0.29 to 0.72 L/min; a-vDO2: 10.1 to 12.4 ml/100 ml O2; HR: 56 to 84 beats/min) However despite this, RV ejection fraction and RV cardiac output declined between 25 and 50 W from 49.0% to 44.6% and 5837 and 5737 ml/min respectively. Visual assessment reflected deteriorating RVD as workload increased.

Conclusion: Exercise CMR may be a useful tool in assessing exercise limitation and RVD in PHT. Further research is needed to determine the long-term impact and safety of exercise prescription.

Key words: exercise cardiac magnetic imaging, pulmonary hypertension.

Grant Support: Queensland Health Practitioner Research Scheme, The Prince Charles Hospital Research Foundation.

ISOLATION AND CHARACTERIZATION OF A DEFINED POPULATION OF ENDOTHELIAL PROGENITOR CELLS FROM THE LEFT VENTRICLE: A PILOT STUDY

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Introduction: Endothelial progenitor cells (EPC’s) are rapidly becoming a great source of information on disease processes as well as showing a potential in exerting therapeutic effects in cardiac disease models. Pulmonary arterial hypertension (PAH) is a rare and fatal disease caused by abnormal cellular signalling in the pulmonary vasculature. Despite a new era of therapeutics, survival is still poor. Thus, there is a need to further understand the pathogenesis of this disease as well as develop more effective therapies.

Aim: To culture EPC’s from whole blood taken from both the pulmonary artery (PA) and leftventricle (LV), characterize these cells and perform functional analysis to compare the disease state with health controls.

Methods: Right heart catheterization was performed on a PAH subject, during which 8 ml of blood is taken from the PA and another 8 ml from the LV. Immediately following, mononuclear cells are isolated, washed and seeded in a gelatine (Sigma) coated well. Cells are cultured in endothelial medium (EGM-2MV Lonza) for 6 weeks and characterized using flow cytometry.

Results: Outgrowth cells were observed at 4 weeks in the LV sample only and were cultured to 6 weeks. LV cells were observed to proliferate rapidly from 4–6 weeks, displaying endothelial like morphology of rounded cells with a cobblestone appearance. Flow cytometric analysis characterized the cells as: vonWillbrand factor+, CD144+, CD146-, CD31+, VEGFR2+, CD133+, CD14+ and CD45-.

Conclusion: This pilot study has identified a highly proliferative endothelial progenitor cell population, displaying mature vascular endothelial cellular markers that may be restricted to the downstream side of the pulmonary vascular bed. These cells have the potential to provide functional information on the pathogenesis of PAH in human subjects, as well as be potentially useful as a surrogate for in situ endothelial cells to evaluate therapeutic gene delivery approaches for PAH.
PULMONARY HYPERTENSION AS A COMPLICATION OF COMBINED PULMONARY FIBROSIS AND EMPHYSEMA

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Introduction: Combined pulmonary fibrosis and emphysema (CPFE) is a rare clinical syndrome where both conditions occur simultaneously. Pulmonary hypertension is a known complication of CPFE.

Aim: Review of the approach to management of an individual with CPFE.

Method: A 69 year old ex-smoker female presented with a six month history of progressive dyspnoea and severe hypoxaemia (NYHA Class 4 functional symptoms). Recurrent hospital admissions with dyspnoea had been attributed to acute pulmonary oedema and congestive cardiac failure, treated with diuretics and increasing home oxygen (FiO2 40%). Transthoracic echocardiograms (Echo) over one year identified rapidly progressive severe pulmonary hypertension (RVSP 85 mmHg) with associated significant right ventricular dilatation with reduced systolic function and severe tricuspid regurgitation, from a normal baseline. Pulmonary function tests showed preserved spirometry and lung volumes, but progressively declining gas transfer (DLCO/Va) to 1.42 L/m²/min. CT pulmonary angiograms (Echo) over one year identified rapidly progressive severe pulmonary hypertension (mPAP 39 mmHg). Other causes of pulmonary hypertension were excluded, with negative autoimmune serology, normal Echo bubble study, and normal nuclear perfusion scans.

Results: One year after commencing treatment 6MWD declined to 40 metres. Clinical improvement. At three months 6MWD increased to 90 metres, however subsequent decline.

Conclusion: Recognition of CPFE and treatment of associated pulmonary hypertension can result in symptomatic and functional stabilization before subsequent decline.

OUTPATIENT PHYSIOTHERAPY IMPROVES QUALITY OF LIFE FOR NON CF BRONCHIECTASIS

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Aim: To prospectively evaluate the impact of specialist respiratory physiotherapy on health-related quality of life (QoL) in patients with non-CF bronchiectasis and/or chronic cough and increased sputum production.

Method: Patients attended two outpatient sessions of 45–60 min, 4–6 weeks apart for individualized physiotherapy assessment and education of airway clearance techniques (ACT), exercise, and use of adjunct inhalation therapies by a senior cardiorespiratory physiotherapist. The focus was on developing an effective, practical and sustainable independent programme. Health-related QoL was measured using the Leicester Cough questionnaire (LCQ) and COPD assessment tool (CAT) prior to and after the physiotherapy consultations. Patient rated VAS scales measuring education outcomes and perceived efficacy of the sessions was also collected.

Results: 22 patients (16 females): mean age 69.4 ± 10.5 years, BMI 29 ± 6, FEV1 1.54 ± 0.5 l/min, and FEV1% predicted 62.8 ± 15.7. Ten patients (46%) established a home routine using independent breathing techniques and 12 (54%) used adjunct oscillating positive expiratory pressure devices. All patients were prescribed a home exercise programme, eight (36%) attended pulmonary rehabilitation, and eight commenced saline nebulization as an adjunct to ACT. Following the two-session intervention significant improvement in cough-related health status (mean difference 2.2; 95% CI 1.0 to 3.5, p < 0.01), all LCQ health-related domains [physical, psychological and social] (p < 0.014) and total CAT scores (mean difference 3.5, 95% CI 0.4 to 6.5). Patients reported increased understanding of bronchiectasis (p < 0.05) and rated the physiotherapy intervention as helpful to their overall management (VAS mean 94 ± 9).

Conclusions: This two-session physiotherapy intervention with a specialized respiratory physiotherapist improved health-related QOL in patients with primarily non-CF bronchiectasis and appears to be a clinically cost-effective programme. Further study is required to determine if specialist outpatient physiotherapy interventions may improve other hospital cost utilization including reducing hospital admissions.

TOMM40 GENE POLYMORPHISMS AND HUMAN PULMONARY ARTERIAL HYPERTENSION

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Introduction: The pathogenesis of pulmonary arterial hypertension (PAH) is yet to be fully elucidated. Modern theories implicate aberrant mitochondrial function with downstream proliferation and apoptosis resistance in pulmonary artery endothelial and smooth muscle cells. The recent development of a murine model of PAH with a causative mutation in the key mitochondrial protein transport gene, translocase of the outer mitochondrial membrane 40 (TOMM40), suggested that TOMM40 mutations may also be associated with human PAH.

Aim: The aim of this pilot study was to detect novel TOMM40 mutations or known mutations occurring with altered frequency in human PAH as compared to a healthy reference population.

Method: Participants with idiopathic PAH (IPAH), heritable PAH (HPAH) and PAH associated with a connective tissue disorder were eligible for inclusion. Caucasian populations sourced from the 1000 genomes project acted as a control. Mutational analysis was performed by direct sequencing of the TOMM40 gene of 53 participants.

Results: An association between IPAH and HPAH and the minor allele of rs2075850, a mutation previously associated with human Alzheimer’s disease, was detected (P < 0.05).

Conclusion: The clinical significance of the detected association remains unclear. The rs2075850 TOMM40 SNP may be considered as a candidate for investigation in a larger and more comprehensive genetic association study in the future.
FIBROSIS

Introduction: Idiopathic Pulmonary fibrosis (IPF) is a lethal respiratory disease with no effective treatments. Potential therapies for this disease have thus far failed to translate the success from pre-clinical murine models to clinical settings.

Aim: We sought to improve on limitations associated with existing small animal models of fibrosis in using a more physiologically relevant species using a lung segmental model to investigate pulmonary fibrosis in sheep.

Methods: Two separate lung segments in eight sheep received two challenges two weeks apart of either 3 U bleomycin (BLM) (1 × BLM) and 30 U (10 × BLM) in the lung and a third segment received saline as a control. Lung function in these segments was assessed for changes in resistance, BAL samples and lung tissue were used to assess for inflammation, fibrosis and collagen content two weeks after the final dose.

Results: Instillation of both 1 × BLM and 10 × BLM resulted in prominent fibrosis (pathology scores: 1 × BLM: 11 and 10 × BLM: 11.75 vs. saline: 0.75, p < 0.0001, n = 8) and collagen deposition in the isolated lung segments of sheep, not observed in controls. Compared with 10 × BLM dosing, 1 × BLM dosed segments reduced inflammatory cells in BAL. Prominent alveolar epithelial cell (AEC) hyperplasia was observed in both these lobes, but a more heterogeneous pattern and less significant loss of alveolar airspace volume of fibrosis was observed in 1 × BLM segments (1 × BLM 48 ± 2.4% vs. 10 × BLM 34 ± 3.5%, p = 0.01, n = 8). Importantly, both BLM doses induced an increase in resting airway resistance compared to saline alone (R_{awg} % increase from baseline: 1 × BLM vs. control 564 ± 200 vs. 13 ± 6%, p = 0.05; 10 × BLM 614 ± 340 vs. 13 ± 6%, p = 0.01, n = 8).

Conclusions: The results from this novel model of pulmonary fibrosis in sheep show that we were able to successfully induce fibrotic lesions with features reminiscent of usual interstitial pneumonia (UIP), observed in IPF. The large animal model may be a potential niche for investigating novel therapies for IPF.

Conflict of Interest: No.

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THE DEVELOPMENT OF A SHEEP MODEL FOR PULMONARY FIBROSIS

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TP 123

DIFFUSE PANBRONCHIOLITIS IN AN AUSTRALIAN ABORIGINE

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Diffuse panbronchiolitis (DPB) is a distinct clinicopathological syndrome that involves the upper and lower respiratory tracts. It occurs mainly in the Japanese and has rarely been reported outside of the Far East. We have recently described a case series in Melanesians. A 65 years old Aboriginal man was referred to our clinic with ‘nodular lung disease’. The clinical, radiological and serological criteria for DPB were fulfilled in his case. The known efficacy of low dose erythromycin therapy was again demonstrated after six months of treatment with clinical and radiological improvement.

We present the first case of DPB in an Indigenous Australian man. This has implications for chronic respiratory disease including bronchiectasis in Aborigines.

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AN ACUTE PRESENTATION OF AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS TREATED WITH WHOLE LUNG LAVAGE, RECOMBINANT GM-CSF AND RITUXIMAB

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Prior studies of PAP show the mean duration of symptoms at presentation is 7 months (range 3–19 months). We present a case of a 40-year-old male from a coal mining town who presented to a regional hospital with acute severe hypoxic respiratory failure, extensive bilateral alveolar opacities, mediastinal lymphadenopathy and rash. Symptoms included 3 weeks of progressive dyspnoea, productive cough, lethargy and rash despite 14 days oral corticosteroids and Erythromycin for presumed Asthma exacerbation, prescribed by his GP. Background included mild Asthma and 15 pack years smoking. Routine blood tests were unremarkable but inflammatory markers raised. He was treated unsuccessfully with broad-spectrum antibiotics for 72 hours. Bronchoscopy revealed milky secretions; transbronchial biopsy showed alveolar filling with eosinophilic PAS-positive proteinaceous material.

He was intubated and transferred to the Prince Charles Hospital and received WLL right lung (22 litres) at day 7, and subcutaneous recombinant GM-CSF. He required inotropic support post-lavage but over 48 hours, gas exchange improved and he was discharged from ICU. WLL left lung was performed at day 12 (2.76 litres). He was discharged home at day 18 with home oxygen (2 L/minute). Anti-GMCSF antibody titres from BAL fluid returned positive. Skin biopsy revealed spondiosis with non-specific inflammation and the rash subsided.

Treatment with recombinant GM-CSF was ceased after 4 weeks due to symptomatic IJV thrombus. Further WLL of both lungs was required within 4 months. Rituximab was commenced. BAL fluid later cultured Mycobacterium Intracellulare.

Two months following Rituximab, the patient has oxygen saturations of 96% room air at rest and no sputum production, but has persistent extensive radiological findings.

Conclusion: Our case is an illustration of an acute severe presentation of Autoimmune Pulmonary Alveolar Proteinosis treated with WLL, recombinant GM-CSF and Rituximab.

Key words: pulmonary alveolar proteinosis, recombinant GM-CSF, whole lung lavage, rituximab.
UTILITY OF THE COPD ASSESSMENT TEST (CAT) IN EVALUATING COPD SEVERITY

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Aim: The COPD Assessment Test (CAT) is an eight-item questionnaire designed to assess the impact of chronic obstructive pulmonary disease (COPD) on patient health status. Recent studies have demonstrated that the CAT is sensitive to changes in health status following exacerbations. We hypothesized that CAT scores in stable COPD relate to disease severity as measured by FEV1 and exacerbation frequency.

Method: A prospective study was undertaken of stable COPD patients who were enrolled into a community based, multidisciplinary COPD clinic. All patients completed the CAT during the baseline visit.

Results: Twenty nine patients were enrolled for the study. Mean age (±SD) was 70.6 (±7.6) years and 16 (55%) were male. Fifteen (52%) patients had reported to have one or more hospital admissions for COPD exacerbation in the preceding year. Patients had a mean forced expiratory volume in one second (FEV1) equal to 49.7% (±21.2) of the predicted value and a mean CAT score of 16.0 (±7.5) units. There was no association between the FEV1 (percentage of predicted value) and CAT score (p = 0.907). There was no association between the CAT score in the patients who had ≥1 hospital admissions in the preceding year compared to those who did not have any admissions (median CAT score, 16.8 vs 15.2, p = 0.400).

Conclusion: We did not observe a relationship between CAT, FEV1 and exacerbation frequency in our cohort of COPD patients. This is a surprising finding, since other studies have reported a relationship, albeit weak, between CAT, FEV1 and exacerbation frequency. A limitation of our study is the small sample size and ongoing study will allow us to validate our findings in a larger cohort.

Key words: COPD, CAT, exacerbation frequency, FEV1.

Nomination: Young Investigator Award.
NON-INVASIVE VENTILATION: BETTER THAN YOU THINK-INSIGHTS FROM ‘BEHIND THE MASK’

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Introduction: The increasing burden of chronic disease and focus on person-centred care suggests a need for frank discussions of the benefits and burdens of treatment. Non-invasive ventilation (NIV) is increasingly used in the management of acute respiratory failure due to decompensated chronic cardiopulmonary disease. Understanding the patient’s perspective is critical for the delivery of person-centred care.

Aim: To describe the subjective experience of individuals undergoing NIV for acute hypercapnic respiratory failure.

Method: Face-to-face interviews, analysed using qualitative thematic analysis.

Results: Thirteen participants were interviewed. Six interrelated themes emerged: A passenger on a journey dominated by chronic illness; balancing benefits and burdens of NIV; looking to another chance; knowing what alleviates my distress; struggling and suffering; and feeling vulnerable and trusting staff.

Participants viewed NIV as a two-edged sword; providing substantial relief from symptoms, but engendering discomfort and burden. No participant would forgo this treatment in the future. While participants sometimes appeared passive, they often had significant insight into what worked for them. Participants expressed both a sense of compulsion to accept NIV and gratitude for NIV as it facilitated another chance at life. Many participants described minimal recollection of their acute hospitalization, and placed a great amount of trust in health care providers.

Conclusions: Participants described balancing benefits and burdens of NIV, with the goal of achieving ‘another chance’. A tension exists between knowing what alleviates distress and being a passive recipient of care. Findings of this study have implications for the management of patients requiring NIV and advance care planning.

RAISED CARBOXYHAEMOGLOBIN (COHB) IN AN EX-SMOKER WITH HAEMOLYTIC ANAEMIA

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Introduction: TSANZ guidelines state that supplemental O2 therapy is contraindicated in current smokers. Blood COHb is elevated in smokers and used to screen patients for smoking. Here, we discuss a patient with chronic haemolytic anaemia whose supplemental O2 prescription was delayed due to persistently elevated COHb levels after smoking cessation.

Case Description: A patient with severe COPD (ABG: PaO2 54 mmHg, PaCO2 52 mmHg, pH 7.41, bicarbonate 32 mmol/L) and right heart failure stopped smoking in order to qualify for supplemental O2 therapy. His COHb level prior to smoking cessation was 12.2% and 6.5–8.4% post cessation (N < 2.0% in non-smokers). The patient denied continued smoking. After 2 measurements of elevated COHb over a 2 week period, increased endogenous COHb production due to his chronic haemolytic anaemia secondary to pyruvate kinase deficiency was considered to be the likely cause of the raised COHb. The patient was prescribed supplemental O2. His COHb fell to 5.5% and his exercise tolerance and right heart failure improved. Such improvements may have resulted in part from supplemental O2 reducing the capacity for endogenous carbon monoxide to bind to haemoglobin.

Discussion: COHb is produced endogenously in excess in haemolytic anaemia as it is a break-down product of red blood cells. It is raised in haemolytic anaemia, haemotoma breakdown and massive transfusion. Other causes of modest increase in COHb include certain drugs, severe COPD and pregnancy. In this case, prescription of supplemental O2 was delayed due to suspicion of smoking from elevated COHb. We recommend that other screening tests such as measurement of Cotinine, a break-down product of nicotine, be used to assist in cases where COHb is raised and smoking status is uncertain. The importance of elevated COHb to O2 transport will be discussed.

PULMONARY REHABILITATION OUTCOMES IN THE GOLD COAST HEALTH SERVICE DISTRICT

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Aim: Pulmonary rehabilitation (PR) is an evidence-based, multidisciplinary intervention for patients with chronic respiratory diseases. Benefits include decreased dyspnoea, improved health-related quality of life (QOL) and decreased health-care utilization. Studies have shown that overall completion rates of PR are poor (30–50%) and impacted by complex health issues. The aim of this study was to review clinical data and 12-month hospitalization rates of patients who had completed the Gold Coast Hospital and Health Service (GCHHS) PR programme versus those who attended less than 80% of sessions.

Methods: A retrospective review was undertaken of consecutive patients enrolled into the GCHHS PR programme. Hard-copy and electronic medical records were reviewed. Unpaired t-tests and Mann-Whitney tests were used to compare those who completed and those who failed to complete PR. Paired t-tests and paired Wilcoxon tests were used to compare baseline to post-PR data for those who completed PR and also those who attended less than 80%.

Results: Sufficient data were available for 63 patients (50 completed PR and 13 failed to complete PR). There were no significant differences between the two groups in number of hospitalizations within 12 months following PR. There was a significant improvement in St George Respiratory Questionnaire (SGRQ) and 6-minute walk distance from baseline in those who completed PR (p = 0.001 for both) but no significant improvement in SGRQ in those who did not complete PR (p = 0.055).

Conclusion: These GCHHS PR programme outcomes match published data suggesting QOL and functional exercise capacity significantly improves with rehabilitation. We did not find a reduction in hospital admissions post rehabilitation. A limitation of the study was the lack of a comparative cohort that did not commence PR.

WARD-BASED NON-INVASIVE VENTILATION HAS IMPROVED AVAILABILITY AND SHORTEST LENGTH OF STAY IN COPD EXACERBATIONS COMPARED TO AN ICU-BASED MODEL OF CARE

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Introduction: Bilevel non-invasive ventilation (NIV) is a standard care for acute exacerbations of COPD (AECOPD) with acute respiratory acidosis. We previously reported our ICU-based NIV service treated fewer patients, had increased intubation rates, and resulted in longer hospital length of stay (LOS) compared to a ward-based service at another institution. Accordingly we implemented a ward-based NIV service.

Aim: To compare our transition from an ICU to a ward-model of care.

Methods: Prospective single-centre observational study of patients admitted with AECOPD, acute respiratory acidosis (pH < 7.35, PaCO2 > 45 mmHg) and treated with NIV. In the first phase, NIV delivered exclusively in the ICU setting. Subsequently NIV delivered in the ward-setting, but targeted a milder group of AECOPD patients (pH 7.25–7.35, single organ involvement). Patient demographics, survival, intubation rates, LOS and physiological parameters were recorded.

Results: 16 cases were treated in the ICU-based service over 16-months and 32 in the ward-based service over 12-months. There was no significant difference in patient demographics and clinical outcomes of mortality (0/0%) vs 3/9%); p = 0.54), intubation [2(25%) vs 0(0%), p = 0.11] or change in ABG indices. However the ward-based service treated more patients per month (1 vs 2.75, p < 0.01) and had shorter LOS (13.4 days 95% CI, 9.3–17.5 vs 8.6 days 95% CI 6.2–10.9, p = 0.03), with a trend towards greater number of days receiving NIV (2 days 95% CI 1.6–3.3 vs 4.2 days 95% CI 2.9–5.5, p = 0.07) and more total hours of NIV received (16.1 hours 95% CI 6.6–25.7 vs 29.6 hours 95% CI 18.4–40.7; p = 0.12).

Conclusion: Transition to a ward-based NIV service enabled us to treat more patients and resulted in shorter LOS, whilst clinical outcomes were non-inferior to an ICU-based delivery model.
COHABITATION NOT COORDINATION – DIFFERENCES BETWEEN HOW PEOPLE WITH COPD AND THEIR SPOUSES USE THEIR TIME

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Aim: To explore patterns of time use in people with COPD and their spouses.

Background: Distinct activities, independent of energy expenditure, can influence health in different ways (i.e. reading and watching TV impact eating behaviours and cognitive loads differently). Use of time recalls allow construction of detailed daily activity profiles, offering unique insights into time use choices. Symbiotic relationships are common in couples where one member has a chronic disease. This is particularly evident in people with COPD where avoidance of dyspnoea inducing activities may lead to spouse reliance. Data detailing how people with COPD and their spouses cohabit are lacking.

Methods: 19 people with COPD and their spouses (COPD Age 74.4 ± 8.4 yrs. FEV1 58% ± 24%, Spouses Age 69.0 ± 11.6 yrs., FEV1 106% ± 20%), recalled four separate 24 hour time use profiles using the Multimedia Activity Recall in Children and Adults (MARCA). Using structured interviews, the MARCA systematically records individual activities, durations and where appropriate, intensities between anchor points (breakfast, lunch, dinner). Over 500 discrete activities are embedded in the adult MARCA. Contextually similar activities are collapsible into one of ten superdomains (sports/exercise, screen time, transport, quiet time, self-care, cultural, work/study, chores, social and sleep). Deviations from predicted superdomain durations (min/day) were obtained by averaging the four time use profiles from each participant and regressing superdomain durations (min/day) against age according to sex. Differences in superdomain durations between spousal members were assessed using paired t tests.

Results: People with COPD devoted more time to superdomains where low energy expenditure activities were prevalent (screen time and quiet time) than their spouses, while spouses spent more time engaging in activities contained in the superdomains chores and social. Conclusion: Differences in how people with COPD and their spouses use their time are evident.

VALIDATING PREVIOUSLY DEFINED RELEVANT 6-MINUTE WALK CHANGES

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Introduction: The previously reported 6 minute walk test (6MWT) minimal important difference (MID) is 35 metres or 10% change (Puhan et al. 2008). Aim: To validate this previously determined MID in an Australian pulmonary rehabilitation (PR) population.

Method: Retrospective data analyses from an out-patient PR programme (January 2009 to June 2013) were used. Selected patients possessed either a primary diagnosis of COPD, asthma, or bronchiectasis with airflow limitation and at least a pre and post PR measurement of: 6MWT, FEV1, and either the St Georges Respiratory Questionnaire (SGRQ) or Chronic Respiratory Questionnaire (CRQ). Four statistical methods were used to establish the MID of 6MWT distance: one anchor-based and three distribution-based methods.

Results: Analysis using an anchor-based method did not fulfil the requirement of having a correlation coefficient above 0.5 between the anchors of health related questionnaires and the 6MWT. Therefore, this analysis was terminated. An analysis based on Cohen’s estimate resulted in a MID of 28 metres (0.5×SD of change pre-post PR in 6MWT distance). Applying the empirical rule of effect of ~8% of the range of 6MWD scores (Sloan et al.) gave a MID of 11 metres. Lastly, we compared pre and post PR change scores of the SGRQ and CRQ changes with the Standard Error of the Mean (SEM) of the 6MWT (SEM defined as SD/√4, with baseline SD of 6MWT distances; 19 metres (95%CI 17–22)). Comparing the CRQ and SGRQ change scores that were established, 90.9% (CRQ) and 66.7% (SGRQ) of patients exceeded the MID, compared to 54% for the 6MWT proposed as the average threshold for MID of 28 metres.

Conclusion: These analyses conducted in respiratory patients with a wide severity range suggest that a MID for change in 6MWT of 35 metres as previously suggested may be higher than required when evaluating PR outcomes.

FAILURE TO PASS THE STEP TEST: QUALIFYING CRITERIA IN A MULTI-CENTRE RANDOMIZED CROSS-OVER STUDY OF PORTABLE OXYGEN FOR PATIENTS WITH COPD

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Aim: To identify participant and environmental factors that may have influenced the outcome of a step test used as a screening tool for subject recruitment into a multi-centre randomized cross-over trial.

Method: Patients with stable COPD under supplemental oxygen therapy were considered for inclusion into a multi-centre randomized cross-over study comparing battery powered portable oxygen concentrators to portable cylinders. Comparative analyses were used to investigate participant and environmental factors (including gender, age, Charleston co-morbidity index, step height and season) that may influence the outcome of the screening step test recruitment criteria.

Results: Thirty-five subjects out of n = 106 screened (33%) qualified for oxygen according to the criteria of the step test. Of those participants who passed 46% were female, mean age was 72.54 ± 9.06 years, mean Charleston Co-Morbidity Index was 1.68 ± 1.63 and age adjusted index was 4.65 ± 2.12. For participants who failed to pass the step test 35% were female, mean age was 72.06 ± 8.14 years, mean Charleston index was 1.74 ± 1.05 and age adjusted index was 4.55 ± 1.54. Subjects who passed the step test were more likely to have a test performed in Spring (63%) compared to those who failed to pass (46%). Seventy-four per cent of subjects who passed the step test had the greater step height of 16 cm, compared to 57% of subjects who failed to pass (lower step height is 10 cm); however, none of these factors produced statistically significant differences between groups.

Conclusion: None of these demographic or environmental factors produced a statistically significant effect on the step test screening outcome. Patients prescribed oxygen supplementation need to be regularly reassessed to ensure they still require oxygen therapy.

Key words: oxygen, concentrator, cylinder, COPD, portable, step test, qualify.

Grant Support: Nil.
SENSATION OF BREATHLESSNESS IN PEOPLE WITH AND WITHOUT CHRONIC OBSTRUCTIVE PULMONARY DISEASE: COMPARISON OF TWO INSTRUMENTS
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Introduction: Dyspnoea is a multidimensional sensation which includes intensity, sensory quality (descriptors) and unpleasantness. Previous research has produced conflicting results concerning whether the sensory quality of breathlessness differs between chronic medical conditions. Two new instruments have recently become available with which to assess the sensation of dyspnoea; the Dyspnoea-12 (D-12) and the Multidimensional Dyspnoea Profile (MDP). Both instruments assess physical and affective dimensions and use continuous rating scales.

Method: Participants with and without spirometric confirmed COPD (FEV1/FVC < 0.7) completed the D-12 and MDP, recalling sensations of breathlessness at rest. Differences between total score from the D-12 and the sub-scores from the MDP (breathlessness unpleasantness, sensory quality intensity and affective intensity) were analysed using t-test and analysis of variance with p < 0.05 considered significant.

Results: Groups were similar for age and gender (COPD, n = 106, 54 men, mean age 70 ± 9, mean FEV1 % predicted 48 ± 17, mean FEV1/FVC 0.43 ± 0.15; non-COPD, n = 47, 22 men, mean age 73 ± 11, mean FEV1 % predicted 83 ± 14, mean FEV1/FVC 0.75 ± 0.10). Preliminary analysis indicates, with the exception of affective intensity (MDP sub-score; COPD 10.6, non-COPD 15.7 (p = 0.02), no significant differences were found between the two groups for the sub-scores of the MDP sensory quality intensity (COPD 16.0, non-COPD 16.8) and breathlessness unpleasantness (COPD 4.7, non-COPD 4.7) or for the D-12 (Total score; COPD 12.4, non-COPD 13.5). Similarly, no significant differences were found for scores in either instrument for GOLD stage, though the MDP sub-score for affective intensity approached significance (p = 0.08).

Conclusion: When the sensation of breathlessness is recalled, affective intensity was greater in people with spirometrically confirmed COPD.

ANXIETY AND DEPRESSION DURING SELF-MANAGEMENT FOR COPD – AN EXPLORATORY ANALYSIS OF A MULTICENTRE RANDOMIZED CONTROLLED TRIAL (PRSM)
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Introduction: The limited access to pulmonary rehabilitation (PR) in Australia has resulted in renewed interest in alternative models of care in COPD such as the Stanford Chronic Disease Self-Management (CDSM). This programme aims to improve self-efficacy, which may be advantageous given the high prevalence of anxiety and depression in COPD. The effects of anxiety and depression on CDSM are largely unknown, as are the effects of CDSM on healthcare utilization.

Aim: To investigate the impact of anxiety and depression on hospital admissions in participants undergoing CDSM.

Methods: Retrospective, exploratory analysis of a multicentre randomized controlled trial of PR vs CDSM (PRSM). 169 participants (mean age 68 years, mean FEV1 52% pred, 73 female) attended PR (8 weeks, 16 sessions; n = 85) or CDSM (6 weeks, 6 sessions; n = 84). Hospital anxiety and depression scale (HADS) scores and self-reported hospital admissions were recorded after 3, 6 and 9 months. Data were analysed via generalized estimating equations (GEE).

Results: Across both groups, participants with high anxiety scores (≥ 10) had a tendency towards more hospital days than others (p = 0.082), whilst anxiety ‘responders’ (reduction ≥ 1.5 points) had more frequent hospitalizations (beta = 0.09, SE 0.05; p = 0.043). Within the CDSM group, high anxiety was associated with more hospital days (beta = 2.77, SE = 1.01; p = 0.006) but not a significantly greater need for hospitalization (p = 0.056) or more frequent hospitalizations (p = 0.197). High levels of depression did not affect any outcomes relating to hospital admissions. The effect of CDSM on hospitalizations did not differ between anxiety or depression ‘responders’ and ‘non-responders’.

Conclusion: The effectiveness of the Stanford CDSM programme on hospital admissions in people with COPD appears to be influenced by high levels of anxiety but not depression.
PREVALENCE AND IMPACT OF COGNITIVE IMPAIRMENT IN COPD

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Introduction: Patients with Chronic Obstructive Pulmonary Disease (COPD) are at risk of developing cognitive impairment due to a variety of reasons. Reported prevalence rates vary. There is a lack of research within Australia on the prevalence and impact of cognitive impairment in COPD.

Aim: To assess the prevalence of cognitive impairment in COPD patients referred to pulmonary rehabilitation using the Mini Mental State Examination (MMSE), and to assess the impact of this on pulmonary rehabilitation (PR) outcomes.

Method: A prospective cross sectional study of COPD patients referred to PR was conducted. Patients were screened for cognitive impairment using the MMSE. Six minute walk test, inhaler device technique, Bristol COPD knowledge questionnaire, self-management scenarios and the St George Respiratory Questionnaire were administered pre and post PR.

Results: 29 patients with COPD were recruited. The mean (SD) age was 69.4 (8.8) years and 15 (52%) were male. Mean (SD) baseline FEV1 was 52.27% (19.72). Of the 29 patients who consented 19 (66%) completed 75% of the scheduled exercise sessions, deeming them a ‘PR completer’. The mean (SD) MMSE score was 27.4 (1.8). Only 8 (28%) of the participants were considered to have mild cognitive impairment (MMSE score 21–26); all other participants were in the normal range. There was no difference in the proportion that completed PR according to their cognitive status; mild impairment 6 (75%) versus normal cognitive function 13 (62%); p = 0.42.

Conclusion: In this population the majority of patient referred to PR had normal cognition according to the MMSE, almost 1/3 showed only mild impairment. This may reflect clinician selection bias for pulmonary rehabilitation referral. Mild impairment did not impact on their ability to complete PR. Further work is required to assess the effect of more severe cognitive impairment on pulmonary rehabilitation outcomes.

ARE TWO SIX-MINUTE WALK TESTS NECESSARY DURING ACUTE EXACERBATIONS OF COPD?

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Background: The six-minute walk test (6MWT) is a valid, reliable and widely used measure of exercise tolerance in COPD. Repeat testing is recommended during stable disease, however its necessity during an acute exacerbation of COPD (AECOPD) is unclear. This study investigated the repeatability of the 6MWT during AECOPD.

Methods: 17 participants (7 male, mean age 69 years, FEV1, 42% pred) who presented to hospital with AECOPD and sputum expectoration were recruited. Two 6MWTs (T1, T2) were performed in accordance with ATS/ERS guidelines at hospital discharge. Distance walked (6MWD) at T1 and T2 were compared via Bland-Altman plots. Exploratory comparisons between ‘responders’ (T2 – T1 > 30 m) and ‘non-responders’ were performed via unpaired t-tests.

Results: Mean 6MWD difference was ~4.9 m but limits of agreement were wide (~114 to 104 m). Compared to ‘non-responders’, ‘responders’ (n = 6) had a significantly lower smoking history 22.1 (14) vs 75.5 (48) years, p ≥ 0.02; shorter length of stay 2.7 (0.7) vs 7.0 (4.6) days, p = 0.04; and a trend towards more rest 1.7 (1) vs 0.6 (0.9), p = 0.052.

Conclusion: There is marked variability between two 6MWDs on the same day at the end of a hospital admission for COPD exacerbation. A single 6MWD may not be a reliable measure of functional exercise tolerance immediately following a COPD exacerbation.

Supported by: Physiotherapy Research Foundation, Institute for Breathing and Sleep, La Trobe University.

Nomination: Physiotherapy prize.

Conflict of Interest: No.

AIRWAY RESPONSE TO DEEP INSPIRATION: RELATIONSHIP TO SMOOTH MUSCLE STRUCTURE

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Aim: To examine the relationship between the in vivo airway response to DI and the structure of the ASM layer.

Methods: Subjects (control, asthma or COPD) due to have lung resection surgery completed a questionnaire on respiratory health, had allergy skin tests and had their response to DI assessed before and after bronchodilator inhalation. Response to DI was determined from the ratio of expiratory flow measured after maximal expiration (M) and partial expiration (P) from a submaximal lung volume (i.e. M/P ratio). Post-operative tissue was fixed for structural assessment of the area of ASM, numerical density and mean volume of ASM cells, and estimation of the volume fractions (Vv) of ASM, ECM and ‘Other’ within the ASM layer.

Results: M/P ratios were typically <1 in the asthmatic and COPD groups indicating bronchoconstriction following a DI. When all subjects were combined, the pre-bronchodilator M/P ratio positively correlated with the FEV1/FVC ratio and was inversely related to age, but not to subject height or weight. Pre-bronchodilator M/P ratio was positively correlated with the number of ASM cells per volume (favouring reduced bronchoconstriction after DI) but not with mean ASM cell volume or VASM, VECM or Vaso. There was no relationship with post-bronchodilator M/P ratios for subject characteristics, lung function or ASM layer parameters.

Conclusion: The airway response to DI is related to the volume density of ASM cells before, but not after bronchodilator. Findings suggest that the established relationship between response to DI and ASM structure is determined by contractile rather than passive properties of ASM.

ARE TWO SIX-MINUTE WALK TESTS NECESSARY DURING ACUTE EXACERBATIONS OF COPD?

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Background: The six-minute walk test (6MWT) is a valid, reliable and widely used measure of exercise tolerance in COPD. Repeat testing is recommended during stable disease, however its necessity during an acute exacerbation of COPD (AECOPD) is unclear. This study investigated the repeatability of the 6MWT during AECOPD.

Methods: 17 participants (7 male, mean age 69 years, FEV1, 42% pred) who presented to hospital with AECOPD and sputum expectoration were recruited. Two 6MWTs (T1, T2) were performed in accordance with ATS/ERS guidelines at hospital discharge. Distance walked (6MWD) at T1 and T2 were compared via Bland-Altman plots. Exploratory comparisons between ‘responders’ (T2 – T1 > 30 m) and ‘non-responders’ were performed via unpaired t-tests.

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Conclusion: There is marked variability between two 6MWDs on the same day at the end of a hospital admission for COPD exacerbation. A single 6MWD may not be a reliable measure of functional exercise tolerance immediately following a COPD exacerbation.

Supported by: Physiotherapy Research Foundation, Institute for Breathing and Sleep, La Trobe University.

Nomination: Physiotherapy prize.

Conflict of Interest: No.

THE BENEFITS OF REPEATING A PULMONARY REHABILITATION PROGRAMME (PRP): A RETROSPECTIVE ANALYSIS OF PATIENTS WITH CHRONIC LUNG DISEASE (CLD) DOING REPEAT PRP AT WESTMEAD HOSPITAL, NSW

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Aim: There is little evidence to guide: whether repeat PRP is helpful; the ideal interval between PRP repeats; the indications to repeat; the sub-population that benefits most from PRP repeat. We sought to characterize the patient population that has repeated the PRP in our centre, and to assess outcomes after repetition of PRP.

Method: A retrospective review (12 years) of patients with CLD who participated in the PRP on more than one occasion was undertaken to assess outcomes over repeated PRP (increase in 6 minute walk distance [6MWD] and FEV1). Data presented as mean ± SD.

Results: 872 patients completed PRP between September 2001 to September 2013, of whom 140 (16%) had completed PRP more than once. 109 completed twice (PRP2), 23 completed three times (PRP3), 7 completed four times (PRP4), and 1 completed six times (PRP6). The change in 6MWD after PRP1 was 59 m (413 ± 88 m to 472 ± 104 m, p < 0.0001), and this diminished after PRP2 to 31 m (from 374 ± 109 m to 414 ± 112 m, p < 0.0001), and after PRP3 was 26 m (374 ± 101 m to 400 ± 103 m, p < 0.003). The FEV1 was 1.03 ± 0.44 L pre PRP1, 0.92 ± 0.4 L pre PRP2, and 0.84 ± 0.38 L pre PRP3.

Conclusion: Patients with CLD who repeated PRP at least twice tended to have worse lung function at the time of repeat, but still had significant gains in 6MWD with repeat PRP, although the increase in 6MWD over time appeared to relate to worsening lung mechanics.

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PERCEPTIONS OF PATIENTS WITH VERY SEVERE COPD TOWARDS END-OF-LIFE CARE

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Introduction: Little research has shown how illnesses with longer trajectories such as chronic obstructive pulmonary disease (COPD) fit with palliative care services that have been developed for cancer patients. Patients with severe COPD have high and often complicated end-of-life needs that are currently not being met by health services. The transition and timing for referral of COPD patients to palliative care services has not been straightforward as prognostication is notoriously difficult.

Aim: To investigate the attitudes and opinions of patients with COPD regarding specialist palliative care services.

Method: Patients with a diagnosis of COPD requiring an admission for non-invasive ventilation were invited to participate in the study. All patients had very severe COPD many with chronic respiratory failure. Interviews were conducted focusing on understanding of health, planning for future care and end-of-life issues. Inductive analysis was used to draw out three key themes.

Results: Patients with severe COPD did not perceive a role for their General Practitioner in their acute care. Psychologically and emotional support was expected to be provided by acute services. Those with end-stage disease had a connection with secondary care and many wanted to die in hospital surrounded by health professionals they trust. The interviewees did not see the relevance of specialist palliative care services. There was no easy-to-identify entry point into these services or the need to plan for an exit point. As no clear entry point into secondary respiratory services was identifiable, so was there no need to plan for an exit point.

Conclusion: Specialist palliative care services are charged with extending care services to those with chronic illness however the palliative services developed for cancer patients don’t seem to serve COPD patients with a long illness trajectory. We demonstrated a mismatch between perceptions of those leading health systems and those of people living with conditions such as COPD.

INTUBATION RATE, MORTALITY AND ARTERIAL BLOOD GAS (ABG) OUTCOMES IN EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WITH ACIDOTIC HYPERCAPNIC RESPIRATORY FAILURE TREATED WITH NON INVASIVE VENTILATION (NIV) – RESULTS FROM A DEDICATED NIV UNIT

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Introduction: NIV is the treatment of choice for acidotic hypercapnic respiratory failure during exacerbations of COPD. A recent audit of general respiratory units in the UK showed hospital mortality for patients undergoing NIV was 26%.1

Aim: To assess the intubation rate, mortality rate and ABG outcomes of patients with COPD exacerbation undertaking NIV in a dedicated NIV unit and to determine predictors of intubation and mortality.

Method: Data of successive COPD patients admitted with respiratory failure requiring NIV at a dedicated NIV unit in a UK hospital were collected. Intubation rate, in-hospital mortality rates and ABG data (pre NIV and one hour after NIV establishment) were analysed for admissions between February 2004 and February 2010.

Results: 708 COPD patients underwent NIV. There were 19 (2.7%) intubations (hospital survival 63%) and 101 (14%) deaths. Pre NIV ABG measurements (mean ± SD) were: pH 7.26 ± 0.07, pCO2 (mmHg) 76.1 ± 19.1, pO2 (mmHg) 77.3 ± 37.1. After 1 hour of NIV, there was a significant improvement in pH 7.32 ± 0.07 and pCO2 64.2 ± 17.4. pO2 78.2 ± 33.9 remained unchanged. Not all NIV patients were clinically indicated for intubation. Intubated patients were more acidotic when commencing NIV (pH 7.20 ± 0.08) and after 1 hour of NIV (pH 7.26 ± 0.10). The leading causes of death were 1) end stage COPD, 2) elderly with frailty status and 3) other organ failure.

Conclusion: NIV can be successfully performed in a dedicated NIV unit on respiratory ward in COPD patients with acute respiratory failure low intubation rates. Of those intubated, hospital survival was 63%. Those intubated were also more acidotic before and 1 hour after NIV. End stage COPD, elderly and frailty and co-morbidities accounted for a high risk of death.

Key words: NIV, COPD, respiratory failure.

Support: Nil.

Conflict of Interest: None.

Reference
1. Roberts CM et al. Thorax 2011; 66: 43–8.
CORRELATION BETWEEN HYPOXAEAMIA AND LUNG FUNCTION TESTING IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Aim: Long-term oxygen therapy (>15 hours a day) is the only therapy that has been shown to improve the survival rate in COPD. There are no clear pathways to identify which patients are likely to require long-term oxygen therapy. The aim of this study was to determine whether lung function testing can be used to predict hypoxaemia and hence the need for supplementary oxygen in patients with COPD.

Methods: 346 patients with COPD had lung function testing (spirometry and lung diffusing capacity) and oxygen assessment (arterial blood gas analysis and six-minute walk test) when clinically stable. STATA was used for statistical analysis.

Results: Of the 346 patients, 182 did not qualify for supplementary oxygen, 99 qualified for ambulatory oxygen therapy and 65 qualified for continuous oxygen therapy.

1) The mean percent predicted forced vital capacity (FVC) was lower in the continuous oxygen therapy group, otherwise there were no statistically significant between-group differences in lung function.

2) On analysis of continuous variables, there was no significant correlation between the arterial partial pressure of oxygen (PaO2) and any of the parameters of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), forced expiratory ratio (FEV1/FVC), diffusion capacity for carbon monoxide (DLCO) or transfer coefficient for carbon monoxide (KCO). An example scatterplot demonstrating the lack of correlation between PaO2 and DLCO is shown in the attached figure.

Conclusion: There was no clear correlation between hypoxaemia and lung function in COPD.

LOGAN HOSPITAL WARD BASED NIV DATABASE AUDIT

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Aim: To review the first year of ward based Non-Invasive ventilation (NIV) at Logan Hospital. To identify patient demographics, outcomes, length of stay versus duration of NIV therapy in addition to smoking status, pulmonary rehab completion and home oxygen status in an effort to improve patient care.

Method: An audit of a clinical database was undertaken. Patient admissions from 19/05/2011 to 19/05/2012 were reviewed. Patients requiring admission for NIV were reviewed. Admissions from the Intensive Care Unit and interhospital transfers already established on therapy were excluded as the initial care was not provided in the ward. Thirty three admissions were identified as requiring NIV which was provided in the ward.

Results: Thirty three admissions (17 Female) with an mean age 65.9 ± SD 11.9 (range 32–83). In the COPD cohort the FEV1 ranged from 0.30–1.94 litres (18%–52% predicted). The most common indication for NIV therapy was type 2 respiratory failure (85%), other indications included pneumonia, decompensated obstructive sleep apnoea and hypoxic respiratory failure. 51.5% of patients were on home oxygen therapy, 27% had completed a pulmonary rehabilitation programme, 64% were ex-smokers and 33% were current smokers. Twenty eight (85%) patients were successfully managed with ward based NIV. Three patients required transfer to ICU and required invasive ventilation, two survived. Two patients had NIV withdrawn and died.

Conclusion: Ward based NIV is safe and achieves acceptable clinical outcomes.

Key words: Non-invasive ventilation, T2RF, FEV1.

Grant Support: None.

CAN VENOUS BLOOD GAS EVALUATION RELIABLY PREDICT ARTERIAL BLOOD GAS LEVELS IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE?

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Introduction: Arterial blood gas (ABG) evaluation is a common and important aspect in workup of patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) to define respiratory failure and also to assess oxygen requirement accordingly. However it is procedure with some risks particularly local injury to artery or nerves, haematoma formation, infection and not to mention adequate knowledge and skill required to obtain a sample.

Aims: This study aimed to assess whether venous blood gas (VBG) evaluation can reliably predict ABG levels in patients admitted with AECOPD. This in turn would effectively prevent arterial puncture trauma and related complications.

Material and Methods: In this prospective observational study we included 38 patients who presented to Gold Coast Hospital emergency department and were admitted under Respiratory unit with symptoms of AECOPD. Informed consent was obtained from all patients. All underwent ABG and VBG within 24 hours of admission. All patients were treated similarly in terms of AECOPD.

Results: 34 patients were enrolled in the study comprising of 16 males (47%) and 18 females (53%). Median age was 70.6 (range 57–89) years. The correlation coefficient between ABG and VBG were: pH (0.699, p < 0.001), pO2 (0.356, p = 0.039), pCO2 (0.683, p < 0.001), HCO3 (0.961, p < 0.001) and base excess (BE) (0.979, p < 0.001).

Conclusion: Our study demonstrates that there is indeed a correlation between ABG and VBG parameters (very strong: HCO3 and BE, moderate: pH and pCO2, and weak: pO2). This suggests that VBG may have clinical utility in the respiratory failure management of AECOPD patients. A limitation of our study is the small sample size and ongoing study will allow us to validate our findings in a larger cohort.
EVALUATION OF INHALER TECHNIQUE AND MEDICATION ADHERENCE IN COPD PATIENTS

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Introduction: Chronic Obstructive Pulmonary Disease (COPD) imposes a significant health and economic burden on patients, their families and society as a whole. Multiple-inhaler use has been associated with higher rates of non-adherence than single-inhaler use in COPD patients. Increased awareness of the inhaler medication adherence of COPD patients may improve treatment outcomes.

Aim: The aim of this study was to review the adherence and inhaler-technique of patients admitted to hospital with an acute exacerbation of COPD (AECOPD).

Method: A prospective study was undertaken of patients who were admitted to Gold Coast Hospital for management of AECOPD. During the admission, inhaler medication adherence was assessed using the Medication Adherence Report Scale (MARS) and inhaler-technique was evaluated using the National Asthma Council’s standardized ‘Inhaler technique in adults with asthma or COPD’ checklist.

Results: Forty-six patients were interviewed with a mean age (± SD) of 71 (± 9) years and 28 (59.6%) were male. Twenty-three (50%) of the patients made critical errors while demonstrating their inhaler technique. Thirty-three (72%) patients had good self-reported adherence to inhaler medications (MARS ≥ 23); the remaining 13 (28%) had self reported poor adherence (MARS ≤ 22).

Conclusion: This study suggests that while the majority of COPD patients report good adherence to their inhaler medications, about half of the patients made critical errors that would result in inadequate amounts of drug reaching the lung. Health care professionals should consider routinely evaluating COPD patients’ inhaler technique and provide counselling.

Nomination: Young Investigator Award.

RISK OF FALLS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A 12-MONTH PROSPECTIVE COHORT STUDY

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Introduction: People with chronic obstructive pulmonary disease (COPD) may present with underlying risk factors associated with an increased incidence of falls; however, the falls rate over 12 months and the risk factors have not been identified.

Aim: The aims of this study were to determine the falls prevalence, incidence and time to first fall, as well as the risk factors in COPD, using recommended prospective falls outcome data.

Method: Forty-one community-living participants with stable COPD, (mean ± SD) age 71 ± 8 years and FEV1: 45.1 ± 16.2 %pred, were included. At baseline, COPD-related, physical function measures and falls-risk assessment tools were used. The number of falls was collected prospectively using monthly calendars over 12 months. Negative binomial regression was used to quantify the incidence rate ratios (RR), taking into account all falls adjusted for varying duration of follow-up, while Cox regression models identified hazard ratios (HR) for time to first fall; related to baseline measures.

Results: The falls prevalence was 40%, with an overall incidence rate ratio of 1.17 falls/person-year. In adjusted models, pack-years (RR: 1.01; 95%CI: 1.00 to 1.03; p = 0.04), prescribed number of medications (RR: 1.16; 95%CI: 1.00 to 1.35; p = 0.04), number of falls reported in previous year (RR: 1.84; 95%CI: 1.10 to 3.17; p = 0.02) and fear of falling scored in the Falls Efficacy Scale-International (RR: 1.07; 95%CI: 1.01 to 1.13; p < 0.01) were associated with falls incidence. Unadjusted survival models indicated longer smoking history (HR: 1.02; CI: 1.00 to 1.04; p < 0.01), higher number of days in hospital due to acute exacerbation (HR: 1.05; CI: 1.00 to 1.09; p = 0.02), and advanced age (HR: 1.09; CI: 1.01 to 1.18; p = 0.01) as factors associated with an earlier time to first fall.

Conclusion: A combination of patient and disease-related factors was associated with falls incidence and a faster time to first fall in community-living people with COPD.

Reference
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OWNERSHIP OF WRITTEN ASTHMA ACTION PLANS IN A LARGE SURVEY OF AUSTRALIANS LIVING WITH ASThma

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Introduction: Asthma self-management education is highly effective in reducing the burden and risk of asthma. Essential components include self-monitoring of symptoms and/or peak flow, a written asthma action plan (WAAP) and regular medical review.

Aim: We sought to determine the proportion of Australians with current asthma with a WAAP, and identify the factors associated with WAAP ownership and use.

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. Subjects were asked whether they had a WAAP that was provided by a doctor and, if they did, whether they followed it. Using the Asthma Control Test (ACT), asthma control was categorized as well-controlled (WC) (20–25), near-well controlled (NWC) (16–19) or very poorly controlled (VPC) (9–15).

Results: 9388 respondents with ever-diagnosed asthma were identified. 2610 completed the WAAP question. Ownership rates were 34% in WC, 26% in NWC and 20% in VPC asthma and 42% vs 19% in those who did vs did not require acute asthma care in the previous year. Having and following a WAAP was more common when the WAAP was considered practical, personalized and easy to understand.

Discussion: WAAP ownership remains low despite more than two decades of active promotion in Australia. It is somewhat higher in more at-risk patients. Simple strategies could make WAAP more acceptable to people with asthma.

CD14 PROMOTER METHYLATION AND IGE LEVELS IN ‘EAST-WEST’ KARELIAN CHILDREN

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Rationale: The huge disparity in worldwide prevalence of asthma and allergy is still to be elucidated. As the hygiene hypothesis only explains some of these differences, we propose the novel hypothesis that epigenetics, of which DNA methylation is a key component, may have a profound effect by controlling gene expression and thereby cellular phenotype.

Aim: To assess the role of CD14 methylation in determining the differences in the levels of IgE as a surrogate for the high allergy disparity observed in the genetically similar Karelian population east and west of the Finnish-Russian border.

Methods: Total serum IgE levels were measured using a radioallergosorbent test (UniCAP 1000 v.2). Methylation levels of the 3 CpG sites in the promoter of CD14 gene were determined in 250 Finnish and 250 Russian Karelian children. Bisulfite-treated DNA samples were amplified and subsequently pyrosequenced. CpG site 2 is located at a single nucleotide polymorphism (SNP) site (rs2569191: CD14 -1145CT) that is in linkage with a functionally important SNP (rs2569190: CD14 -159/ -260 CT).

Results: Methylation levels of sites 2 and 3 of the promoter were higher in Finnish Karelian children (59.0% and 92.7%, respectively) compared to Russian children (57.7%, p = 0.006; and 90.1%, p < 0.001, respectively). Methylation levels at all 3 promoter sites correlated with total serum IgE levels only in Russian children (site 1: Pearson correlation = -0.192, p = 0.002; site 2: Pearson correlation = 0.24, p = 0.002; site 3: Pearson correlation = -0.141, p = 0.026). Furthermore, methylation levels were associated with the functionally important CD14 -159/ -159CT SNP in the Karelian children (CC: 59.4%, CT: 57.9%, TT: 57.4%, p = 0.009).

Conclusion: Methylation of CpG sites in the CD14 promoter was associated with IgE levels in children living in the ‘Eastern’ environment. Differences in CD14 methylation levels in Russian and Finnish Karelian children may partially explain the disparity in allergy seen in that population.

Funding Source: NHMRC and Asthma Foundation of Western Australia.
PRACTITIONER ASTHMA COMMUNICATION AND EDUCATION (PACE) PROGRAMME IMPROVES PHARMACISTS CARE OF CHILDREN WITH ASTHMA

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Introduction: Research is consistently demonstrating a gap between best practice and actual clinical practice in primary care. Practitioner Asthma Communication and Education (PACE) Australia is an educational programme for general practice physicians, aimed to address challenges with managing paediatric asthma in regions where asthma morbidity in paediatrics stems from deficiencies in guideline-recommended care, clinician-patient communication and patient education. The implementation of PACE Australia has resulted in improved GPs’ paediatric asthma management practices.

Aim: The aim of this study was to adapt PACE to the community pharmacy setting (PACE for Pharmacy), to test its feasibility and to gauge the potential impact of PACE for Pharmacy on the practice of pharmacy.

Method: Forty-four pharmacists were recruited and trained in the PACE for Pharmacy programme. Pharmacist self-reported data relating to patient education and communication strategies were collected pre and one month post programme completion. The mean pharmacist self-reported scores for each item was compared pre and post training using a Paired Samples T-Test (significance 0.05, power 0.8). Shapiro Wilks test was used to determine the normal distribution of data. Pharmacist self-reported data surrounding programme satisfaction/acceptability was also collected.

Results: Pharmacist mean self-reported data show a statistically significant increase in scores in relation to the communication strategies provided in the PACE for Pharmacy workshops. Specifically, significant improvements were seen in pharmacist confidence in using strategies, perceived helpfulness of specific strategies, frequency of use of strategies and use of strategies when counselling on new medication. Pharmacist mean self-reported data also showed a significant increase in confidence in educating around inhaled corticosteroid use. The workshops were judged to be very valuable with 88% of pharmacist participants indicating that they ‘gained a lot’.

Conclusion: This study provides preliminary evidence that PACE Australia can be translated into community pharmacy and that it has potential to improve pharmacists’ communication skills and patient education.

ENDOTHELIN-1-MEDIATED CONTRACTION OF INTRAPULMONARY AIRWAYS AND ARTERIES IN RAT LUNG SLICES

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Introduction: Intrapulmonary airways and arteries are an important therapeutic target in many lung diseases. Endothelin-1 (Et-1) is a potent constrictor of smooth muscle implicated in lung diseases such as asthma and pulmonary hypertension. The lung slice technique allows direct observation of intrapulmonary airway and artery reactivity in situ, and whilst airway reactivity has been extensively characterized, assessment of vascular pharmacology within lung slices is relatively limited.

Aims: Our aim was to compare Et-1 reactivity between intrapulmonary airways and arteries in rat intrapulmonary airways.

Methods: Male Sprague-Dawley rats (350–400 g) were used for preparation of lung slices. Briefly, heparin (500 IU in HBSS/HEPES) was injected into the right ventricle, followed by agaron (2% in HBSS/HEPES) into the trachea via cannula, and the lungs bathed in cool HBSS/HEPES before slices (150 μm thickness) were cut using a vibratome. After overnight incubation at 37°C, the changes in airway and artery areas within slices were imaged using phase-contrast microscopy during perfusion with Et-1 antagonists (ETAr – bosentan, ETa – BQ123, ETA – BQ788), or dilator agents.

Results: Rat intrapulmonary airways (~200–300 μm diameter) and arteries (100–200 μm) contracted to a similar level in response to Et-1, with pEC50 values of 7.9 ± 0.4 and 7.7 ± 0.2, respectively. Bosentan (10 μM) significantly antagonized Et-1-induced contraction in both airways and arteries, with contraction mediated via ETα receptors. The β2-adrenoceptor agonist salbutamol relaxed intrapulmonary airways but not arteries, and the novel dilator rosiglitazone was able to elicit both airway and artery relaxation.

Conclusion: We have characterized contractile responses to Et-1 and differential responses to dilators in rat intrapulmonary airways and arteries in lung slices. This technique can now be applied to disease models to explore the mechanisms underlying altered reactivity and for assessment of novel therapeutics for asthma and pulmonary hypertension.

PRESENCE AND MAGNITUDE OF FACTORS ASSOCIATED WITH POOR ASTHMA CONTROL IN PATIENTS WITH ASTHMA AT WESTERN HEALTH, MELBOURNE: PATIENT AND PHYSICIAN PERSPECTIVE

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Introduction: Achieving optimum asthma control in patients remains an ongoing challenge nationally and at Western Health. Asthma exacerbations are frequent in our patients with high attendances at the Emergency Department (ED) and low attendance in our asthma clinics.

Aim: The aim of this study was to identify the local barriers to optimum asthma control in our community.

Method: Adult patients (n = 50) with asthma admitted to ED, inpatient ward and those in outpatient clinics participated in a structured questionnaire assessing demographic profile, asthma severity, medications, exacerbating factors, socioeconomic factors, asthma education and WAP usage. Physicians (n = 30) were surveyed anonymously with an online questionnaire regarding the usage and barriers in implementing WAP.

Results: The preliminary analysis demonstrated mean (SD) age of participants was 43 years; 53% men, 80% non smokers; 30% had a tertiary qualification. Psychological issues were common (70%). While 70% felt their asthma was well controlled the Asthma Control Questionnaire (ACQ5) demonstrated only 30% were well controlled. All could afford the cost of their medications, inhaler technique was correct in over 90%. The median (range) of presentations to the ED last year was 2. Asthma health literacy was poor in 80%; only 30% had a WAP. Most (70%) did not follow their WAP for a variety of reasons and 57% were not confident using it. Physician limitations to use of WAP included lack of time and difficulty in obtaining an action plan easily.

Conclusion: The major drivers of poor asthma control identified in our population include poor asthma education coupled with the low uptake and adherence to a WAP. Measures to improve asthma education and self-management skills in addition to increased support and treatment of psychological issues need to be explored.

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INFECTION WITH LIVE HELICOBACTER PYLORI ATTENUATES AIRWAY HYPER-RESPONSIVENESS IN ADULT MICE

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Introduction: In recent years, the incidence of asthma in developed countries has increased markedly. Of particular relevance, epidemiological studies show an inverse correlation between asthma incidence and chronic infection with the gastric bacterium Helicobacter pylori.

Aim: We aimed to assess whether *H. pylori* infection would attenuate an asthmatic phenotype in a mouse model of allergic airways disease.

Method: We infected adult female C57BL/6 mice (n = 10 per treatment) with 106 cfu of a proprietary strain of live Helicobacter pylori via gavage. The live *H. pylori* used was fully active and capable of colonizing the gastric mucosa in mice. Control mice were gavaged with saline. Eight weeks after infection, mice were subjected to a standard systemic ovalbumin sensitization protocol. This was followed by five daily ovalbumin aerosol challenges for infected mice and the positive control group. The negative control group received five daily saline aerosols. Twenty four hours after the last aerosol, we assessed responsiveness to methacholine (MCh) via the forced oscillation technique and cellular inflammation in bronchoalveolar lavage.

Results: Infection was confirmed via bacterial culture. Airway resistance at the maximum dose of MCh was not significantly different between *H. pylori* infected mice and negative control mice. Both groups had significantly lower airway resistance at the maximum dose of MCh compared to positive controls, (positive control = 1.55 ± 0.45 cm.H2O.s.mL−1, *H. pylori* infected mice = 1.11 ± 0.21 cm.H2O.s.mL−1, negative control = 0.97 ± 0.18 cm.H2O.s.mL−1). Infected mice had significantly fewer eosinophils and significantly more lymphocytes (p < 0.05 in both cases) in their lavage compared to positive controls.

Conclusion: Infection with live *H. pylori* significantly attenuated an ovalbumin induced allergic airways disease phenotype in adult mice. Our finding supports the notion that exposure to microbial antigens live *H. pylori* can contribute to normal immune system development and function.

A MOUSE MODEL OF ASTHMA

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Introduction: Mouse models show that prolonged transforming growth factor alpha (TGF-α) expression promotes chronic lung disease particularly in early growth response-1 (Egr-1) deficient mice. Notably, airway smooth muscle (ASM) is thickened and the exaggerated increase in lung resistance following bronchoconstrictor challenge supports a role in airway disease.

Aim: We aimed to determine the effect of short-term TGF-α expression on ASM thickening and the development of airway hyperresponsiveness (AHR).

Method: TGF-α was conditionally expressed in the airway epithelium of transgenic mice (Clara cell secretory protein-rtTA4/−)/tetO(7)/TGF-α4/−) following 10 d exposure to doxycycline in Chow. Egr-1 deficient mice on doxycycline (n = 5) were compared with a control group (n = 4) that were wild type for Egr-1 and did not receive doxycycline. Airway and lung mechanics were assessed by the forced oscillation technique and lungs fixed for subsequent airway morphology.

Results: ASM thickening was detected in TGF-α transgenic Egr-1 deficient mice (P < 0.05) following doxycycline treatment for 10 d. AHR was also demonstrated, defined by an exaggerated increase in Newtonian resistance after methacholine challenge (P < 0.05) compared with controls. In comparison, there was no effect on lung elastance or tissue damping before or after methacholine.

Conclusion: Doxycycline induced-TGF-α expression in Egr-1 deficient mice, after 10 d, produces ASM remodelling and AHR with no change in parenchymal mechanics. Short-term TGF-α expression in airway epithelial cells promotes features characteristic of asthma.

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PATTERNS OF HEALTH CARE UTILIZATION IN A REPRESENTATIVE COHORT OF AUSTRALIANS LIVING WITH ASTHMA

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Introduction: Asthma management aims to both improve symptomatic control and reduce need for urgent health care.

Aim: To determine the spectrum of planned and urgent health care professional (HCP) interactions over a year in Australians with current asthma.

Methods: Members of a large panel were invited to participate in an online survey. The cohort selected was representative of the national population with current asthma aged 15+ by age, gender and State. In analysis, reweighting was applied to ensure that the individual datasets were representative. Within the previous year, the frequencies of planned and urgent General Practitioner (GP) visits, Emergency Department (ED) attendances, hospital visits and discussions with a pharmacist about asthma were recorded.

Results: 9388 respondents with ever-diagnosed asthma were identified: after stratification, 3033 subjects with current asthma were selected of whom 2986 completed the survey. 76.3% of the cohort had had an interaction with one or more HCP in the period. The rates of attendance for the weighted population in the period by type of HCP are reported.

| None | One | Two or three | Four to six | Over six |
|------|-----|-------------|------------|---------|
| Planned GP visit | 26.6% | 36.6% | 26.6% | 7.5% | 2.7% |
| Urgent GP visit | 66.1% | 19.6% | 10.1% | 3.0% | 1.2% |
| ED/hospital visit | 90.0% | 7.4% | 1.9% | 0.5% | 0.2% |
| Pharmacist | 79.5% | 9.1% | 8.8% | 2.0% | 0.6% |

Of 269 patients who attended an ED, 98 (3.7% of the whole population) were admitted overnight.

Conclusions: Urgent health care episodes for asthma remain common despite the majority of people with asthma reporting one or more planned GP visits about their asthma in the previous year. Improving the frequency of visits should provide an important opportunity to enhance asthma knowledge, refine asthma care and improve asthma outcomes. Pharmacists appear under-utilized as a clinical resource.

ANTI-RHINOVIRUS ANTIBODIES IN CHILDREN WITH ASTHMA EXACERBATIONS

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Introduction: Asthma exacerbations are associated with human rhinovirus (HRV) infections and more severe exacerbations in young children are associated with HRV-C. No detailed serological study of infection with HRV and the relationship with asthma has been performed.

Aim: To determine antibody binding to antigens of each HRV species in plasma from children admitted to hospital with asthma exacerbations, and compare it to that of healthy children.

Methods: Recombinant polypeptides of viral capsid protein 1 (VP1) representing two genotypes from each HRV-A, B and C species were expressed and purified by affinity and size exclusion chromatography. The presence of secondary structure similar to the natural antigens was verified by circular dichroism. Specific and absolute IgG1 measurements were quantitated by immunoassays and immunoaabsorption using plasma from healthy (n = 96) and asthmatic (n = 47) children. HRV, found in the majority of children at the time of their exacerbation (72%), was analysed using molecular typing.

Results: Asthmatic children had higher total IgG1 antibody responses to HRV and the IgG1 titres specific to HRV-A, and to a lesser extent HRV-B, than the non-asthmatic controls. The species-specific responses to HRV-C were significantly lower than titres to HRV-A and HRV-B in both asthmatic and non-asthmatic children (p < 0.001) and were not associated with the susceptibility to asthma exacerbation or the detection of HRV-C at the time of recruitment.

Conclusion: The total anti-HRV antibody titres of children hospitalized with asthma, including those to HRV-C, did not indicate susceptibility to rhinovirus infections due to a defective immune response. The low species-specific HRV-C titres found in all groups, even when virus was found, point to a different and possibly less efficacious immune response to this species.

HRV-C IS ASSOCIATED WITH NEUTROPHILIA IN CHILDREN WITH ACUTE SEvere WHEEZE

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Introduction: Human rhinovirus (HRV) group C (HRV-C) is the most common cause of severe wheezing exacerbations in children and recent studies suggest it is more pathogenic than HRV-A or B.

Aim: To examine whether HRV-C infection induces greater systemic inflammation in children presenting to hospital with acute severe wheeze.

Methods: Children (n = 427) aged 0–16 were prospectively recruited on presentation to hospital with an acute wheezing illness. Blood and nasal aspirates were collected. Viral RNA was extracted from nasal aspirates, reverse transcribed and tested for all common respiratory viruses. A two-step PCR of the HRV 5’ non-coding region was sequenced for typing. A full blood count was completed. Maximum temperature for each case was obtained through retrospective analysis of case files. Data analyses were adjusted for age, sex and systemic steroid use.

Results: Virus was detected in 86.2% (n = 368) of samples with HRV-C the most common (46.2%, n = 177) compared with HRV-A (22.5%, n = 86), HRV-B (1.6%, n = 6), and RSV (10.5%, n = 45). HRV-C was the only virus that demonstrated a higher blood neutrophilia (mean = 11.51 × 10⁹ [95% CI 9.10–14.55] cells/L) than any other virus when compared to all other cases (mean = 9.55 [95% CI 7.43–12.27] × 10⁹ cells/L) (p = 0.012). HRV-C was not associated with differences in other cell counts. HRV-C was associated with a trend to lower mean maximum temperature (37.1°C) versus other cases (37.6°C) (p = 0.075). Acute systemic corticosteroid use was also higher in those with HRV-C (91.4%) compared to those without (75.9%) (p < 0.001).

Conclusions: HRV-C was the most common virus causing severe acute wheezing exacerbations and was associated with neutrophilia but a lower maximum temperature compared to other viruses. This relationship cannot be separated from higher acute systemic corticosteroid administration in those with HRV-C, however these findings still suggest HRV-C causes a more severe disease phenotype.

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HAPLOTYPES IN MNDA, A GENE IDENTIFIED BY MICROARRAY, WERE ASSOCIATED WITH ACUTE VIRAL RESPIRATORY ILLNESS CHARACTERISTICS

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Introduction: Asthma and acute wheezing illnesses are the most common reason for children to need emergency medical treatment in Western Australia and are predominantly triggered by human rhinovirus (HRV), particularly group C. We completed a micro-array on acute and convalescent peripheral blood mononuclear cells (PBMC) from 50 children to investigate the immune response to acute viral wheeze. Myeloid nuclear differentiation antigen (MNDA) expression was upregulated. This gene is induced by interferon α and associated with apoptosis and inflammation.

Aim: Assess the relationship between MNDA gene haplotypes and measures of acute respiratory illness severity.

Methods: Children with acute viral wheeze (n = 484) were recruited from the PMH ED. Severity was assessed using validated measures in children less than and over 2 years of age and then Z scores for each age group were calculated separately. Blood was collected for a full blood count and DNA extraction. Gene variations that identified 110 TP 159

Results: Children with one or more rare haplotypes had a mean increase of 1.67 standard deviations in their acute severity Z score (95% confidence interval (CI) = 0.945–2.40, p < 0.003) compared with other haplotypes (mean = 0.196, 95% CI = −0.001–0.398). Children homozygous for CGCTCAATC had mean %basophils of 1.97 (95% CI = 1.39–2.54, p < 0.001) compared with other haplotypes (mean = 0.34, 95% CI = 0.248–0.437). Those with one or more copies of CGCTCAATC had mean % monocytes of 3.60 (95% CI = 2.69–4.51, p = 0.03) compared with the most common haplotype CGACCTATT (mean = 4.37, 95% CI = 3.71–5.02).

Conclusion: MNDA may play a role in the systemic inflammation and severity of childhood acute wheezing illnesses.

HRV-B AND HRV-C ARE MORE RECURRENT IN CHILDREN WITH ACUTE WHEEZE AND CONTROLS FOLLOWED FOR 12 WEEKS

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Introduction: The high frequency and severity of childhood acute wheezing illnesses in Australia contributes to a large proportion of hospital emergency visits. We have found that 59.4% of children presenting to hospital with acute wheeze had human rhinovirus (HRV) group C and that children with HRV-C had increased; exacerbation severity, number of hospital admissions and severity of atopy by skin prick test and IgE, compared to no HRV-C. What is unclear is whether children with acute wheezing illnesses are more susceptible to HRV-C.

Aim: To determine the persistence and recurrence of HRV species in children presenting to hospital with acute wheeze and controls over a 12-week period spanning winter.

Methods: Cases (n = 20) were recruited on presentation to hospital with an acute wheezing illness and controls (n = 23) from the community. Flocked nasal swabs were collected at Day 1 and every two weeks by study parents. Viral RNA was extracted from nasal aspirates and reverse transcribed. A two-step PCR of the HRV 5’ non-coding region was sequenced for typing. Statistical analyses were completed using SPSS v22.

Results: Children were mostly female (cases 8/20 = 40% and controls 12/23 = 47.8%) with a mean age of 5.9 years (cases) compared with 5.1 (controls, p = 0.522) and were followed for a mean 66.4 days, range = 1–86. Between cases and controls there was no difference in the persistence (mean = 13.2 vs 15.7, respectively, p = 0.147) or the rate of recurrence (median = 70.0 days vs 84.0, respectively, p = 0.714). There was no difference in the persistence of HRV-C (mean = 13.6 days, SD = 2.2, p = 0.424) compared with HRV-A (mean = 15.0, SD = 4.1). However, HRV-C and HRV-B recur more often (n = 16/30) and in fewer days (median = 56 days, 95% CI = 39.8–72.2, p < 0.001) than others (n = 2/31, median = 77).

Conclusion: HRV-C recurs faster than HRV-A and thus may be either more pathogenic and/or induces less host protection.

MATERNAL VITAMIN D DEFICIENCY IS ASSOCIATED WITH IMPAIRED LUNG FUNCTION AND ASTHMA IN CHILDREN

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Aims: There is growing interest in the association between vitamin D and chronic lung diseases including asthma and COPD. We have in vivo experimental data suggesting that early life vitamin D deficiency has a strong impact on lung development. The aim of this study was to determine whether there is an association between maternal vitamin D status and post-natal lung function in children.

Methods: We conducted a sub-analysis of data collected as part of the West Australian Pregnancy (Raine) Cohort. Serum levels of 25(OH)D were measured at the time of recruitment (16–18 weeks gestation) and measured by immunoassay. Lung function was measured by spirometry at 6 and 14 years of age in children according to ATS guidelines at the time of collection. Linear regression was used to assess the association between maternal serum 25(OH)D and lung function (Z-scores; GLI reference equations). Logistic regression was used to assess associations between maternal vitamin D status and categorical outcomes (wheeze, asthma and atopy). Analyses were adjusted for relevant confounders (e.g. maternal age, SES, foetal growth).

Results: Maternal serum 25(OH)D was associated with 1) FVC Z-score ([β95% CI], 0.00[0.001, 0.013]; p = 0.02) in both sexes at 6 years of age, 2) FEV1 Z-score ([β95% CI], 0.00[0.001, 0.013]; p = 0.02) in females at 6 years of age and, 3) FEV1/FVC Z-score ([β95% CI], 0.01[0.000, 0.023]; p = 0.05) in females at 14 years of age. Maternal vitamin D deficiency was also associated with asthma (OR95% CI), 3.03[1.02, 9.02]; p = 0.04) in males at 6 years of age.

Conclusions: Our analysis of data from a prospective community based cohort show sex specific associations between maternal vitamin D status and lung outcomes in children. These data support the notion that maternal vitamin D is an important determinant of early lung development.
POLYSOMNOGRAPHY RESULTS IN CYSTIC FIBROSIS

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Introduction: In patients with cystic fibrosis (CF), self-reported sleep quality is often worse when compared with the normal population. This may be due to airway abnormalities such as rhinosinusitis, impaired mucous clearance or other contributors such as medications, bowel dysfunction, chronic anxiety or depression.

Aim: The aim of this study was to investigate breathing abnormalities during sleep in our CF population at the Westmead Hospital CF Unit.

Method: In-laboratory polysomnography (PSG) was performed on CF subjects following an in hospital admission for a pulmonary exacerbation. The PSG recordings were manually analysed by sleep technicians, with the objective measurements of sleep efficiency, arousal index (AI) and respiratory disturbance index (RDI) measured. Subjective questionnaires including the Epworth Sleepiness Scale (ESS) and Pittsburg Sleep Quality Index (PSQI) were administered at the time of the PSG.

Results: Fifteen patients, male = 6, age = 32 ± 6 (mean ± SD) years were recruited. Baseline characteristics included: percent predicted FEV1: 47 ± 14, BMI 22 ± 4 kg.m², ESS 6 ± 3; PSQI: 7 ± 3 (indicating overall poor sleep quality). Sleep efficiency was within normal range, 84 ± 11%. Arousal index was 17 ± 11 events per hour (normal <20 events per hour). The RDI was 9 ± 15 events per hour (normal <5 events per hour).

Conclusion: Objective in-laboratory PSG measurements of breathing disturbances in these CF subjects were mildly elevated. This sleep disruption impacts on PSQI scores. Poor self-reported sleep quality may have been due to an increased number of arousals from sleep that were caused by abnormal breathing events. These arousals, such as cough arousals, need to be further evaluated.

Key words: polysomnography, sleep disorders, breathing, cystic fibrosis.

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TIME TRENDS IN CLINICAL INDICATORS FOR CYSTIC FIBROSIS (CF) PATIENTS AT TRANSITION TO ADULT CARE

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Introduction: Historically, most patients with CF have chronic Staphylococcus aureus and Pseudomonas aeruginosa infection by late adolescence. Aggressive eradication protocols may have changed this pattern.

Aim: To investigate whether respiratory infection in CF patients transitioning to adult care changed over 14 years.

Method: We randomly selected 152 CF patients attending Royal Children’s Hospital (RCH) and TPCH CF centres from 2001 to 2008. Isolates were subjected to mexZ and lasR sequencing and assigned individual sequence types (ST). Antimicrobial susceptibility was assessed by broth microdilution minimal inhibitory concentrations (MIC).

Result: Two mexZ (M2 and M3) and 34 lasR STs (L1-L34) were identified. The proportion of AUST-02 with mutant M3 increased three-fold during the study period (5% vs. 17%; p-value: 0.0003). All AUST-02/ M3 isolates were identified in patients attending RCH. Similarly, lasR mutations were more common in the recent collection (2006 onwards) than earlier years (2001–02) (60% vs. 36%; p < 0.01) and amongst patients attending TPCH compared with RCH (58% vs. 37%; p-value: 0.001). 16 AUST-02 isolates from 10 unrelated patients shared a novel mexZ / lasR ST combination (aka M3L7) which was identified only in TPCH between 2006–08 and was absent from earlier isolates or RCH. All M3L7 isolates were MDR and resistant to most antibiotics tested including colistin. Patients with M3L7 infection were older (25 vs. 22 years; p < 0.05) and required more IV antibiotics than other STs. (34 vs. 16 days/ past 12 months; p < 0.05).

Conclusion: We demonstrated ongoing microevolution in AUST-02 with emergence and recent cross-transmission of an MDR variant (M3L7) in adults with CF attending TPCH.

EVIDENCE OF CROSS-TRANSMISSION OF A MULTIDRUG RESISTANT (MDR) PSEUDOMONAS AERUGINOSA STRAIN IN PATIENT WITH CYSTIC FIBROSIS (CF)

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Introduction: Intraclonal diversification of P. aeruginosa (Pa) occurs during adaptation to the CF airways when chronic infection occurs. The resistance gene, mexZ, and virulence gene, lasR, are common mutation targets. Forty percent of The Prince Charles Hospital (TPCH) CF patients have AUST-02 Pa strain infection.

Aim: To assess the intraclonal diversity in mexZ and lasR genes in AUST-02 in patients with CF between 2001–08.

Method: We randomly selected 152 CF patients attending Royal Children’s Hospital (RCH) and TPCH CF centres from 2001 to 2008. Isolates were subjected to mexZ and lasR sequencing and assigned individual sequence types (ST). Antimicrobial susceptibility was assessed by broth microdilution minimal inhibitory concentrations (MIC).

Result: Two mexZ (M2 and M3) and 34 lasR STs (L1-L34) were identified. The proportion of AUST-02 with mutant M3 increased three-fold during the study period (5% vs. 17%; p-value: 0.0003). All AUST-02/ M3 isolates were identified in patients attending TPCH. Similarly, lasR mutations were more common in the recent collection (2006 onwards) than earlier years (2001–02) (60% vs. 36%; p < 0.01) and amongst patients attending TPCH compared with RCH (58% vs. 37%; p-value: 0.001). 16 AUST-02 isolates from 10 unrelated patients shared a novel mexZ / lasR ST combination (aka M3L7) which was identified only in TPCH between 2006–08 and was absent from earlier isolates or RCH. All M3L7 isolates were MDR and resistant to most antibiotics tested including colistin. Patients with M3L7 infection were older (25 vs. 22 years; p < 0.05) and required more IV antibiotics than other STs. (34 vs. 16 days/ past 12 months; p < 0.05).

Conclusion: We demonstrated ongoing microevolution in AUST-02 with emergence and recent cross-transmission of an MDR variant (M3L7) in adults with CF attending TPCH.

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PROPORTIONAL ANTIMICROBIAL SUSCEPTIBILITY TESTING OF WHOLE CYSTIC FIBROSIS SPUTUM—A PILOT STUDY

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Introduction: The use of standard antibiotic sensitivity testing to assess individual isolates from cystic fibrosis (CF) airway secretions yields data of questionable relevance and antibiotic choice according to these results does not improve clinical outcomes.

Aim: To develop a rapid throughput method for assessing proportional antimicrobial susceptibility of whole CF sputum to identify antibiotic combinations most likely to be effective in mixed pseudomonal infections.

Methods: MacConkey broth containing single and combination antibiotics at clinical EUCAST breakpoint concentrations was inoculated with homogenized sputum from pseudomonas-colonized CF patients. Method development involved measurement of antibiotic susceptibility by two methods: inhibition of bacterial growth by optical density measurement at 600 nm (OD600), and inhibition of bacterial metabolic activity using Resazurin. Both assessments were spectrophotometric, and performed in a 48-well plate format.

Results: OD600 measurements in 2 sputum samples were highly reproducible, whether measured in samples overall (ICC 0.92, p < 0.001), or as intrasample (CoV 0% to 36%, median 8.5%; CC 0.9–0.98, p < 0.0001) and intersample (CoV 0 to 26%, median 19%; CC 0.95, p < 0.0001) duplicates. In contrast, the third sample was poorly reproducible. However, every result identified the same antibiotic combinations as the ‘best’ choice (tobramycin/meropenem for patients 1 and 2, and tobramycin/ceftazidime for patient 3). Metabolic activity measurements were less reproducible overall (ICC 0.71, p = 0.09), and for intersample duplicates (CoV 0–39%, median 11%, CC 0.90, p = 0.01) but good for intrasample triplicates (CoV 0–38%, median 3%, CC’s 0.89–0.97, p < 0.001), however this method also identified ‘best’ antibiotic combinations reliably, although had lower discriminatory power than OD600 measurements for antibiotics with high antimicrobial efficacy. The 2 methods appeared comparable (CC 0.9 for means, p < 0.0001).

Conclusions: PST performed in a high throughput format is feasible and in this preliminary evaluation appears to have satisfactory reproducibility by both methods. Even where numeric reproducibility was suboptimal, all samples identified the same best antibiotic combinations, implying utility as a clinical tool.
PATTERNS OF BRONchodilATOR USE DURING ADMISSION FOR ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN A TERTIARY RESPIRATORY UNIT

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Introduction: Long-acting bronchodilators (BD) have become the mainstay of therapy for stable chronic obstructive pulmonary disease (COPD). The addition of short-acting BD is advocated for the management of acute exacerbations (AE-COPD). Current guidelines do not specify treatment regimens for the acute setting. Given the concerns for potential cardiac complications using these drugs, an examination of their prescription during inpatient admission is warranted.

Aim: To describe patterns of long- and short-acting BD administration before, during, and at discharge from inpatient admission for AE-COPD.

Methods: A retrospective review of medical records for AE-COPD in a single tertiary hospital respiratory department.

Results: To date, 55 records have been examined. The mean age was 68 years. Thirty eight percent of patients were current smokers, and 31 percent had pre-existing cardiac comorbidities. Pre-admission use of long-acting muscarinic antagonists (LAMAs) and long-acting beta-adrenergic agonists (LABAs) was common (75 percent and 77 percent, respectively; 65 percent were using both). Pre-admission use of short-acting beta-adrenergic agonists (SABA) was common (78 percent), however the use of short-acting muscarinic antagonists (SAMAs) was rare (5 percent). During admission, prescription of SAMA (67 percent) was less common than SABA (98 percent). Seventy three percent of patients continued on LAMA and 88 percent continued on LABA. Concurrent prescription of LABA and SABA was 72 percent, whereas concurrent prescription of LAMA and SAMA was only 11 percent. At discharge, few patients had changes to their pre-admission bronchodilator regimen. Three patients had cardiac complications documented.

Conclusion: Continuation of LAMA and LABA during hospital admission for AE-COPD is common. The concurrent prescription of long- and short-acting beta agonists was very common, however the opposite was true for muscarinic agonists. The rationale behind these prescribing practices requires further investigation.

CHARACTERISTICS OF PATIENTS THAT PROGRESS FROM BRIDGING TO LONG TERM OXYGEN THERAPY

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Aim: Selected patients with persistent hypoxia were discharged from an acute hospital admission with bridging hospital-funded domiciliary oxygen, as per the 2005 TSANZ position statement. This study evaluated the characteristics of these patients, and aimed to identify factors which may influence the need for ongoing oxygen therapy at review 4–8 weeks later.

Method: Retrospective analysis of all patients discharged from Alfred Health during 2011 and 2012 with bridging domiciliary oxygen. Data were collated from the domiciliary oxygen service database and online medical records.

Results: 68/123 patients discharged from hospital with bridging domiciliary oxygen returned within 4–8 weeks for review. Of those that did not attend for review: 7% lung transplantation in the interim, 79% palliative (60% of these patients documented to have died within 3 months), 14% other. Of the 68 patients reviewed in clinic, baseline characteristics revealed: mean age 67 (SD 13.5) years, 54.4% female, mean BMI 26.5 (SD 8.4) kg/m², documented airflow obstruction 63%, restriction 18% (no spirometry documentation 19%). Serum bicarbonate level was the only parameter that demonstrated a significant difference between those who qualified and those who did not qualify for ongoing domiciliary oxygen (31.7/27 mmol/L, p = 0.012) at review. No other variable demonstrated a significant difference, including FEV1 (obstructed patients 42.9% predicted, other patients 61.2% predicted), PaCO2, underlying medical condition(s), admission unit and acute diagnosis at admission. Patients who had documented co-morbid cardiac failure demonstrated a trend in their association with ongoing domiciliary oxygen provision (p = 0.052). In a sub-group analysis of all patients with documented airflow obstruction (n = 43), those who qualified for long term oxygen also had a significantly higher PaCO2 (p = 0.045).

Conclusion: A higher serum bicarbonate and PaCO2, as well as underlying co-morbid cardiac failure were associated with need for ongoing domiciliary oxygen therapy.

Key words: domiciliary oxygen, chronic hypoxia.

TIOSPIR: SAFETY AND EFFICACY TRIAL OF TIOTROPIUM RESPIMAT VERSUS HANDIHALER IN COPD

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Introduction: Tiotropium Respimat 5 μg and HandiHaler 18 μg are equally effective as therapy for chronic obstructive pulmonary disease (COPD). While tiotropium HandiHaler showed lower mortality than placebo, pooled data from Tiotropium Respimat 5 μg registration studies showed a higher number of deaths compared to placebo.

Methods: TIOtropium Safety and Performance In Respimat (TIOSPIR), a large-scale, 2–3 year, randomized, double-blind trial compared safety and efficacy of once-daily Respimat 5 and 2.5 μg with HandiHaler 18 μg.

Results: Overall, 17,135 patients were randomized and treated. Across groups, there was similar time to death (Respimat 5 μg versus HandiHaler: hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.84–1.09; Respimat 2.5 μg versus HandiHaler: HR, 1.00; 95% CI, 0.87–1.14) and time to first exacerbation (Respimat 5 μg versus HandiHaler: HR, 0.98; 95% CI, 0.93–1.03). Noninferiority of Respimat 5 and 2.5 μg to HandiHaler 18 μg in time to death was shown, while superiority of Respimat 5 μg to HandiHaler 18 μg in time to first COPD exacerbation was not shown. Causes of death and overall incidence of cardiovascular adverse events were similar between groups.

Conclusions: Tiotropium Respimat 5 and 2.5 μg and tiotropium HandiHaler 18 μg present similar safety and exacerbation efficacy profiles in patients with COPD.
Results: events: negative binomial model. Diovascular AE. Time-to-event analysed using Cox proportional hazards; no. of hospitalized exacerbations; time to: first hospitalized exacerbation, major exacerbation (superiority analysis). Secondary endpoints: no. of: exacerbations, endpoints: time to death (all-cause; non-inferiority analysis), time to first exacerbation, emergency admission (all-cause; non-inferiority analysis).

Baseline demographics

| Variable                  | Value          |
|---------------------------|----------------|
| Treated pts, N            | 17135          |
| Age, y                    | 65.0 ± 9.1     |
| Male, %                   | 71.5           |
| Current smoker,%          | 38.1           |
| Smoking history, pack-y   | 43.8 ± 24.8    |
| FEV1,L*                   | 1.34 ± 0.48    |
| FEV1, % pred*             | 48.3 ± 13.9    |
| FVC,L*                    | 2.71 ± 0.85    |
| FEV1/FVC*                 | 0.499 ± 0.114  |

**GOLD stage,%**

| Stage | Value |
|-------|-------|
| I     | 0.3   |
| II    | 48.5  |
| III   | 40.1  |
| IV    | 10.8  |

| History of myocardial infarction,% | 6.0 |
| Coronary artery disease,%         | 15.2 |
| Cardiac arrhythmia,%              | 10.6 |
| Heart failure class,%             |     |
| None                             | 92.1 |
| I                                | 3.1  |
| II                               | 4.1  |
| III                              | 0.6  |
| IV                               | 0.0  |

ASSESSING THE USE OF INITIAL OXYGEN THERAPY IN COPD PATIENTS: A RETROSPECTIVE AUDIT OF PRE-HOSPITAL AND HOSPITAL EMERGENCY MANAGEMENT

**Methods:** Randomized, active-controlled, double-blind, double-dummy, parallel-group, non-inferiority, event-driven, international multicentre (50 countries) trial of pts aged ≥40 y with COPD (postbronchodilator [postBD] FEV1 < 70% pred., FEV1/FVC < 70%), smoking history ≥10 pack-y. Primary endpoints: time to death (all-cause; non-inferiority analysis), time to first exacerbation (superiority analysis). Secondary endpoints: no. of exacerbations, hospitalized exacerbations; time to: first hospitalized exacerbation, major cardiovascular AE. Time-to-event analysed using Cox proportional hazards; no. of events: negative binomial model.

**Results:** Enrollment completed in April 2011; 17135 pts began treatment (Table).

**Conclusion:** TIOSPIR® will provide robust data on relative safety and efficacy of tiotropium Respimat® vs HH from moderate to very severe COPD and across comorbidities.

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COST EFFECTIVENESS OF PORTABLE OXYGEN CONCENTRATORS COMPARED TO PORTABLE OXYGEN CYLINDERS: A MULTI-CENTRE RCT

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Aim: To determine the cost effectiveness and associated economic impact of battery powered portable oxygen concentrators (BPPOC) compared to portable oxygen cylinders when used by stable COPD patients currently prescribed oxygen for mobility/exertion.

Method: Twenty-three participants diagnosed with stable COPD and prescribed oxygen were recruited into a multi-centre randomized cross-over study of BPPOC versus portable cylinders (one month each). For each arm costs and QALYs (Quality Adjusted Life Years) were estimated based on the typical usage for portable cylinders and standard provision of BPPOCs. QALYs were computed from AQoL utility scores using the standard AQoL-8D algorithm in Stata.

Results: Mean cost of oxygen supply for a patient on cylinders was $95/month while it was $179/month for a patient on BPPOC, an incremental cost of $84/month (an extra $1008 per patient per year). Overall a decreased mean AQoL utility score was observed for patients on BPPOC compared to portable cylinders (one month each) with a trend to significance. For patients requiring continuous supplemental oxygen (i.e. 16 hours or more usage a day), the mean AQoL utility score was 0.57 on BPPOC and 0.56 on cylinders, a difference of 0.01; an incremental costs-effectiveness ratio of $102,387 per QALY gain. For patients that need oxygen for exertional purposes only, the mean utility score was also the same regardless of oxygen modality. Exploratory analyses revealed a mean score on BPPOC of 0.56, which was almost identical to the mean score while on portable oxygen cylinders of 0.57 for patients requiring continuous oxygen (i.e. 16 hours or more a day). Mean scores on independent living, pain, senses, mental health, happiness, coping, relationships, and self-worth were also calculated.

Conclusion: Utility scores are volatile over time with large differences in scores observed across the three data collection points for participants, even among patients in this study, making reliable conclusions about the impact of BPPOC on quality of life are difficult to discern.

Grant Support: Nil.

QLITY OF LIFE AMONG PARTICIPANTS OF A MULTI-CENTRE RCT COMPARING PORTABLE OXYGEN CONCENTRATORS TO PORTABLE OXYGEN CYLINDERS

LAWTON K1,2, KOTAL L1, NGUYEN H1, JURISEVIC M1,2, SEGAL L2, LIVERSIDGE C1, ALEXANDER S1, KEATLEY D1, KIDD P1, LIU X1, CARSON K1,2, BRINN M1,2, ESTERMAN A5, VEALE A1, SMITH B1,2,3
1Respiratory Medicine, The Queen Elizabeth Hospital, 2Clinical Practice Unit, The Basil Hetzel Institute for Translational Health Research, SA, 3School of Population Health, The University of South Australia, SA, 4School of Nursing and Midwifery, The University of South Australia, SA

Aim: To examine the effect of battery powered portable oxygen concentrators (BPPOC) compared to portable oxygen cylinders on quality of life in a cohort of subjects with stable COPD requiring oxygen.

Method: Twenty-three subjects with stable COPD and prescribed portable oxygen were randomized to either BPPOC or portable cylinders in a multi-centre cross-over study (one month each with one-week wash-out). A standard AQoL-8D algorithm in Stata was used to produce AQoL utility scores with AQoL survey instruments completed at baseline. Eight specific dimensions (independent living, pain, senses, mental health, happiness, coping, relationships, and self-worth) were also calculated.

Results: Mean AQoL-8D utility scores did not vary by oxygen modality. Exploratory analyses revealed a mean score on BPPOC of 0.56, which was almost identical to the mean score while on portable oxygen cylinders of 0.57 for patients requiring continuous oxygen (i.e. 16 hours or more a day). Mean scores on independent living, coping, relation and self-worth were slightly higher when on BPPOC than on cylinder. For patients using oxygen for exertional purposes only, the mean utility score was also the same regardless of oxygen modality. Non-parametric tests for paired difference between scores while on BPPOC and cylinder were not statistically significant for either patient group (p = 0.86 for continuous and p = 0.79 for exertional patients). The mean score across all participants and time points was significantly lower than the AQoL-8D population norm (0.86).

Conclusion: Utility scores are volatile over time with large differences in scores observed across the three data collection points for participants, even where modality of oxygen delivery had not changed. As such reliable conclusions about the impact of BPPOC on quality of life are difficult to discern.

Grant Support: Nil.

BETA BLOCKER USE IN COPD

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Introduction: Some studies suggest that concurrent beta blocker use is associated with decline in pulmonary function test. Others have suggested a trend to benefit with reduced cardiovascular events and mortality with no impact on pulmonary functions.

Aim: To examine the impact of beta-blockers in COPD patients on readmission, non-invasive ventilation and cardiovascular event rates.

Method: Retrospective cohort study of new patients seen at Christchurch Respiratory Clinic for COPD from 01/01/2008 to 01/10/2011. Patients’ notes, discharge summaries and investigations were reviewed and followed up for two years.

Results: A total of 177 new COPD patients were seen in the study period. Of these 63 patients were not beta-blockers although 27 had a history of ischaemic heart disease. Only 14 patients taking beta-blockers of these 11 had a history of ischaemic heart disease. In patients not on beta-blockers the admission rate for respiratory ailments was 0.4 admissions per patient year and non-invasive ventilation rate of 0.08 (95% CI 0–0.23); patients on beta-blockers had rates of 0.4 and 0.1 respectively. Cardiac event rates were 0.06 in group not on beta blockers and 0.18 on beta-blockers (p 0.02). When corrected for presence of heart disease, the cardiac event rates were 0.12 and 0.18 respectively (p 0.4).

Conclusion: Less than 10% of patients with COPD were taking beta-blockers despite traditional indications for beta-blocker use. None of the outcome measures reached statistically significant besides a higher number of cardiac event rates in the beta-blocker group; it lost significance when corrected for presence of ischaemic heart disease.

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DUAL BRONCHODILATATION WITH ONCE-DAILY QVA149 HAS A GOOD SAFETY PROFILE IN PATIENTS WITH COPD: A NETWORK META-ANALYSIS ACROSS MULTIPLE SAFETY DATABASES

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Aim: QVA149 combines a long-acting β₂-agonist indacaterol (IND) and long-acting muscarinic antagonist glycopyrronium (GLY) as dual bronchodilators for the treatment of COPD. Safety information from data in the QVA149 IGNITE programme was integrated with available relevant information from the IND and GLY safety databases to investigate the impact of individual patient level factors and time.

Method: A network meta-analysis using individual patient data was undertaken (n = 8627) focusing on deaths, serious cardio- and cerebro-vascular (CCV) events, major adverse cardiovascular events (MACE), serious pneumonia, serious COPD exacerbation and atrial fibrillation/flutter (AF/F). All completed randomized clinical studies of QVA149, IND and GLY of ≥3 months duration with at least two of the following treatment groups included in the meta-analysis: QVA149 110/50 μg, GLY 50 μg, IND 150 μg and placebo. The analysis used Cox proportional hazard model for QVA149 (n = 1547) vs placebo (n = 2141).

Results: The hazard ratio (HR) for QVA149 vs placebo showed no significant increase in risk for death (HR [95%CI]: 0.922 [0.338–2.511]), serious CCV (0.597 [0.287–1.241]), MACE (0.984 [0.417–2.319]), serious pneumonia (1.076 [0.526–2.203]), serious COPD exacerbation (0.598 [0.395–0.906]), or AF/F (1.017 [0.479–2.157]). The combination of IND+GLY had similar safety profiles to the single ingredients.

Conclusion: Based on the analysis of the available safety databases, including pivotal RCTs in COPD patients, there is no evidence of increased risk of all-cause mortality, serious CCV, MACE, serious pneumonia, serious exacerbations and AF/F associated with use of the once-daily dual bronchodilator QVA149.

Key words: COPD, QVA149, safety.

Grant Support: This study was sponsored by Novartis Pharmaceuticals AG.

ONCE-DAILY QVA149 DEMONSTRATES SUPERIOR OUTCOMES IN COPD PATIENTS PREVIOUSLY TREATED WITH FIXED-DOSE LONG-ACTING β₂-AGONIST/INHALED CORTICOSTEROID (LABA/ICS): THE ILLUMINATE STUDY

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Aim: The ILLUMINATE study evaluated the superiority of the once-daily QVA149 110/50 μg, a dual bronchodilator combining the LABA indacaterol and the LAMA glycopyrronium, compared to twice-daily LABA/ICS, salmeterol/fluticasone 50/500 μg (SFC), in terms of efficacy, safety and tolerability in patients (pts) with moderate-to-severe COPD. This analysis reports the efficacy and safety of QVA149 vs. SFC in the sub-group population using fixed-dose LABA/ICS prior to study enrolment.

Method: 122 pts on LABA/ICS prior to study entry were randomized to QVA149 (n = 54) and SFC (n = 68). FEV1 area under the curve for 0–12 h (AUC0–12h), pre-dose trough FEV1, rescue medication use, exacerbations and safety were assessed after 26 wks.

Results: QVA149 significantly improved FEV1 AUC0–12h, pre-dose trough FEV1, rescue medication use, exacerbations and safety were assessed after 26 wks.

Conclusion: In the subpopulation previously treated with LABA/ICS, QVA149 demonstrated significant improvements in lung function and rescue therapy use compared to SFC. These results were consistent with the overall study population.

| Parameter                          | Treatment difference, QVA149 vs. SFC |
|------------------------------------|-------------------------------------|
|                                    | Pts with LABA/ICS prior to baseline (n = 122) | Overall pt population (N = 522) |
|                                    | Wk 12 | Wk 26 | Wk 12 | Wk 26 |
| FEV1 AUC0–12h, mL                  | 180(34)* | 160(38)* | 120(16)* | 140(19)* |
| Pre-dose trough FEV1, mL           | 140(35)* | 150(40)* | 90(17)* | 100(19)* |
| Rescue medication use, puffs/day   | −0.56(0.34) | −0.71(0.34)* | −0.28(0.16) | −0.39(0.17)* |

*p < 0.001; *p < 0.05.
ONCE-DAILY CO-ADMINISTRATION OF GLYCOPPYRRONIUM AND INDACATEROL IMPROVES LUNG FUNCTION AND SYMPTOMS IN PATIENTS WITH COPD VERSUS INDACATEROL ALONE: THE GLOW6 STUDY

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Aim: Current COPD management strategy recommends combining bronchodilators with different mechanisms for treating symptomatic patients with moderate-to-severe COPD. We compared once-daily dual bronchodilation by co-administration of the long-acting muscarinic antagonist (LAMA) glycopyrronium 50 μg (GLY) and long-acting β2-agonist (LABA) indacaterol 150 μg (IND), to monotherapy with IND 150 μg alone.

Method: In this multicentre, double-blind, parallel group study, patients with moderate-to-severe COPD were randomized (1:1) to GLY+IND or IND+Placebo for 12 weeks. We assessed lung function, dyspnoea (via the transition dyspnoea index [TDI]), patient-reported symptoms, and safety and tolerability.

Results: Of the 449 patients randomized (GLY+IND [n = 226]; IND [n = 223]), 94.0% completed the study. At Week 12, GLY+IND treatment demonstrated greater improvement in mean trough FEV1 over IND (84 mL; p < 0.001), greater improvements in FEV1 area under curve from 30 min to 4 hours (AUC30min-4h) and Forced Vital Capacity (FVC) with GLY+IND vs IND on Day 1 (105 mL, 112 mL) and at Week 12 (111 mL, 93 mL), all p < 0.01. GLY+IND treatment significantly improved TDI total score and proportion of patients with clinically meaningful improvement (≥1 point) vs IND at Week 12 (0.49, p = 0.037; Odds Ratio 1.97 in favour of GLY+IND; p = 0.004). GLY+IND was also associated with significantly greater improvements in mean daytime respiratory symptom score and % days able to perform usual daily activities vs IND at Week 12 (−0.1 and 6.2; both p < 0.05). The overall incidence of adverse events (AEs) and serious AEs (SAEs) was comparable for the GLY+IND and IND groups (AEs: 37.6% vs 34.1%; SAEs: 2.2% vs 2.3%, respectively).

Conclusion: Compared to indacaterol monotherapy, once-daily co-administration of glycopyrronium and indacaterol provided superior improvements in lung function from the first dose and dyspnoea, without adversely affecting safety and tolerability.

Grant Support: This study was sponsored by Novartis Pharmaceuticals AG.

EFFICACY AND SAFETY OF ONCE-DAILY GLYCOPPYRRONIUM COMPARED WITH BLINDED TIOTRIOPUM IN PATIENTS WITH COPD: THE GLOWS STUDY

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Aim: Glycopyrronium, a once-daily long-acting muscarinic antagonist (LAMA), has demonstrated a similar efficacy and safety profile to open-label tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). The GLOWS study compared the efficacy and safety of glycopyrronium with blinded tiotropium.

Method: In this multicentre, 12-week, blinded study, patients with moderate-to-severe COPD were randomized to glycopyrronium 50 μg (via Breathing®) or tiotropium 18 μg (via HandiHaler® device). The primary objective was to demonstrate non-inferiority of glycopyrronium versus tiotropium for trough FEV1 at Week 12. Other endpoints included FEV1 area under the curve from 0 to 4 hours (AUC0-4h) on Day 1, Transition Dyspnoea Index (TDI), St George’s Respiratory Questionnaire (SGRQ), rescue medication use, exacerbation rate, safety and tolerability.

Results: Of the 657 patients randomized, (glycopyrronium [n = 327]; tiotropium [n = 330]), 95.9% completed the study; Glycopyrronium demonstrated non-inferiority to tiotropium for trough FEV1 at Week 12 (Least Squares Mean [LSM] = 1.11 L for both groups; 95% confidence interval [CI]: −0.032, 0.031 L). Glycopyrronium had a higher FEV1, AUC0-4h on Day 1 compared to tiotropium (LSM = 58 mL; p = 0.001). At Week 12, TDI total score (−0.188; p = 0.385), SGRQ total score (0.65; p = 0.488) and percentage of days with no rescue medication use (1.5; p = 0.528) were comparable between the groups. Rate of moderate/severe COPD exacerbations per year were similar (glycopyrronium 0.38 versus tiotropium 0.35 [rate ratio = 1.10, 95% CI: 0.62, 1.93]; p = 0.754). Overall, the incidence of adverse events was similar in the glycopyrronium (40.4%) and tiotropium (40.6%) groups.

Conclusion: Glycopyrronium and blinded tiotropium showed similar improvements in lung function, dyspnoea, health status, exacerbation rate and rescue medication use, with a similar safety and tolerability profile. Onset of bronchodilation with glycopyrronium was significantly more rapid following the first dose.

Key words: glycopyrronium, tiotropium, COPD.

Grant Support: This study was sponsored by Novartis Pharmaceuticals AG.

A NOVEL STUDY DESIGN FOR THE COMPARISON BETWEEN ONCE-DAILY QVA149 AND TWICE-DAILY SALMETEROL/FLUTICASONE ON THE REDUCTION OF COPD EXACERBATIONS: THE FLAME STUDY

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Aim: Current COPD treatment guidelines recommend LABA/ICS for severe COPD patients (pts) with a history of exacerbations (exac). The 26 wk ILLU-

MINATE study in moderate-to-severe COPD pts showed superiority of QVA149 vs the LABA/ICS salmeterol/fluticasone (SFC) in lung function. A novel study design to evaluate the effect of QVA149 vs. SFC on COPD exacerbation in more severe pts with a history of exac is presented.

Method: This multicenter, double-blind, active-controlled study will randomize ~3332 pts with moderate-to-very severe COPD (1:1) to once-daily QVA149 (110 μg indacaterol/50 μg glycopyrronium) or twice-daily SFC (50/500 μg) for 52 wks. The study will have a 1 wk screening, a 4 wk run-in where tiotropium rather than rescue therapy alone will be provided to all pts, a 52 wk blinded treatment, and a 30 day follow-up period. Pts > 40 yrs, history of ≥1 COPD exacerbation in the past 12 months requiring systemic glucocorticosteroids and/or antibiotics and post-bronchodilator forced expiratory volume in 1 second ≥25 and <60% predicted value will be included. Primary objective: to show that QVA149 is non-inferior to SFC for annual rate of all COPD exacerbations (mild/moderate/severe). Secondary outcomes: evaluating potential superiority of QVA149 vs. SFC for annual rate of all exacerbation, trough FEV1 use, health status, safety and tolerability.

Conclusion: The results from this study should elucidate the potential place in therapy for dual bronchodilation with QVA149 vs LABA/ICS in a moderate-to-very severe COPD population with a history of exacerbations.

ONCE-DAILY QVA149 COMPARED WITH BLINDED INDACATEROL IN MODERATE-TO-SEVERE PATIENTS WITH COPD: THE GLOW5 STUDY

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Aim: Current COPD management strategy recommends combining bronchodilators with different mechanisms for treating symptomatic patients with moderate-to-severe COPD. We compared once-daily dual bronchodilation by co-administration of the long-acting muscarinic antagonist (LAMA) glycopyrronium 50 μg (GLY) and long-acting β2-agonist (LABA) indacaterol 150 μg (IND), to monotherapy with IND 150 μg alone.

Method: In this multicentre, double-blind, parallel group study, patients with moderate-to-severe COPD were randomized (1:1) to GLY+IND or IND+Placebo for 12 weeks. We assessed lung function, dyspnoea (via the transition dyspnoea index [TDI]), patient-reported symptoms, and safety and tolerability.

Results: Of the 449 patients randomized (GLY+IND [n = 226]; IND [n = 223]), 94.0% completed the study. At Week 12, GLY+IND treatment demonstrated greater improvement in mean trough FEV1 over IND (84 mL; p < 0.001), greater improvements in FEV1 area under curve from 30 min to 4 hours (AUC30min-4h) and Forced Vital Capacity (FVC) with GLY+IND vs IND on Day 1 (105 mL, 112 mL) and at Week 12 (111 mL, 93 mL), all p < 0.01. GLY+IND treatment significantly improved TDI total score and proportion of patients with clinically meaningful improvement (≥1 point) vs IND at Week 12 (0.49, p = 0.037; Odds Ratio 1.97 in favour of GLY+IND; p = 0.004). GLY+IND was also associated with significantly greater improvements in mean daytime respiratory symptom score and % days able to perform usual daily activities vs IND at Week 12 (−0.1 and 6.2; both p < 0.05). The overall incidence of adverse events (AEs) and serious AEs (SAEs) was comparable for the GLY+IND and IND groups (AEs: 37.6% vs 34.1%; SAEs: 2.2% vs 2.3%, respectively).

Conclusion: Compared to indacaterol monotherapy, once-daily co-administration of glycopyrronium and indacaterol provided superior improvements in lung function from the first dose and dyspnoea, without adversely affecting safety and tolerability.

Grant Support: This study was sponsored by Novartis Pharmaceuticals AG.
ONCE DAILY QVA149 PROVIDES SUPERIOR IMPROVEMENTS IN LUNG FUNCTION COMPARED WITH GLYCOPYRONIUM AND TIOTRAPIUM IN SEVERE COPD PATIENTS: A 52 WEEK POOLED ANALYSIS

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Aim: QVA149 is a once daily, dual bronchodilator with a fixed-dose combination of indacaterol (a long-acting β2-agonist) and glycopyrronium (a long-acting muscarinic antagonist) for treatment of patients with COPD. We present the pooled analysis of lung function data from severe patients from the QVA149 SPARK, ARISE, and ENLIGHTEN studies.

Method: Data from 1871 patients with severe COPD (stage III; post-bronchodilator forced expiratory volume in 1 s (FEV1) <70% of predicted and FEV1/FVC <70%) were pooled (QVA149 [110/50 μg] = 696; glycopyrronium [50 μg] = 584; tiotropium [18 μg] = 591). FEV1 and forced vital capacity (FVC) were analysed using ANCOVA.

Results: Demographics and baseline characteristics were balanced across the treatment groups; overall 63.8 yrs mean age, 80.1% Caucasians, 6.9 yrs mean duration of COPD, 72.4% patients used inhaled corticosteroids at baseline, 37.9% current smoker, and 41.4% of FEV1/FVC. Pre-dose FEV1 and FVC were significantly greater with QVA149 than glycopyrronium and tiotropium at all visits (p < 0.001). Spirometric analyses of QVA149 vs. glycopyrronium and tiotropium after 52 weeks of treatment are shown in table.

Conclusion: QVA149 improved lung function significantly better than glycopyrronium and tiotropium in patients with severe COPD at Week 52.

Key words: severe COPD, QVA149, lung function.

Grant Support: This study was sponsored by Novartis Pharmaceuticals AG.

Table: Treatment differences in lung function.

| Parameter, L | QVA149 vs. glycopyrronium | QVA149 vs. tiotropium |
|--------------|---------------------------|----------------------|
| Pre-dose (Week 52) | 0.082 ± 0.0133 | 0.081 ± 0.013 |
| FEV1 | 0.114 ± 0.026 | 0.117 ± 0.026 |
| FVC | 0.097 ± 0.018 | 0.155 ± 0.018 |
| Post-dose FVC (Overall) | 0.115 ± 0.019 | 0.162 ± 0.019 |

p < 0.001 for all comparisons

BARRIERS FOR SETTING UP A PULMONARY REHABILITATION PROGRAMME IN THE EASTERN PROVINCE OF SAUDI ARABIA

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Aim: To determine the main barriers for setting up pulmonary rehabilitation (PR) programmes in Saudi Arabia.

Method: A cross-sectional study was conducted in the eastern province in Saudi Arabia. Health care providers involved in treatment of COPD patients were recruited from 22 general government hospitals in this region. Data were collected using questionnaires.

Results: Only 4% of the recruited health care providers (physicians (n = 44), nurses (n = 49), and respiratory therapists/technicians (n = 30); n = 123) had heard of PR programmes. According to the health care providers, the main barriers for setting up PR programmes in the eastern province in Saudi Arabia were; lack of trained health care providers (72.4%), lack of hospital capacity (56.9%) and lack of funds (48%). There was a significant difference in barriers reported by different groups of health care providers, with nurses more likely to nominate that PR is an expensive approach (38.6%) compared to physicians (18%; P < 0.05) being a significant barrier. According to health care providers’ perception, smoking status (76.2%), interruption to patient’s routine (59.8%) and lack of transportation (59%), social/family support (41.8%), and perceived benefit (38.5%) may prevent patients with COPD from attendance, adherence and not completing PR programmes.

Conclusion: There is an enormous lack of knowledge regarding content and benefits of PR programmes amongst Saudi health care providers treating COPD patients. Lack of trained health care providers, limited hospital capacity, insufficient funds, and low knowledge were barriers for setting up PR programmes in the eastern province in Saudi Arabia. These findings imply that improving awareness and increasing education of health care providers regarding PR will be required before PR can be more widely implemented as an integral treatment modality for patients with COPD in Saudi Arabia.

TARGETO2 PATHWAY FOR OXYGEN TREATMENT IN PATIENTS WITH COPD AND ACUTE BREATHLESSNESS

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Introduction: We performed a pilot study to implement the pathway for titrating inspired oxygen to the target saturation of 88–92%.

Aim: The aims of the pathway were timely diagnosis of acute respiratory failure (ARF, arterial pH < 7.35 and pCO2 > 45 mmHg), prevention of ARF associated with hyperoxia, and minimization of arterial blood gas (ABG) samples.

Method: Oxygen was titrated to target saturation 88–92% in 24 patients presenting to the emergency department with breathlessness and an additional risk factor for acute ARF (COPD 16, home oxygen or positive airway pressure 6, obesity 1, reduced level of consciousness 1), ABGs were recommeded for oxygen saturation <88%, or if venous pH < 7.35 or pCO2 > 45 mmHg at presentation.

Results: At presentation, oxygen saturation was at or above target while breathing air in 5 patients, <87% on air or oxygen in 8, and above target on supplemental O2 in 11. Inspired O2 was adjusted appropriately in 17 and inappropriately in 7 patients. After 1 hour 16 patients reached target oxygen saturation, and 8 patients exceeded target saturation on supplemental oxygen. AVF was diagnosed by ABGs at presentation in 3 patients. AVF was diagnosed by ABGs within 1 hour in further 6 patients in whom venous pCO2 > 56 mmHg at presentation. No cases of AVF associated with hyperoxia were identified. 5 of 18 ABGs were not indicated by the pathway. Normal or trivial increases in arterial pCO2 were associated with venous pCO2 46–50 mmHg in 5 patients. Feedback from users identified handoff at each step as a cause of delay or failure to achieve targets.

Conclusion: The Target O2 pathway can diagnose ARF in COPD. Adherence to the pathway could be increased with improved handoff procedure at each step. Calibration of the venous CO2 threshold may reduce unnecessary ABGs.
LUNG FUNCTION EFFICACY OF OLODATEROL QD DELIVERED VIA RESPIMAT® IN COPD PATIENTS: RESULTS FROM TWO 48-WEEK STUDIES

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Background: The novel inhaled LABA olodaterol (O) has 24-h bronchodilator activity.

Objective: To assess the efficacy of O QD in GOLD 2–4 COPD patients (pts).

Methods: In two replicate, randomized, double-blind, placebo (P)-controlled, parallel-group studies, pts with post-bronchodilator FEV1 < 80% predicted normal and FEV1/FVC < 70% received O (5 or 10 μg) QD or P (both via Respimat®) for 48 weeks (wks) (Study 1: NCT00782210; Study 2: NCT00782509). Pts continued to receive usual care background COPD maintenance therapy, including SAMA, LAMA, ICS and xanthines. Co-primary end points were change from study baseline (response) in FEV1 AUC0-3 and trough FEV1 after 12 wks.

Results: 624 (Study 1) and 642 (Study 2) pts were treated. In both studies, O 5 and 10 μg provided statistically significant improvements in the co-primary end points after 12 wks vs P.

| FEV1 response: difference vs P, L | Study 1 | Study 2 |
|----------------------------------|---------|---------|
|                                  | AUC0-3  | Trough  | AUC0-3  | Trough  |
| O 5 μg                           | 0.172   | 0.091   | 0.151   | 0.047    |
| O 10 μg                          | 0.176   | 0.101   | 0.143   | 0.048    |

p < 0.05 vs P Results were consistent for FEV1 AUC0-3 and trough FEV1 response over 48 wks.

Conclusions: O 5 and 10 μg QD over 48 wks provided significant improvements in lung function vs P in pts with moderate to very severe COPD with a magnitude of response in line with expectations for a bronchodilator used in a pt population on multiple concomitant COPD therapies.

Funding: Boehringer Ingelheim.
LUNG FUNCTION EFFICACY OF OLODATEROL QD DELIVERED VIA RESPIMAT® VS PLACEBO AND FORMOTEROL BID IN PATIENTS WITH COPD: TWO 48-WEEK STUDIES

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Background: Olodaterol (O) is a novel LABA with 24-h bronchodilator activity.

Objective: To evaluate the efficacy of O QD in patients (pts) with GOLD 2–4 COPD.

Methods: In replicate, randomized, double-blind, placebo (P)-controlled, parallel-group studies, pts with post-bronchodilator FEV1 < 80% predicted and FEV1/FVC < 70% received O (5 or 10 μg) QD via Respimat®, formoterol (F; 12 μg) BID via Aerolizer® or P for 48 weeks (wks; A: NCT00793624; B: NCT00796653). Pts continued to receive usual care background COPD maintenance therapy including SAMA, LAMA, ICS and xanthines. Co-primary lung function end points were change from study baseline (response) in FEV1 AUC0-3 and trough FEV1 after 24 wks.

Results: 904 (A) and 934 (B) pts were treated. O 5 and 10 μg and F provided statistically significant improvements in co-primary end points after 24 wks vs P; there were no significant differences between O and F.

FEV1 response: difference vs P, L

|        | A                  |        | B               |        |
|--------|--------------------|--------|-----------------|--------|
|        | AUC0-3             | Trough | AUC0-3          | Trough |
| O 5    | 0.151              | 0.078  | 0.129           | 0.053  |
| O 10   | 0.165              | 0.085  | 0.154           | 0.069  |
| F      | 0.177              | 0.054  | 0.150           | 0.042  |

P < 0.05 for all time points in Studies 1 and 2

Results were consistent for co-primary end points over 48 wks.

Conclusions: O 5 and 10 μg QD significantly improved lung function vs P over 48 wks. Response magnitude was comparable to F BID and in line with expectations for a QD bronchodilator considering the pt population and concomitant therapy.

Funding: Boehringer Ingelheim.
SYMPTOMATIC BENEFIT OF OLODATEROL QD DELIVERED VIA RESPIMAT® VS PLACEBO AND FORMOTEROL BID IN PATIENTS WITH COPD: COMBINED ANALYSIS FROM TWO 48-WEEK STUDIES

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Background: The novel LABA olodaterol (O) has 24-h bronchodilator activity.

Objective: To evaluate the symptomatic benefit of O QD in patients (pts) with GOLD 2–4 COPD.

Methods: In replicate, randomized, double-blind, placebo (P)-controlled, parallel-group studies, pts with post-bronchodilator FEV1 < 80% predicted normal and FEV1/FVC < 70% received O (5 or 10 μg) QD via Respimat®, formoterol (F; 12 μg) BID via Aerolizer® or P for 48 weeks (wks; Study A; NCT00793624; Study B: NCT00796653). Pts continued to receive usual care background COPD maintenance therapy, including SAMA, LAMA, ICS and xanthines. In addition to FEV1-based primary end points, TDI and SGRQ after 24 wks were identified as co-primary and key secondary symptomatic end points, respectively.

Results: 904 (Study A) and 934 (Study B) pts were treated. In the primary analysis using a mixed model for repeated measures (MMRM; combined dataset), there was no significant difference in TDI focal score after 24 wks for O or F vs P. A post hoc analysis using pattern mixture modelling (PMM) to account for discontinued pts demonstrated statistical significance for O vs P. There were significant improvements in SGRQ total score with O, but not F, vs P after 24 wks using MMRM and PMM.

### Adjusted mean difference vs P after 24 wks (combined dataset)

|        | MMRM focal score | MMRM SGRQ total score |
|--------|-----------------|-----------------------|
| O 5 μg | 0.3*            | −2.8†                 |
| O 10 μg| 0.2*            | −3.4†                 |
| F 12 μg| 0.2*            | −1.2*                 |

*P = ns; †p < 0.05

Conclusions: Lung function improvements with O QD translated into symptomatic benefit in COPD pts receiving usual care background therapy.

Funding: Boehringer Ingelheim.

DIETARY NITRATE SUPPLEMENTATION IN STABLE COPD

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Aim: Dietary nitrate has been demonstrated to have beneficial vascular effects1 and enhance performance in healthy individuals and elite athletes. The aim of this study is to investigate whether dietary nitrate administered as beetroot juice can enhance exercise capacity in subjects with COPD and if it is a safe dietary supplement for this population.

Method: 19 patients with COPD had lung function testing, incremental shuttle walk test and endurance shuttle walk test to assess exercise capacity. Patients also completed a safety phase; postural blood pressure, heart rate and symptoms were recorded periodically up to 4 hours post consumption of beetroot juice.

Results: 19 subjects have completed the safety phase. An insignificant change in systolic pressure was observed at post consumption of the beetroot juice (mean decrease 5.03 mmHg; maximum 30 mmHg). An insignificant drop in postural systolic pressure was observed post dose compared to baseline (5.42 vs 8.58 mmHg). Postural heart rate response was similar pre and post consumption (8.26 vs 8.11).

Conclusion: Ingestion of dietary nitrate caused an insignificant drop in systolic pressure in subjects with COPD. One patient developed symptomatic postural hypotension and was therefore excluded from the study. On the basis of these results, we believe it is a safe dietary supplement for this patient population. On completion of the study, the effect of dietary nitrate on exercise capacity will be reported.

BEBOLDER, ß-BLOCKERS BENEFIT OBSTRUCTIVE LUNG DISEASE BY EVENT REDUCTION

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Aim: 1. Examine the relationship between exacerbations of COPD, occurrence of cardiovascular events and mortality and ß-blocker therapy. 2. Review utilization of ß-blockers in patients admitted with an exacerbation of COPD.

Method: Retrospective review of 100 patients admitted to The Prince Charles Hospital prior to 31 December 2012 with an exacerbation of COPD. Medical records were evaluated for history of IHD, heart failure/ cardiomyopathy or arrhythmia. Information on smoking history, lung function and ß-blocker prescription was collected. Frequency of cardiovascular events before and after the admission was documented.

Results: 86 patient records were evaluated. Fifty-five patients (64%) had a history of cardiac disease. Of the patients with COPD and cardiac disease, 36 patients (65.5%) were not on ß-blockers. Of this group, 15 patients had a history of cardiac failure. 21% of patients on ß-blockers were either readmitted to hospital with cardiovascular events or died within six months, compared to 19.4% for the group not on ß-blockers. The group not on ß-blockers had poorer lung function (mean FEV1 1.5 litres, compared with 1.42 litres for those on ß-blockers), 25% required readmission to hospital with an exacerbation of COPD within 6 months of the admission compared with 21% in the ß-blocker group.

Conclusion: Patients with COPD and a cardiac indication for ß-blockers are frequently not receiving this therapy. Patients not on ß-blocker therapy had a lower average FEV1, which may have contributed to their physicians’ decision not to commence ß-blocker therapy. The rate of COPD exacerbations however was similar between the two groups. There was no association between ß-blocker therapy and reduced cardiovascular events and mortality in patients admitted to hospital with exacerbations of COPD. Our study has identified a patient population with COPD and cardiac disease not receiving ß-blocker therapy.

Key words: beta blockers, COPD, cardiovascular.
THE PREVALENCE OF ASTHMA AND COPD IN ‘BABY BOOMERS’—THE BUSSELTON HEALTHY AGEING STUDY

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Introduction: Australia’s population is undergoing a demographic change with the first wave of Baby Boomers (adults born 1946–1964) now reaching retirement age. By 2050 up to one quarter of the population will be aged over 64 years. The impact of chronic respiratory diseases such as COPD and asthma will provide greater challenges in health care delivery and the treatment and prevention of diseases in an ageing population.

Aim: To estimate the prevalence of asthma and COPD and associated respiratory symptoms in Baby Boomers randomly sampled from the Shire of Busselton, Western Australia as part of a comprehensive, multidisciplinary health survey of ageing.

Methods: Medical history and respiratory symptoms were collected using standardized questionnaires and lung function was measured using pre and post-bronchodilator spirometry.

Results: Among the first 1997 attendees (mean age 55.7 years, 54% women) the prevalence of respiratory symptoms including recent wheeze (18%), chest tightness (17%), and dyspnoea under mild exertion (20%), were similar in both sexes. The prevalence of doctor-diagnosed asthma was higher in women (18%) than men (11%), while both sexes had similar levels of reversible spirometry (>12% and >200 ml increase in FEV1 post-salbutamol) consistent with asthma (5% men, 4% women) and FEV1 < 80% predicted (12% men, 14% women). Current tobacco smoking was more prevalent in men (12%) than women (9%). The overall prevalence of COPD (GOLD stages I–IV) was 10.3% (12.2% men, 8.8% women). Despite 6% of Baby Boomers having moderate to severe COPD (GOLD stages II or higher), the prevalence of self-reported doctor-diagnosis of COPD was less than 1% in either sex.

Conclusion: Spirometric measures of asthma (significant bronchodilator response) and COPD, and self-reported respiratory symptoms are common in middle-aged adults. While objective measures of airway function are similar between the sexes, doctor-diagnosed asthma is more common in women. COPD is under-diagnosed in both sexes.

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Conflict of Interest: No.

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THE ASSOCIATION BETWEEN BMI AND SHORTNESS OF BREATH IN THE 1981, 1994/5 AND 2005/7 BUSSELTON SURVEYS

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Introduction: We have previously shown that in the general community, SB (& other respiratory symptoms) is associated not only with diagnosed respiratory illness but also independently with obesity. From 1981 to 2005, the prevalence of obesity has increased while the prevalence of SB has remained stable.

Aim: To determine if the association between BMI & SB has changed.

Methods: For adults attending the 1981, 1994 & 2005 Busselton Health Surveys, SB was categorized as present based on standard British Medical Research Council questionnaire. Logistic regression models (with SB as outcome variable) were used to obtain the estimated effect of BMI on SB & the interaction term sex*BMI tested to determine if the effect of BMI was different in men & women.

Results: The prevalence of SB was slightly lower in 1994 than in 1981 & 2005. The overall age & sex adjusted odds ratio (OR) for the effect of BMI on SB ranged from 1.065 in 1981 to 1.140 in 1994 with 2005 being between these two values at 1.096. Thus an increase of 1 kg/m2 in BMI was associated with a 6.5% to 14.0% increase in the odds of having SB. Further adjustment for smoking, recent wheeze, cough/phlegm, diagnosed asthma, diagnosed bronchitis, dust, family history of asthma or family history of hay fever, FEV1 (% predicted), chest pain/angina & level of exercise only slightly attenuated the OR to 1.060, 1.107 & 1.071 respectively for 1981, 1994 & 2005. In all cases the effect of BMI on SB was stronger in women but was not significant after multivariable adjustment.

Conclusion: BMI continues to be related independently to SB, has not changed appreciably from 1981 to 2005 in the Busselton population with similar effect in men & women.

INDIGENOUS RESPIRATORY OUTREACH CARE (IROC)—ENHANCING RESPIRATORY HEALTH IN RURAL AND REMOTE ABORIGINAL AND TORRES STRAIT ISLANDER COMMUNITIES

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Aim: Respiratory diseases are the leading cause of hospitalization in Aboriginal and Torres Strait Islander Peoples and the 4th leading cause of mortality accounting for 8.7% of all deaths. Despite this, there are limited approaches to specialist respiratory care in rural and remote communities that are culturally appropriate. The Indigenous Respiratory Outreach Care (IROC) is to enhance specialist respiratory services (both adults and paediatrics) in rural and remote Aboriginal and Torres Strait Islander communities and enrich community capacity to reduce the burden of lung disease.

Method: A multi-disciplinary steering committee governs the programme. Multi-disciplinary teams (incorporating specialist nurses, doctors, Indigenous Health Workers (IHW’s) and scientists) service five Queensland Health Service Districts. Sites were identified based on a perception of unmet need, burden of respiratory disease and/or capacity to utilize the clinical service and capacity building support offered. IROC services include intensive pre and post support and follow up, ongoing training of IHW’s and health staff, enhancing community awareness of respiratory issues and the development and dissemination of culturally appropriate education materials.

Results: The service commenced in March 2011. To date, IROC has been implemented or received support for, in 12 communities (both rural and urban). Early data suggest that the service is being received positively by communities and local health service providers with high clinic attendance and IHW’s involvement. In some regions, new diagnoses of paediatric chronic lung disease that were not previously recognized have been detected.

Conclusion: The delivery of culturally sensitive specialist respiratory services for Aboriginal and Torres Strait Islander adults and children is critical to addressing the excess burden of disease in this population. IROC provides a successful model for achieving this goal that is readily transferrable to other regions in Australia.

Key words: respiratory disease, Indigenous and rural.

Grant Support: Nil.

1. O’Grady, K.F., et al., Lung Health Services for Aboriginal and Torres Strait Islander Peoples in Queensland. 2010.
MOBILE PHONES SUPPORT ADHERENCE AND RETENTION OF INDIGENOUS PARTICIPANTS IN A RANDOMIZED CONTROLLED TRIAL

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Introduction: Ensuring adherence to treatment and retention is important in clinical trials, particularly in remote areas and minority groups. We describe a novel approach to improve adherence, retention and clinical review rates of Indigenous children.

Methods: This descriptive study was nested within a placebo-controlled, randomized trial (RCT) on weekly azithromycin (or placebo) for 3-weeks. Indigenous children aged ≥24 months hospitalized with acute bronchiolitis were recruited from two tertiary hospitals (Darwin and Townsville). Using mobile phones embedded within a culturally-sensitive approach and framework, we report our strategies used and results obtained. Our main outcome measure was rates of adherence to medications, retention in the RCT and self-presentation (with child) to clinic for a clinical review on day-21.

Results: Of 301 eligible children, 76 (21%) families declined participation and 187 enrolled. Of those enrolled, 71.6% were female and 83.4% were aged 18 years and over. One hundred and 21 participants completed a survey and 45 people engaged in yarning’s. Major issues identified were a lack of knowledge about respiratory symptoms and the respiratory system and that respiratory health was not a priority unless there were current symptoms.

Conclusion: Despite the burden and origins of respiratory disease, lung health is not a priority. To reduce the burden of disease and impact on future lung health, awareness of respiratory health needs to be enhanced.

Reference
1. O’Grady KF, Revell A, Maguire G, Millong R, Newman M, Reid D, et al. Lung Health Services for Aboriginal and Torres Strait Islander Peoples in Queensland. 2010 July 2010. Report No.

INCIDENCE OF OCCUPATIONAL AND NON-OCCUPATIONAL ASBESTOS EXPOSURE IN THOSE WITH LUNG CANCER

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Aim: Exposure to asbestos can lead to the development of lung cancer and it has been estimated that approximately 2–3% of all male lung cancer deaths are due to asbestos. The aim of this study was to compare the incidence of occupational and non-occupational exposures to asbestos between those with lung cancer and a control group.

Methods: Structured telephone interviews were conducted with adult subjects who had lung surgery for either lung cancer (LC group) or other clinical conditions (control group). The interview questionnaire was designed to survey lifetime occupational and residential asbestos history, ‘do it yourself’ (DIY) home renovation activities and other possible environmental exposures.

Results: Interviews were conducted in 75 participants (36 LC, 39 controls) with 51% being males (n = 38). There was no significant difference in the incidence of occupational or non-occupational exposure to asbestos between the groups (Table 1).

| Table 1 LC (n = 36) | Controls (n = 39) | p |
|---------------------|------------------|---|
| Age, mean (SD)      | 62.7 (7.7)       | 58.3 (11.2) | 0.054 |
| Ex-smoker/smoker/non-smoker | 29/3/4 | 21/5/13 | 0.03 |
| Occupational exposure | 8 (22.2%) | 7 (17.9%) | 0.64 |
| DIY exposure | 10 (27.8%) | 8 (20.5%) | 0.46 |
| Exposure during childhood | 5 (13.9%) | 10 (25.6%) | 0.43 |
| Other non-occupational exposure | 5 (13.9%) | 8 (20.5%) | 0.75 |
| Ever lived in house with asbestos | 21 (58.4%) | 27 (69.2%) | 0.33 |
| Ever lived with a potentially exposed worker | 23 (63.9%) | 29 (74.4%) | 0.33 |

Conclusions: Using the interview questionnaire we were unable to detect a difference in the incidence of occupational and non-occupational asbestos exposure between lung cancer and control groups. However, there are several potential confounders and the sample size was small.

Supported by: NH&MRC 1006088.

Conflict of Interest: None.

DEGREE OF ASBESTOS EXPOSURE IN AGE SEX MATCHED COHORT OF PERITONEAL MESOTHELIOMA AND PLEURAL MESOTHELIOMA PATIENTS

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Introduction: Patients with peritoneal mesothelioma are thought to require a heavier exposure to airborne asbestos fibres compared to patients with pleural mesothelioma.

Aim: The aim of our study was to assess the degree of asbestos exposure in a cohort of 110 age and gender matched peritoneal and pleural mesothelioma patients.

Method: Detailed historical data of the patients’ exposure were provided for each patient as assessed by lawyers involved in the care of the patients. Based on this, exposure was categorized by type and dose. Type of exposure was classified as Domestic (childhood or otherwise); Bystander and Occupational. Dose of exposure was sub-classified to low-dose or substantial.

Results: Age and gender matched cohorts of 55 patients with peritoneal and pleural mesothelioma were compared. There were 76% Male and 24% Female in each group. In the Peritoneal Mesothelioma group 36% had occupational exposure while 28% had bystander/domestic exposure to asbestos. In 36% exposure to asbestos was unknown. In the pleural mesothelioma group 29% had occupational exposure, 11% had bystander or domestic exposure while exposure details were unknown in 59%. 23.6% (13/55) of patients with peritoneal mesothelioma had low-dose exposure compared to 14.81% (8/55) of patients with pleural mesothelioma in our study cohort.

Conclusion: This study indicates that relatively low dose exposures can result in peritoneal mesothelioma, and it supports the current understanding that there is no threshold of exposure below which peritoneal mesothelioma will not occur, similar to pleural mesothelioma.

Conflict of Interest: None.

Supported by: NH&MRC 1006088.
SELF-REPORTED NON-OCCUPATIONAL ASBESTOS EXPOSURE IN THE GENERAL POPULATION IN NEW SOUTH WALES

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Aim: Home renovation as a non-occupational exposure to asbestos may be contributing to a rising incidence of malignant mesothelioma in Australia. The aim of this study was to compare the frequency of non-occupational exposure to asbestos in younger compared with older NSW residents and to assess trends in these exposures.

Methods: Structured telephone interviews were conducted with adult subjects who have had lung surgery for various clinical conditions. The interview questionnaire was designed to survey lifetime occupational and residential history, ‘do it yourself’ (DIY) home renovation activities and other possible environmental exposures. Subjects ≥40 years were compared with those <40 years old.

Results: Interviews were conducted in 77 participants (38 subjects <40 years, 39 subjects ≥40 years old) with 56% being males (n = 43). Self-reported DIY exposure occurred in approximately 13% of subjects and approximately 25% subjects reported childhood exposure (Table 1). Five subjects (13.2%) from the <40 group and 8 subjects (20.5%) in the ≥40 group reported other non-occupational asbestos exposure (p = 0.28).

Table 1

| Exposure                                      | <40 (n = 38) | ≥40 (n = 39) | p     |
|-----------------------------------------------|--------------|--------------|-------|
| DIY exposure                                  | 2 (5.3%)     | 8 (20.5%)    | 0.09  |
| Childhood exposure                            | 9 (23.7%)    | 10 (25.6%)   | 0.88  |
| Ever lived with a potentially exposed worker  | 22 (57.9%)   | 29 (74.4%)   | 0.13  |
| Ever lived in a house containing asbestos     | 17 (44.8%)   | 27 (69.2%)   | 0.03  |
| Other non-occupational exposure               | 5 (13.2%)    | 8 (20.5%)    | 0.07  |
| Occupational exposure                         | 4 (10.5%)    | 7 (17.9%)    | 0.35  |

Conclusions: Asbestos exposure during DIY home renovation is occurring in approximately 13% of the population in NSW, including those <40 years old. There has been no significant decline between the groups in the self-reported history of other non-occupational exposures to asbestos; however, the proportion of people who have ever lived in a house containing asbestos has fallen. Supported by: NH&MRC 1006088.

Conflict of Interest: No.

DRUG RESISTANT GENE EXPRESSION CHANGES IN CARBOPLATIN TOLERANT MESOTHELIOMA CELLS

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Aim: A proportion of patients with mesothelioma respond to standard chemotherapy consisting of cisplatin and pemetrexed and platinum, but tumour resistance most often becomes blunted after several cycles. To discover circumstantaneous mechanisms of loss of chemotherapeutic sensitivity by comparing expression of genes implicated in cancer drug resistance between platinum naïve and platinum exposed mesothelioma cells.

Method: Four mesothelioma cell lines were exposed to stepwise increments of carboplatin until in vitro tolerance to carboplatin at 20 μg/ml was established. Control cells from each line were passaged in parallel without carboplatin. Cells were in log phase growth and culture medium was free of platinum for at least two days prior to sensitivity testing for carboplatin and extraction of RNA using QiaGen RNAeasy Mini kits. High quality RNA (assessed by denaturing gel electrophoresis) was then DNase treated and reverse transcribed using QiaGen RT Profiler PCR Array reagents. Gene expression in control and platinum resistant cells was determined from the Cancer Drug Resistance PCR Array according to manufacturer’s instructions. Validation of genes were performed using Taqman gene expression PCR.

Results: Mesothelioma cell lines were intrinsically resistant to carboplatin, tolerant to levels of 20 μg/ml in culture medium and also show no persistent change in carboplatin IC50, SULT1E1, ESR1, AR and EPBB3 genes were highly expressed in mesothelioma cells tolerant to 20 μg/ml carboplatin than drug naïve cells.

Conclusion: Although mesothelioma cells become tolerant to 20 μg/ml carboplatin, we could not propose a mechanistic explanation for this tolerance to changes in expression of genes implicated in known drug resistance mechanisms. More comprehensive exploration of molecular changes in carboplatin tolerant mesothelioma is needed to improve understanding of the limitations of carboplatin as a therapeutic agent for mesothelioma.

Key words: mesothelioma, carboplatin, resistance.

Grant Support: Cancer Australia.

PULMONARY ALVEOLAR PROTEINOSIS SECONDARY TO ALUMINIUM DUST INHALATION

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Case Report: An Australian boatbuilder presented with increasing dyspnoea over 12 months associated with dry cough and reducing exercise tolerance. For at least 7 years of his boatbuilding career he was heavily exposed to aluminium dust. CT chest showed bilateral patchy parenchymal inﬁltrates with a crazy-paving appearance, and calcified mediastinal lymph nodes. Physical examination was unremarkable, but spirometry showed restriction. His six-minute walk distance was 345 m, and he desaturated to 85% after four minutes’ walking. Broncho-alveolar lavage returned a milk-white lipoproteinaceous fluid which stained positive with periodic acid-Schiff (PAS). Electron microscopy showed lamellar bodies in macrophages and in the fluid itself, suggestive of alveolar proteinosis. The diagnosis was conﬁrmed after GM-CSF antibodies were identiﬁed on the lavage ﬂuid. Mediastinal lymph node biopsy revealed high levels of aluminium and aluminium oxide on scanning electron microscopy with energy dispersive spectroscopy. He underwent periodic whole lung lavages as indicated by lung function testing and symptoms. After two years he left the boatbuilding industry, following which his symptoms improved.

Discussion: Alveolar proteinosis is a rare lung disease characterized by the diffuse accumulation of PAS-positive lipoproteinaceous fluid in the alveoli. Symptoms are non-specific, but restrictive change in lung function is typical. Autoimmune (90%) and non-autoimmune (10%) forms of alveolar proteinosis have been described, with the latter encompassing congenital and secondary causes. Silicate inhalation and haematological malignancy are the commonest secondary causes. Only one case linking aluminium to alveolar proteinosis has so far been reported, but metallurgical analysis of tissue in this patient supports the conclusion that aluminium was the cause of his disease.

Conclusion: This case further strengthens the causative association between aluminium and this rare but potentially disabling condition. It also reiterates the need for measures to prevent excessive aluminium inhalation in those working in relevant industries.
THE EPIDEMIOLOGY OF SPONTANEOUS PNEUMOTHORAX IN WESTERN AUSTRALIA

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Aim: Spontaneous pneumothorax (SP) is broken down into primary (PSP: no known underlying lung disease), secondary (SSP: known lung disease). Male sex and smoking are strongly associated risk factors for PSP. We analysed population data on the incidence of SP in Western Australia (WA) between 1969–2012.

Methods: We searched the WA Department of Health Hospital morbidity database for coded diagnosis of SP and any concurrent or subsequent code for lung disease. Australian Bureau of Statistics data for population number were used to calculate incidence rates and smoking prevalence. As PSP affects teenagers we defined ‘adult’ as age 14 upwards.

Results: 17,151 episodes of SP were retrieved on 12,577 patients (97.4% adults), 2,702 (21.5%) patients had 2 or more admissions. In adults there were 12,484 PSP admissions and 4,294 for SSP. For PSP, median age was 37 (IQR23–61) years, 67.4% were male; for SSP median age was 65 (IQR 48.5–74) years, 66.1% male. For males with PSP, incidence (per 100,000) in 1971–1980 was 23.08, females 9.00; in 2001–2010 the incidence was 27.96 and 16.01 respectively (Chi-square for trend p = 0.02 for males and p < 0.0001 for females). For males with SSP, incidence (per 100,000) in 1971–1980 was 3.55, females 1.19; in 2001–2010 the incidence was 11.32 and 6.88 respectively (Chi-square for trend p < 0.0001 for males and females). Age standardized rates of current smokers in Australia for males aged over 18 years fell from 45.5% in 1971 to 20.4% in 2011 and declined from 29.1% in 1977 to 16.3% in 2011 for females).

Conclusions: The incidence of PSP in the population is rising, and at a greater rate in females, despite falling prevalence of smoking. The incidence of SP is also rising, equally between sexes, perhaps reflecting previous smoking practice.

INVESTIGATING DELTA LUNG AGE USING INDEPENDENT DATA

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Aim: Smokers have lower lung function than healthy never smokers, which results in higher lung age (LA) than chronological age. The Delta LA (DLA) equation based on FEV1/FVC from NHANES III data is multiethnic (Caucasian, African-American, Mexican) and applies to both sexes. It calculates the difference between chronological age and lung age estimates, and is purported to be superior to LA based on FEV1 alone, although this has not been verified using independent data. The aim of this study was to investigate the behaviour of Delta lung age equations in Australian independent datasets, and compare it with three LA equations based on FEV1 alone.

Methods: Healthy never smokers and current smokers aged between 25 and 74 years of age were defined in three independent datasets. LA was estimated for each subject using each of the four LA equations, based on height, and observed FEV1 or FEV1/FVC ratio. For statistical analysis, a linear mixed effects model was used, with an unstructured covariance structure to account for the variability in LA equations. Separate analysis was performed for each dataset, and statistical significance was set at p < 0.01 to allow for multiple comparisons. Residuals were also explored.

Results: Separate regression equations were defined from the data, for each combination of Equation Group (Hankinson, Hansen, Morris, Newbury) and Sex-Smoking Status (Male HNS, Male CS, Female HNS, Female CS). The DLA equation gives more widely varied and extremely high LA estimates than do the other equations, which is evident in all datasets. This occurs more so in CS than in HNS.

Conclusion: The results using three independent datasets indicate that there is no advantage to be gained in using the DLA equation over LA equations based on FEV1 alone.

COHORT AND PERIOD EFFECTS ARE EVIDENT IN SPIROMETRY PREDICTIVE EQUATIONS

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Aim: Lung age can be used to communicate spirometry results to smokers, as part of smoking cessation counselling; however research results using lung age have been inconclusive. Our aim was to determine if Morris lung age (LA) equations, based on data gathered in the 1960s, are relevant for current-day populations.

Methods: New LA equations were created based on recent Australian data. Study 1: Both Morris LA and Newbury LA were applied to two subgroups of an independent dataset (healthy never-smokers (HNS) n = 340, current smokers (CS) n = 50). Paired t-tests compared the mean LA estimates. Study 2: Further LA equations were created from previously published spirometry predictive equations for FEV1. Predicted FEV1 from each equation were plotted against age; and the six estimated LA were compared by regression analysis in 25–74 years old HNS and CS from a large independent dataset. Earlier and more recent equations from similar regions were able to be compared (USA – Morris/Hankinson; Europe and UK – Quanjer/Falaschetti; Australia – Gore/Newbury).

Results: Morris LA equation consistently estimated LA to be approximately 20 years lower than the newest LA equation, in both HNS and CS in both datasets. As FEV1 increased progressively across the 40-year time span covered by these 6 equations; the associated increase in LA is evident in the successive LA equations. For each region, earlier equations predict lower FEV1 than the later equations.

Conclusions: The increase in predicted FEV1 over the forty-year time span is indicative of the cohort and period effects which relate to differences in subjects linked to improved health and better nutrition, and differences in equipment used and standards applied over time. Our results support the use of recently-developed equations that are relevant to the population being studied. We hypothesize that more recently developed LA equations might have greater clinical utility for smoking cessation quit attempts.

FUNGAL EXPOSURE ASSESSED WITH ENZYME MEASUREMENTS IN HOMES OF PATIENTS WITH ASTHMA AND SARCOIDOSIS

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Background: Fungi is a risk factor for some respiratory diseases. Traditional exposure measurements are time consuming and do not take into account the total fungal cell biomass. Analysis of the enzyme β-N-acetylhexosaminidase (NAHA) has been used as a measure of total fungal biomass.

Aims: To assess the usefulness of the NAHA technique to detect fungal damage and to perform measurements in homes of patients with asthma and sarcoidosis.

Methods: Air samples were taken using a filter cassette. An enzyme substrate was added and the fluorescence was read after incubation. The fluorescent readings were expressed as NAHA units (U/m3). Samples were taken in buildings which were later inspected for fungal damage (n = 162). Measurements were also made in the bedrooms of subjects with asthma (n = 80) and sarcoidosis (n = 88).

Results: At levels above 30 U/m3 in buildings there was a sensitivity of 55% and a specificity of 100% for the presence of fungi. NAHA was higher than controls in homes of persons with nocturnal asthma (31.2 vs 12.5 U/m3, p = 0.001). Among patients with sarcoidosis, the values were higher compared to controls (34.1 vs 18.9 U/m3, p < 0.002). Those with recurrent sarcoitis had higher values than those whose disease had healed (39.9 vs 12.0, p = 0.001). There was significant relationship between NAHA and the extent of granulomatous infiltration and the amount of β-glucan in BAL.

Conclusions: The results suggest that measurements of airborne NAHA are suitable to detect the presence of fungi indoors, particularly as it includes fungal cell fragments. The levels relate to the clinical expressions of nocturnal asthma and sarcoidosis.

Funding: Internal hospital funds only.

Key words: interleukin-10, sarcoidosis, β-glucan, chitin.
COMPARISON BETWEEN BRONCHIAL WASHING (BW) AND BRONCHOALVEOLAR LAVAGE (BAL) IN PATIENTS WHO ARE SMEAR NEGATIVE OR UNABLE TO EXPECTORATE SPUTUM WITH SUSPECTED PULMONARY TUBERCULOSIS (TB)

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Western Health

Introduction: Performing a bronchoscopy is commonly used for investigating patients with possible pulmonary TB when spontaneous sputum is smear negative. Currently there is no evidence that BAL is superior to BW in sputum smear negative pulmonary TB. General consensus varies between clinicians.

Aim: To determine if performing a BAL yields a higher diagnostic rate compared to BW alone in pulmonary TB.

Method: In a prospective study of subjects (n = 50) with possible active pulmonary tuberculosis, the diagnostic yield of BAL was compared to BW. Subjects either produced no sputum or had (acid fast) smear negative sputum. BAL and BW were performed on all the patients. The order of BAL and BW was randomized. Our primary outcome was the percentage of culture positive results in BW and BAL. The secondary outcome was the percentage of smear positive results in BW and BAL.

Results: Interim analysis of the data (n = 20) demonstrated a mean (SD) age of 38 (19.6) years, with subjects mainly from Vietnam (25%), India (25%) and Burma (20%). Five subjects (25%) had culture positive results: 4 in both BW and BAL. In one subject, while the BW was culture negative for Mycobacterium tuberculosis (MTB), the BAL was culture positive, providing an additional confirmatory diagnosis. The agreement between BW and BAL was excellent (0.86 Cohen’s Kappa). The yield of positive smear results was low (1 case) and noted in both the BW and BAL.

Conclusion: In subjects who either cannot expectorate sputum or have a smear negative sputum requiring bronchoscopy, adding a BAL to a standard BW maybe be clinically indicated given the public health issue and importance of making a firm diagnosis.

RISK FACTORS FOR PERIPHERAL LYMPH NODE AND PULMONARY TUBERCULOSIS: A COMPARATIVE CASE-CONTROL STUDY

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Introduction: Lymph node tuberculosis (LNTB) is the most common form of extra-pulmonary TB, accounting for approximately 15% of all TB cases in Australia. However, data on LNTB are sparse.

Aim: To describe clinical and epidemiological characteristics of peripheral LNTB in comparison to pulmonary TB (PTB).

Methods: We conducted a case-control study comparing patients with peripheral LNTB with randomly selected patients with PTB diagnosed at a Sydney TB clinic, between January 2000 and December 2012. Epidemiological and medical data were extracted from the electronic hospital database and medical records. The data were examined for associations between LNTB and age, sex, ethnicity, BCG vaccination status and comorbidities (HIV, diabetes and chronic kidney disease) in comparison to PTB, using logistic regression in a univariate and multivariate analysis.

Results: There were 213 cases with LNTB and 426 randomly selected controls with PTB. Among patients with LNTB, 74% were female and the mean age (SD) was 42 (16) years. Among patients with PTB, 43% were female and the mean age was 44 (22) years. Females, 45–64 year olds, and Southern Asians had an increased risk for LNTB (Odds ratio (OR) 2.98, 95% CI 1.99 to 4.48; OR 2.37, 95% CI 1.22 to 4.60 and OR 3.52, 95% CI 1.34 to 9.24 respectively). Patients with diabetes were at a higher risk of PTB (OR 0.42, 95% CI 0.20 to 0.88 for LNTB).

Conclusion: This is the first Australian study comparing the epidemiology of LNTB to that of PTB. An increased risk for LNTB was found among females, people aged 45–64 years and people born in Southern Asia. An increased risk for PTB was found among patients with diabetes.

INCREASED TUBERCULOSIS TREATMENT SUCCESS WITH COMMUNITY-BASED DOT IN MONGOLIA

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Introduction: A major strength of the Mongolian National Tuberculosis Program (NTP) is a dedicated network of 300 volunteers, coordinated by the Mongolian Anti-Tuberculosis Association (MATA), who provide decentralized tuberculosis (TB) treatment under direct supervision.

Aim: To evaluate the treatment success of two community-supported directly observed therapy (cDOT) strategies (home-DOT and lunch-DOT) in comparison to traditional clinic-DOT in Ulaanbaatar, Mongolia. With ‘home-DOT’ volunteers delivered treatment at home; with ‘lunch-DOT’ volunteers provided treatment after patients had a free meal at a cafe contracted by MATA.

Methods: We analysed NTP data of all sputum smear-positive patients commenced on TB treatment in 9 districts (aimags) of Ulaanbaatar (2010–2011) to assess treatment outcome with different DOT strategies. Treatment success included ‘cure’ and treatment completed based on WHO definitions. Multivariate logistic regression analysis adjusted for age, sex, occupation/ socioeconomic status and patient category (new, default, failure, relapse, transfer-in).

Results: Of 2,315 sputum smear-positive TB patients 1835 (79.3%) received clinic-DOT, 354 (15.3%) home-DOT and 126 (5.4%) lunch-DOT. Patients on cDOT were more likely to be unemployed with 47% of patients on home-DOT and 52% of patients on lunch-DOT being unemployed compared to 41% on clinic-DOT. The median age was 32 (interquartile range, IQR, 19) years in patients on clinic-DOT, 29 (IQR 22) years in patients on home-DOT and 36 (IQR 25) in patients on lunch-DOT. The proportion of males was 58%, 52% and 53% among clinic-DOT, home-DOT and lunch-DOT respectively. In multivariate analysis home-DOT and lunch-DOT had a significantly higher treatment success than clinic-DOT (93%, OR 3.2; 95% CI 2.1 to 4.9 for home-DOT and 98%, OR 16.0; 95% CI 3.9 to 65.4 for lunch-DOT compared to 78% for clinic-DOT).

Conclusion: Higher treatment success was achieved with cDOT, especially lunch-DOT, than with traditional clinic-DOT. Detailed feasibility and cost-benefit analysis seems warranted also assessing its value in managing MDR-TB.
THE BACTERIOLOGY OF PLEURAL INFECTION IN WESTERN AUSTRALIA

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Introduction: There is frequently marked geographical variation in the bacteriology of pleural cultures and differences in nosocomial and community-acquired bacteriology. We undertook an analysis of all pleural fluid cultures from the public hospitals in the Perth metro area, Western Australia.

Method: Data were extracted from the PathWest microbiology laboratory database on any episodes coded to have a positive pleural fluid culture between 2006 to 2011. Casenote and stored electronic health record data were reviewed for demographics, length of stay, survival, biochemistry and systemic inflammatory markers.

Results: 713 cases with 968 positive cultures were available for analysis. Median age was 63.7 years, 502/713 (70.4%) were male and 418/713 (58.6%) right sided. 153 different organisms were isolated; the main isolates are summarized: 11.9% Staphylococcus aureus, 9.49% Streptococcus viridans, 9.1% other aerobes (mixed), 7.12% S. anginosus group, 6.24% gram-negative rods, 5.12% pseudomonas aeruginosa, 4.12% E. coli, 3.62% Klebsiella spp., 3.37% MRSA. Analysis also revealed organisms never before reported in association with pleural infection (e.g. Klebsiella oxytoca). Median (IQR) pleural fluid pH was 7.30 (6.69–7.59), glucose 2.7 mmol/L (0.5–5.8), LDH 600 μL/L (248–3186), white cell count 12.7 × 109 (8.98–17.4), lymphocytes 6.65% (4.67–12.0), procalcitonin 172 mg/L (74–280). Median survival following infection was 68.0 days (20.0–322.0). 151 cases had community-acquired infection (CAI) and 298 hospital-acquired infection (HAI). Compared to HAI, CAI had more isolates of S. anginosus and S. viridans groups (both p < 0.05) and HAI had more MRSA, Enterococci, Klebsiella spp. (all p < 0.005). One-year survival was greater with CAI (OR 1.68, 95% CI 1.14 to 2.35, p = 0.014).

Conclusions: Elucidation of local bacteriology for pleural infection may reveal unique isolates and patterns. In this population, pleural infection is associated with a poor prognosis. Important differences exist in the bacteriology and outcomes of community and hospital acquired infection.

VIRAL AETIOLOGY OF ACUTE LOWER RESPIRATORY INFECTIONS IN CHILDREN IN RURAL MOZAMBIQUE

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Aim: Acute lower respiratory infection (ALRI) is the leading cause of childhood mortality worldwide. The most common cause of viral respiratory infections is human rhinovirus (HRV). Despite high ALRI-associated mortality, the role of viruses in childhood ALRI in sub-Saharan Africa is poorly understood. We aimed to describe the viral aetiology of ALRI in hospitalized children in rural Mozambique.

Method: Nasopharyngeal aspirates were collected from 180 children <10 years of age admitted to Manhiça District Hospital with a fever and (WHO defined) clinical pneumonia as part of a study characterizing children with respiratory distress. HIV and malaria testing was offered and patients underwent chest X-ray and extensive clinical and laboratory screening. Respiratory viruses (adenovirus, respiratory syncytial virus, parainfluenza virus, metapneumovirus, bocavirus, enterovirus, influenza and coronavirus) were identified using two independent multiplex RT-PCR assays with primers specific for each virus and each type. HRV species and genotypes were identified using a molecular method involving RNA extraction, semi-nested PCR amplification, sequencing and phylogenetic tree analysis.

Results: A total of 180 children (49.4% male) with a mean age of 20.8 months were recruited. Twenty-five (13.9%) children were HIV-positive. At least one respiratory virus was identified in 150 (83.3%) children while co-infection with two, three and four viruses were identified in 27 (46.1%), 11 (6.1%) and 3 (1.7%) children respectively. HRV was the most common (51.7%) virus identified, followed by adenovirus (15.6%), respiratory syncytial virus (15.6%), parainfluenza virus (10%), metapneumovirus (8.3%), bocavirus (8.3%), enterovirus (6.1%), influenza (5.0%) and coronavirus (1.7%). Of the 76 HRV genotyped specimens, 41 (53.9%) were HRV-A, 28 (36.8%) were HRV-C and 7 (9.2%) were HRV-B. HRV was associated with HIV-infection (p = 0.028) and respiratory symptoms including wheezing (p = 0.005).

Conclusion: HRV is likely to contribute to ALRI in hospitalised children in Mozambique. HIV has a strong impact on viral infections.

Key words: human rhinovirus, acute lower respiratory infections.
A COMPARATIVE STUDY OF ANTIBIOTIC PRESCRIPTION FOR COMMUNITY ACQUIRED PNEUMONIA IN RESPIRATORY UNITS WITH AND WITHOUT AN ANTIMICROBIAL STEWARDSHIP PROGRAMME

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Introduction: Antibiotic restriction policies are in place in a large number of hospitals, to decrease the emergence of multi-resistant organisms and to prevent side-effects. However, the need and effectiveness of these restrictions in specialty units have not been assessed previously.

Aim: To compare antibiotic prescribing for patients admitted with community acquired pneumonia(CAP) at respiratory units at two teaching campuses within the same region in Adelaide; Flinders Medical Centre (FMC) (with administrative control of antibiotic prescribing), and Repatriation General Hospital (RGH) (with no administrative control of antibiotic prescribing).

Method: Multicentre retrospective observational study.

Results: A total of 37 patients were admitted with diagnosis of CAP (25 at FMC and 12 at RGH) of which FMC had 48% females and RGH had 58% females. The majority of patients in RGH had a Pneumonia Severity Index (PSI) score of IV (75%) or V (17%) while at FMC 24% of patients had PSI of III, 20% had PSI of IV and 24% had PSI of V. CAP guidelines were followed in 60% of patients at FMC compared to 75% at RGH (two-tailed Fisher test p = 1.00). One patient had an antibiotic associated adverse event at FMC compared to none at RGH. There was one death at each of the hospitals. The average length of stay was not significantly different (7 days at FMC and 8 days at RGH).

Conclusion: The adherence of respiratory units to CAP guidelines in this study is high, irrespective of administrative antibiotic restriction. The presence of restrictions did not increase adherence to the guideline and suggest that well produced guidelines, with adequate education of staff may make prescribing limitations unnecessary, especially in a specialty unit dealing with infections involving their area of expertise.

PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR G1 GENE EXPRESSION IN THE AIRWAYS OF NON CYSTIC FIBROSIS BRONCHIECTASIS SUBJECTS IS INVERSELY CORRELATED WITH TOTAL PSEUDOMONAS AERUGINOSA BACTERIAL LOAD BUT POSITIVELY CORRELATED WITH ABSOLUTE MACROPHAGE LEVELS

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Background and Aim: The aim of this experiment is to assess the level of expression of pparγ in non-cystic fibrosis bronchiectasis subjects as compared to healthy controls. Pparγ is an anti-inflammatory nuclear receptor gene expressed widely in the lung. Low levels of airway PPARγ is associated with an increased likelihood of P. aeruginosa positivity in the cystic fibrosis lung. It is postulated that the P. aeruginosa quorum sensing molecule 3-oxo-C12-homoserine lactone antagonizes pparγ, inhibiting its transcription.

Methods: Forty one non-CF bronchiectasis subjects and 20 healthy controls underwent fibroptic bronchoscopy sampling for the collection of lavage fluid. Messenger RNA was extracted from the samples and reverse transcribed to total cDNA using random hexamer primers. Expression of the gene encoding PPARγ was measured using real time PCR, with levels normalized to beta actin gene expression.

Results: Pparγ expression was lower in non-CF bronchiectasis subjects compared with controls (p = 0.0001), and lower in those patients who were PCR positive for P. aeruginosa (p = 0.012). There was an inverse correlation with P. aeruginosa conditioned media (r = -0.531, p = 0.002), which was not seen with either total bacterial load (r = 0.239 p = 0.194) or Haemophilus influenzae load (r = 0.297, p = 0.325). Pparγ expression was positively correlated with absolute macrophage count (r = 0.377, p = 0.044), consistent with the inverse correlation of P. aeruginosa with total macrophage level (r = -0.403 p = 0.025).

Conclusion: Pparγ expression in the airways of bronchiectasis subjects is significantly reduced compared to healthy individuals. This reduction is correlated with lower levels of macrophages (a cell type where the PPARγ gene is highly expressed) and increased levels of P. aeruginosa. Whether the reduction in pparγ is purely a reflection of low macrophage levels or a due to its interaction with P. aeruginosa warrants further study.

VIRAL SURROGATES AND RESPIRATORY VIRUSES DIFFERENTIALLY ACTIVATE NEUTROPHILS

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Introduction: Neutrophils are important in controlling infections, in particular respiratory virus infections. During these times there are increases in neutrophil numbers and products. Neutrophil inflammation is associated with more severe asthma symptoms and corticosteroid insensitivity. Their role in viral-induced asthma exacerbations or if neutrophils directly respond to respiratory viruses is not fully understood.

Aim: To investigate if neutrophils are activated by viral surrogates (TLR agonists) and different infectious respiratory viruses. To identify whether asthmatic and non-asthmatic neutrophils respond differently to viral surrogates.

Method: Peripheral blood samples were collected from mild asthmatic (n = 9–11) and non-asthmatic individuals (n = 13–18). Neutrophils were stimulated with LPS (1 μg/ml), FMLP (100 nM), imiquimod (3 μg/ml), R848 (1.5 μg/ml), poly I:C (10 μg/ml), rhinovirus (RV)-16 (MOI 1), respiratory syncytial virus (RSV) (MOI 1) or influenza virus (MOI 1). Cell free supernatant was collected after 1 h for measurement of neutrophil elastase (NE) and matrix metalloproteinase (MMP)-9 release or after 24 h for interleukin (IL)-8 release.

Results: LPS, FMLP, imiquimod and R848 stimulated the release of IL-8, NE and MMP-9. However, poly I:C induced only IL-8 release. There was no difference between asthmatic and non-asthmatic neutrophil responses, except for R848 in which neutrophils from asthmatic patients released significantly more IL-8 than control patients (p < 0.01). RSV caused the release of IL-8 and NE but not MMP-9 in neutrophils. However, RV-16 and influenza virus did not cause the release of any of the three mediators measured.

Conclusion: Neutrophils can detect and respond to viral surrogates by releasing IL-8, NE and MMP-9. However, neutrophils do not mount a response to RV-16 or influenza virus but they do detect and respond to RSV. Some respiratory viruses may not induce neutrophil inflammation directly but this form of inflammation may be a result of neutrophil interactions with adjacent infected cells.

STARVING COCCUS AUREUS, BUT NOT OTHER BACTERIAL EMPIEYA PATHOGENS, INDUCE THE RELEASE OF SELECTED CYTOKINES FROM MESOTHELIAL CELLS

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Aim: To evaluate and characterize the in vitro cytokine effects of bacterial pleural pathogens on mesothelial cells.

Methods: The benign MeT-SA pleural mesothelial cell line was treated with live or heat-killed Staphylococcus aureus (reference strains and clinical isolates) or Streptococcus species for up to 24 hr. Interleukin (IL)-6, IL-8 and vascular endothelial growth factor (VEGF) release was determined by enzyme-linked immunosorbent assay. S. aureus-conditioned media was subject to protein fractionation based on molecular weight using Amicon® Ultra-4 Centrifugal Filter Units (Millipore).

Results: Live, but not heat-killed, S. aureus reference strains induced IL-6, IL-8 and VEGF release from MeT-SA cells in a time- and dose-dependent manner. This result was verified using S. aureus clinical isolates obtained from blood cultures. Conversely, Streptococcus pneumoniae or S. milleri group bacteria did not induce cytokine release from MeT-SA cells. S. aureus-induced IL-6 and VEGF, but not IL-8, release was mediated via a bacterial exoproduct, which was resistant to heat, deoxyribonuclease and ribonuclease treatment. Selective ultra-filtration of S. aureus conditioned media revealed that the cytokine-inducing activity was retained in concentrates containing exoproducts <30 kDa in size.

Conclusions: Of the most common bacterial empyema pathogens only S. aureus induced the release of the cytokines tested from pleural mesothelial cells in vitro. The results using heat-killed bacteria and conditioned media indicate the causative factor is an actively secreted product from S. aureus.
CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) COMPLIANCE IN OBSTRUCTIVE SLEEP APNOEA (OSA)

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Introduction: CPAP therapy is currently the most effective treatment for management of OSA. Although CPAP is highly effective in controlling OSA, overall adherence rates are poor.

Aim: To assess CPAP compliance and outcomes amongst successive patients who attended the Sleep Investigation Service at Royal North Shore Hospital. In addition we evaluated whether patients valued the CPAP education service.

Methods: A retrospective audit was conducted for the period January to July 2012. One hundred and fifty, consecutive OSA patients were identified initially as requiring CPAP titration studies and a questionnaire was sent via mail. Attempts to contact the remaining participants by phone were made on a maximum of 2 occasions.

Result: Thirty-three out of the 150(22%) surveyed participants responded to the mailed questionnaire. An additional 24 patients completed a verbal questionnaire by phone, giving a total of 57 respondents.

Forty-nine out of 57 patients (86%) went on to trial CPAP at home. 60% were still currently using CPAP. Amongst the 23 patients who failed to take up CPAP 15(26%) had attempted a trial of CPAP at home but then abandoned treatment after 4 months. The remaining 8(14%) did not trial CPAP at home following their titration study. We found that a majority of patients (80%) found CPAP education helpful and would recommend it.

Conclusion: There were a significant number of patients who did not proceed to a trial of CPAP (14%) or who tried CPAP and then abandoned it (26%). Although the majority of patients found CPAP education helpful, we were not able to ascertain to what extent the current education programme influences the take up and use of CPAP. Our audit highlights the need to establish a real time monitoring system for CPAP compliance to better inform the design of a robust CPAP education and clinic model of care.

EFFECTS OF CPAP ON BODY ENERGY EXPENDITURE (BEE), SLEEPINESS AND FUNCTIONAL OUTCOMES IN OBSTRUCTIVE SLEEP APNOEA (OSA)

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Introduction: Excessive daytime sleepiness is common in OSA and can be reversed by CPAP. Reduced daytime sleepiness may enhance BEE, and this effect could potentially be useful for objectively monitoring CPAP efficacy in OSA.

Aim: We examined whether BEE increased in OSA patients after commencement of CPAP therapy, and whether increased BEE correlated with improvements in subjective measures of sleepiness and functional outcomes.

Methods: 7 men with recently diagnosed OSA (age 46 ± 14 years; apnoea-hypopnoea index 32 ± 15/h) were studied. BEE was estimated with a small validated actigraphic device (Actiheart, CamNtech Neurotechnology Ltd, Cambridge UK) which estimates and records BEE over extended periods. BEE was continuously estimated over 3 1-week periods: 1–2 weeks prior to, 1–2 weeks after, and 5–6 weeks after, commencement of CPAP therapy. Each subject also completed the Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ-30) at the end of each of the three study weeks.

Results: During the 8-week study period, significant improvements occurred in BEE (9.527 ± 4.309 vs. 12.038 ± 5.109 kJ/day, P = 0.0011), ESS (10.5 ± 2.5 vs. 3.0 ± 2.2, P < 0.0001) and the FOSQ-30 (3.2 ± 0.4 vs. 3.8 ± 0.1, P = 0.0038). Significant improvements were already evident after 2 weeks of CPAP for ESS (10.5 ± 2.5 vs. 4.1 ± 2.4, P = 0.0005) and the FOSQ-30 (3.2 ± 0.4 vs. 3.7 ± 0.2, P = 0.0053), but not for BEE (9.527 ± 4.309 vs. 10.414 ± 5.812 kJ/day, P = 0.0346).

Conclusions: The results suggest that BEE and subjective ratings of sleepiness and functional outcomes improved in OSA patients within 6 weeks after commencement of CPAP therapy. We speculate that actigraphic estimates of BEE may be useful for physiologically monitoring patient benefits from CPAP in OSA.
SLEEP DISTURBANCE IN A MALE COHORT WITH FABRY DISEASE

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Background: Fabry Disease (FD) is an X-linked lysosomal storage disease caused by deficiency in the enzyme alpha-galactosidase resulting in excessive intracellular storage of globotriaosylceramide. There is a paucity of objective sleep data in FD, however important clinical and physiological features of FD include pain, renal impairment, obstructive lung disease, thickening of the soft and hard palate, cardiomyopathy, cerebrovascular disease and peripheral neuropathy. We hypothesize that these abnormalities are likely to increase the prevalence of sleep disorders in FD.

Methods: Clinical sleep assessment and analysis of in-laboratory polysomnograms (PSG) of male Fabry patients (n = 11) were recruited from the Victorian Fabry cohort. Analysis of PSG was conducted by a sleep scientist and reported by a sleep physician with particular attention to identifying for sleep-disordered breathing (AHI > 5 events/hour) and/or periodic leg movements disorders (periodic leg movements >15/hour).

Results: A total of 11 patients (mean ± SD), age = 43 ± 8 years completed overnight PSG. Baseline characteristics included: BMI = 23.3 ± 3.7, neck circumference = 38.95 ± 12.19. Sleep disordered breathing was identified in 36% (95% CI. 15.1, 64.6) of patients and periodic leg movements were present in 91% (95% CI. 62.2, 98.3) of patients with sleep-disordered breathing had significant periodic leg movements. Of the tested group 11/11 were on enzyme replacement therapy at the time of testing.

Conclusions: Sleep disturbance in FD is likely to be multifactorial with patients having a higher prevalence of periodic leg movement disorder than the general population (approximately 4%). The prevalence of sleep-disordered breathing is slightly higher than the prevalence in large population studies (approximately 24%). Interventions are available for these symptoms and may improve quality of life.

MANDATORY REPORTING FOR PUBLIC ROAD SAFETY MAY CAUSE MORE HARM THAN GOOD—A SURVEY OF DOCTORS

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Aim: To determine whether SA road safety is harmed by the mandatory reporting law requiring doctors to report any driver whom they believed ‘would be likely to endanger the public’.

Method: Structured surveys were mailed to all 57 SA doctors who were either sleep qualified consultants, advanced trainees in sleep or electrocardiologists.

Results: Response rate was 61% (n = 35) with all respondents indicating awareness of the law, however 74% (n = 26) disagreed with it. Few doctors (23%) thought they were the best person to determine fitness to drive, and only 15% had received any form of training regarding making that determination. Nearly all (97%) had seen patients who ‘would be likely to endanger the public’ if they drove yet only 12% reported all patients in accordance with current legislation.

| % of reportable patients reported by doctor | All | >50 | <50 | <50 None |
|---------------------------------------------|-----|-----|-----|---------|
| % of doctors who reported                   | 12  | 24  | 35  | 15 15   |

Most doctors suspected at least some patients of lying (94%), doctor shopping (71%) or discouraging others from seeking medical help (66%) as a consequence of the law. Whilst 52% of sleep doctors used clinical data to determine who should be reported there was little consistency as Epworth Sleepiness Scale reporting thresholds ranged from 8–16 and Apnoea/Hypopnea Index thresholds ranged from 20–50. Eighty per cent of all doctors had received abuse due to the law and 66% knew of other staff members who had also been abused, totalling over 300 incidents of abuse (no known injuries).

Conclusion: Widely disliked, the mandatory reporting law is ignored by some doctors and inconsistently applied by most. This coupled with the adverse and even abusive behaviour of patients as a consequence of the law means that a review of the mandatory aspect of the legislation is called for.

A COMPARISON OF ARTERIAL BLOOD GAS SAMPLING AND TRANSCUTANEOUS MONITORING OF OXYGEN (PO2) AND CARBON DIOXIDE (PCO2) DURING THE HYPoxic Altitude SIMULATION TEST (HAST): A PILOT STUDY

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Aim: To determine the effectiveness of Transcutaneous monitoring (tc) of arterial tensions of Oxygen (pO2) and Carbon Dioxide (pCO2) compared to Arterial Blood Gasses (ABG) during the Hypoxic Altitude Simulation Test (HAST) in patients with COPD and other respiratory diseases.

Method: Currently five outpatients have been included as part of a clinically requested HAST procedure to assess fitness for airline travel and the benefit of supplemental O2 during the flight. The HAST was conducted under the condition of FiO215% concentration and FiO215% plus supplemental O2 at 2 L/min or 4 L/min to maintain pO2 > 60 mmHg. pCO2 and pO2 (mmHg) of room air baseline, FiO215% and FiO215% plus supplemental O2 values were compared with ABG sampling and tc by Radiometer Pacific TCM40. Paired t-tests were used to compare differences between ABG results and tc results, p < 0.05 was considered to be statistically significant.

Results: The mean difference between the tc and ABG measurements was not statistically significant for pO2 at baseline (p = 0.83; FiO215% (p = 0.73) and FiO215% + O2 (p = 0.75) or pCO2 at baseline (p = 0.09; FiO215% (p = 0.78); FiO215% + O2 (p = 0.27). A Bland-Altman plot was used to measure the agreement between the two methods with a smaller range indicating a better clinical utility for tc. For pO2 measurements the 95% CI range from −3.3 (baseline); −6.8, 8.6 (FiO215%); −6.6, 7.6 (FiO215% + O2). For pCO2 measurements the 95% CI range from −1.2, 3.8 (baseline); −2.4 (FiO215%); −2.9, 5 (FiO215% + O2). From this small data set, 78.6% of the measurements for tcpO2 are within 3 mmHg and for tcpCO2 100% are within 3 mmHg.

Conclusion: Our sample size to date indicates a close association between the two methods. These findings, coupled with the simpler, continuous and non-invasive nature of Transcutaneous monitoring warrants further investigation.

RUTHENIUM RED INHIBITS INTRAVENOUS FLUID INDUCED PERMEABILITY LUNG OEDEMA SUGGESTING A TRPV4 MECHANISM

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Background: Administration of bolus intravenous fluids has been associated with increased mortality (Feast study, NEJM 2011); a finding not fully explained by intravascular pulmonary oedema alone. We hypothesized that despite avoiding hydrostatic oedema, fluid administration leads to an increase in lung permeability. Transient receptor potential vanilloid (TRPV)4 ion channel activation by shear/stretch forces leads to disruption of alveolar septal barrier causing acute lung injury.

Aim: To (1) measure permeability to various intravenous fluids (2) test whether this increase in permeability could be prevented by TRPV4 antagonist ruthenium red (RR).

Methods: Healthy male Sprague Dawley rats received i.v. 4% albumin or 0.9% saline at 60 ml/kg over 30 minutes, or no fluids and underwent 2 hours non-injurious mechanical ventilation. Measures of lung physiology, and lung injury included blood gases, lung oedema, respiratory mechanics and whole lung lavage. Left ventricular end-diastolic pressure (LVEDP) is a measure of lung hydrostatic pressure was monitored continuously. Experiments were repeated with administration of intra venous RR (1 µmol/l) before 0.9% saline was administered. Results were analysed by 2-way ANOVA.

Results: Both i.v. fluids led to an increase in LVEDP (p < 0.001) which did not exceed 18 mmHg, the usual threshold of pulmonary oedema. Both fluids led to a rise in CVP and a drop in haematocrit (4% albumin >0.9% saline, p = 0.006).

Both fluids increased lung oedema (p < 0.01), lavage protein (p = 0.03), PaCO2 and decreased PaO2 (p < 0.001). Lung elastance (p = 0.01) deteriorated as did surfactant activity (p < 0.01). Histological injury score also deteriorated (p < 0.001), without an increase in lavage cells, myeloperoxidase activity or TNF-α or IL8. Administration of RR before 0.9% saline caused a reduction in mean lung oedema (p < 0.001), lavage protein (p = 0.01) and PaCO2 and increased PaO2 (p > 0.001) and lung elastance (p < 0.001).

Conclusion: Bolus i.v. fluids can result in permeability pulmonary oedema despite a safe (non-hydrostatic) LVEDP. Administration of RR prevents such permeability oedema suggesting a TRPV4 mechanism.
THE DISTRIBUTION OF AIRWAY CLOSURE IS ALTERED IN OBESITY

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Background: Obesity is associated with a reduction in FRC which may contribute to increased airway closure during tidal breathing and abnormalities in ventilation distribution.

Aim: To determine distribution of airway closure measured as non-ventilated volume (NVV) in obesity before and after bronchocconstriction.

Methods: 9 obese and 10 non-obese subjects underwent baseline ventilation distribution and post-bronchoprovocation SPECT ventilation scans on separate days. Total lung volume and NVV were calculated from matched CT and SPECT lung scans using a previously described algorithm. For analysis, all lungs were divided into upper, middle and lower thirds of equal lung height.

Results: Baseline NVV was similar in the obese and non-obese groups. NVV in each lung third as a proportion of total NVV (NVVprop) was less in the upper third and greater in the middle third in obese compared to non-obese subjects (p = 0.001 and p = 0.004 respectively), but similar in the lower third. Both groups experienced a similar fall in FEV1 after bronchoprovocation. Overall closure (total NVV) increased similarly in both groups following bronchoprovocation. In obese, NVVprop was similar in all thirds compared to baseline, so the increase in airway closure was spread evenly across all thirds. In the non-obese group, NVVprop increased in the lower third and decreased in the upper third compared to baseline (p = 0.03 and p = 0.007, respectively). Therefore, in the non-obese group the increased closure occurred predominately in the lower third of the lung while ventilation increased in the upper third following bronchoconstriction.

Conclusions: The pattern of airway closure differs in obese compared to non-obese subjects at baseline and after bronchoprovocation. The different patterns of airway closure are dominated by obesity rather than intrinsic differences in airway reactivity.

PREVENTIONS AND SIX MINUTE WALK DISTANCE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction: Many COPD patients have limited exercise tolerance. We wanted to assess potential predictors of symptoms and six minute walk distance (6MWD). Dynamic hyperinflation (DH) has been shown to limit exercise tolerance in COPD. EFL is a major determinant of COPD and can be measured non-invasively with forced oscillation technique (FOT). EFL may increase DH and symptoms resulting in exercise limitation.

Aims: We hypothesized that EFL causes increased dyspnoea and reduced 6MWD.

Methods: 6 COPD subjects without cardiac failure or orthopaedic comorbidity affecting exercise capacity were recruited from RNSH Pulmonary Rehabilitation department. Spirometry, lung volumes and carbon monoxide diffusing capacity (DLCO) were obtained prior to 60 seconds tidal breathing FOT measurements at 5 Hz followed by three deep inspirations. Subjects subsequently performed a 6MWT. Borg score of dyspnoea severity was measured every 28 m, and expressed as the slope of Borg vs distance walked (Borg slope). The relationship between EFL, 6MWD and Borg slope were assessed by Spearman’s correlation.

Results: EFL, expressed as difference between mean inspiratory and expiratory reactance (deltaXrs), was not related to 6MWD or Borg slope. EFL was strongly related to DLCO (R² = 0.75). There was great variability in the Borg slope (range 0–0.0145 Borg/m).

| Spearman’s correlation coefficient | Significance (2-tailed) |
|-----------------------------------|------------------------|
| deltaXrs                          |                       |
| 6MWD                              | -0.429                 | 0.397                  |
| Borg slope                         | 0.200                  | 0.704                  |
| DLCO deltaXrs                      | -0.829                 | 0.042*                 |
| FEV1                               | -0.600                 | 0.208                  |
| FER                                | -0.486                 | 0.329                  |

*p < 0.05 = significant.

Conclusions: EFL did not relate to breathlessness or 6MWD, however, this may be due to small numbers or the high degree of dyspnoea variability during a self-paced walk. The differences in breathlessness require further study. Loss of airway tithering and lung elastic recoil in patients with lower DLCO and emphysema could explain the correlation between EFL and DLCO.

EXTERNAL DEAD SPACE WITH EXERCISE MEASURES THE OXYGEN COST OF BREATHING

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Aim: The oxygen consumed by the respiratory muscles with increased ventilation (VO2-RM) is measured by comparing control VO2 with VO2 when ventilation is increased, while peripheral muscle metabolism stays constant. VO2-RM has been studied using external dead space (DS) to reflexly increase ventilation in resting subjects. We sought to validate the novel measurement of VO2-RM with incremental cycle exercise.

Methods: This single blind randomized study included replicate visits which examined (1) rest and (2) constant cycle exercise at 50 W, for conditions of: (a) control, (b) a volume of DS targeting ventilation of 45 L/min during exercise, and (c) a volume of DS targeting ventilation of 65 L/min during exercise. A separate visit examined maximal incremental cycle exercise. VO2-RM was determined from the linear slope of the increase in VO2 (mLs) per increase in ventilation (L/min) using linear mixed modelling. Limits of agreement were determined from comparison of replicate linear regression slopes from individual visits.

Results: 10 healthy male subjects of age 27.5(SE 1.8 years and BMI 22.6(SE 0.5) had VO2-RM 3.10(SE 0.27 mL/L/min with exercise and 2.53(SE 0.40 mL/L/min with rest (NS). VO2-RM at DS-65 was 4.6(SE 0.7 % of the total VO2 at rest and 0.79(SE 0.32 % with exercise (NS). VO2-RM were 0.30(SE 0.03 and 0.007, respectively).

Conclusions: VO2-RM is able to be validly measured with DS during steady state exercise. Repeatability of VO2-RM within an individual is poor for both rest and exercise, which may limit potential for future clinical use of the current technique.
CONGENITAL VS IDIOPATHIC PULMONARY HYPERTENSION: CARDIOPULMONARY RESPONSES TO SIX MINUTE WALK TEST

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Introduction: Recent evidence suggests that long term survival in idiopathic pulmonary hypertension (IPAH) patients may be worse than congenital heart disease (CHD) pulmonary hypertension patients, particularly in those with a shorter six minute walk distance. Moreover in CHD, individuals that tend to desaturate to a greater extent may have poorer long term prognosis.

Aim: The aim of this study was to compare the physiological responses to the six minute walk test (6MWT) between groups of age-matched IPAH and CHD patients.

Method: 18 CHD (NYHA, 2.3 ± 0.5) and 25 IPAH (NYHA, 2.3 ± 0.5) patients completed a 6MWT while gas exchange was measured simultaneously. Standard echocardiography (right ventricular systolic pressure - RVSP) was completed on the same day that of the exercise test.

Results: There was no significant difference between groups in estimated RVSP (IPAH: 76 ± 22, CHD: 85 ± 21 mmHg). The IPAH patients had a greater 6MWT distance (530 ± 93 vs 462 ± 116 m) and end exercise oxygen uptake (14.8 ± 3.2 vs 11.9 ± 3.2 ml.kg⁻¹.min⁻¹). However there was no difference between groups in end exercise breathing efficiency (VE/VECO2) and PETCO2. CHD patients desaturated more than IPAH patients during the 6MWT (IPAH: −6.3 ± 6.2, CHD: −16.0 ± 9.2, p < 0.05). In the CHD group only, the level of desaturation was significantly correlated to the pre to post exercise change in breathing efficiency (r = −0.59, p < 0.01) and PETCO2 (r = 0.59, p < 0.01) i.e. those that tended to desaturate more had the greatest increase in VE/VECO2 and fall in PETCO2.

Conclusion: These results suggest that CHD patients tend to have a lower 6MWT distance and exercise capacity than age-matched IPAH. In CHD patients, the greater degree of desaturation during the 6MWT was related to the changes in breathing efficiency and PETCO2. This suggests that a hypoxic stimulus during exercise may be related to an enhanced ventilatory response during exercise in CHD with PAH, but not in those with IPAH.

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FORCED OSCILLATION TECHNIQUE AS AN INDICATOR OF AIRWAY CLOSURE

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Introduction: Closing volume is the lung volume at which the airways start to close and it is elevated in subjects with asthma. Reactance (Xrs) as measured by forced oscillation technique (FOT) abruptly decreases at low lung volumes during lung deflation. The cause of this abrupt change is postulated to be airway closure.

Aim: To determine if the lung volume at which this change occurs (Volcrit) is related to closing capacity (CC) as measured by single breath nitrogen washout (SBNW).

Method: 17 healthy subjects had measurements of lung volumes, SBWN and FOT. Volcrit was measured relative to TLC, from two different manoeuvres. Manoeuvre 1, the deflation manoeuvre (n = 17): subjects exhaled from TLC to RV using tidal volume sized breaths with a stepwise decrease in EELV. Manoeuvre 2, the slow vital capacity manoeuvre (n = 9): subjects exhaled slowly and steadily from TLC to RV. Closing capacity was determined from SBWN where a vital capacity breath of 100% oxygen was inspired and then exhaled slowly from TLC to RV.

Results: With manoeuvre 1, Volcrit correlated with CC (r = 0.66, p = 0.004) and with age (r = 0.62, p = 0.008). With manoeuvre 2, Volcrit correlated with CC (r = 0.70, p = 0.037). Volcrit was systematically greater than CC by 6.83 %TLC with manoeuvre 1 (p < 0.001) and by 3.96 %TLC with manoeuvre 2 (p = 0.02).

Conclusion: The FOT determined critical volume is equivalent to the CC measured by SBWN in healthy participants. The differences between Volcrit and CC could be due to greater sensitivity of FOT measurements to airway closure, or other factors occurring at low lung volume, such as airway narrowing. Further research is warranted to look at clinical implications of Volcrit in airways diseases, and to examine differences between Volcrit and CC in subjects with airways disease.

Key Words: airway closure, FOT, SBWN.

RETROSPECTIVE LONGITUDINAL STUDY OF PATIENTS WITH ISOLATED REDUCTION IN SINGLE-BREATH DIFFUSING CAPACITY

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Background: Isolated reduction in DLCO and otherwise normal lung function is a commonly seen pattern in lung function testing. This pattern often represents a diagnostic dilemma.

Aim: To examine the spectrum of disease associated with isolated reduction in DLCO and change in lung function over time, in subjects with follow-up up to 7 years.

Methods: Retrospective search of a Respiratory Medicine Database to identify patients with isolated reduced DLCO (below lower limit of normal, after correction for haemoglobin) first detected between January 2006 and June 2008. Only patients who had repeat lung function tests during the follow-up period were included. Medical records and relevant investigations performed after the initial assessment were reviewed to ascertain the final diagnosis of the included patients.

Results: We identified 51 patients, (29 female) with a mean age of 56 years. Forty one patients had a persistently reduced DLCO, while 10 only had a reduced DLCO at the initial assessment. During the follow-up period, 12 patients with persistently reduced DLCO developed spirometric abnormalities, while none from the group who only had a reduced DLCO at initial assessment did (p = 0.05). Of the 51 patients, 90% had CT imaging and 61% had echocardiography. Among patients with persistently reduced DLCO, 31 (76%) had a final diagnosis. These diagnoses included emphysema/interstitial lung disease (ILD) (6), pulmonary hypertension (5), emphysema (4), ILD (4), and drug-related lung disease (3). A diagnosis was also made in seven of the patients with an isolated reduction in DLCO, including ILD (2), drug-related lung disease (2), pulmonary hypertension (1).

Conclusion: Isolated reduction in DLCO, whether persistent or not, often leads to a clinical diagnosis. Those with a persistent reduction are more likely to develop spirometric abnormalities.
OPTIMAL DURATION OF PHYSICAL ACTIVITY MONITORING IN OBESITY HYPOVENTILATION SYNDROME

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Aim: Standard protocols for physical activity (PA) monitoring require four to five days of monitoring including at least one weekend day. The aim of this study was to determine the optimal duration for PA monitoring in people with obesity hypoventilation syndrome (OHS).

Method: PA monitoring was undertaken for seven days (minimum 10 hours wear per day) in people with newly diagnosed OHS using the Sensewear armband Pro 3 (SWA). The amount of time spent sedentary (<1.5 METs) and in moderate to vigorous PA (MVPA, >3 METs) over selected days was determined to investigate variability with different durations of wear. The influence of excluding weekend days was also investigated.

Results: Eighteen people (9 female, mean age 53 [SD 13] years, PaCO2 53 [6] mmHg, BMI 54 [11] kg.m−2) completed seven days of monitoring. Results for the first two, three, four and five days of PA monitoring showed that sedentary behaviour was less variable with four (mean 781 min [SD 189]) or five (790 min [188]) days of monitoring compared to two (752 [212] or three (777 [202]) min) days. Time spent in MVPA was similar for two (30 [36], three (31 [46]), four (29 [42]) and five (29 [40]) min) days of monitoring. Four days of PA monitoring demonstrated similar results regardless of whether or not a weekend day was included (sedentary 825 [201] vs. 850 [192] minutes, MVPA 23 [33] vs. 25 [36] min).

Conclusion: Initial analysis demonstrates monitoring of MVPA levels is not influenced by the duration of time worn (between 2–5 days). However, the optimal duration for analysis of sedentary time appears to require at least four or five days of PA monitoring. Weekend days did not appear to influence PA in people with obesity hypoventilation syndrome.

CLINICAL FACTORS ASSOCIATED WITH OUTCOME IN PATIENTS ADMITTED TO A RESPIRATORY HIGH DEPENDENCY UNIT WITH HYPOXAEMIC RESPIRATORY FAILURE

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Introduction: Hypoxaemic respiratory failure (HRF) is common and associated with a high mortality. While non-invasive ventilation (NIV) is increasingly recognized as an important treatment modality for hypercapnic respiratory failure, the place of NIV in the management of HRF is less well defined.

Aim: This study sought to identify clinical factors associated with outcome in patients admitted to a ward-based respiratory high dependency unit (RHDU) with HRF.

Method: A retrospective cohort study focused on the Princess Alexandra Hospital RHDU was conducted. All patients admitted to the RHDU with HRF between January 2007 and December 2011, were included in this study. Details of clinical factors and outcome were obtained from the RHDU database.

Results: 213 patients were included in this study. Survival to hospital discharge was more likely to occur in those with acute HRF (p = 0.013), asthma (p = 0.002), obstructive sleep apnoea (p = 0.027) and gastrointestinal comorbidities (p = 0.023). In contrast, death in hospital was more likely to occur in patients with poor performance status, both usual performance status (p < 0.001), and performance status on admission to the RHDU (p = 0.025). Death was also more likely in those with prior use of home oxygen therapy (p = 0.036), interstitial lung disease (p < 0.001), non-small cell lung cancer (p = 0.009), non-respiratory malignancy (p = 0.006) and early discontinuation of NIV (p = 0.002). Intensive care unit transfer was more likely to occur in those with short length of stay in the RHDU (p = 0.001), pneumonia (p = 0.034), acute HRF (p = 0.03), NIV use (p = 0.03), short period of NIV use (p = 0.004), RHDU complications (p < 0.001) and increased number of RHDU complications (p < 0.001).

Conclusion: Multiple clinical factors are associated with outcome in patients admitted to a RHDU with HRF.

DEVELOPMENT OF A TELEHEALTH SYSTEM FOR RESPIRATORY AND SLEEP MEDICINE IN RURAL SOUTH AUSTRALIA AND NORTHERN TERRITORY

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Introduction: There are existing rural-urban healthcare inequalities due to geographical location such as access to health services and cost of travel. Telehealth is a successful niche technology and could be ideally suited to assist in the provision of effective health services in respiratory and sleep medicine especially where distance between patient and doctor is more important.

Aim: To describe the implementation and outcomes of telehealth outpatient consultations from the Royal Adelaide Hospital (RAH) and Alice Springs Hospital (ASH) to remote clinic sites.

Method: After liaising with information technology, nursing and administrative staff, a workplace instruction detailing the organization of staff and equipment, triaging of referrals and clinic workflow chart was created. Data were collected on diagnosis, consultation process, patient feedback and cost savings.

Results: 37 consultations were performed on 27 patients (predominantly follow-up reviews) between May and October 2013. Consultations were provided in Port Augusta and Whyalla (300 and 381 km from RAH respectively) and Tennant Creek (500 km from ASH) in the presence of a nurse to assist the patient. Main diagnoses seen were obstructive sleep apnoea, restless leg syndrome, COPD and cystic fibrosis. Only 1 consultation required a subsequent face-to-face review. Overall patient feedback was extremely positive with minor suggestions for improvement. Cost savings to Patient Assistance Transport Scheme totalled $2602. Barriers to telehealth implementation include availability of equipment and remote nursing staff.

Conclusion: The implementation of telehealth requires coordination between a number of staff and a site-specific workplace instruction taking into account local issues and barriers. Patients accept and encourage the use of telehealth. Management decisions were made at most consultations without a face-to-face follow up. Future consultations could be enhanced through the implementation of patient exam cameras and digital electronic stethoscopes.