FEMALE MICE EXPOSED TO INFLEUZNA HAVE GREATER INFLAMMATION AND LUNG RESPONSIVENESS COMPARED TO MALE MICE

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Background: Murine models have been extensively used to study lung development and physiology, and it is apparent that there is sexual dimorphism in various aspects of these processes. Sex differences in immune function are well-established in both animals and humans, with males typically displaying weaker humoral and cell-mediated immune responses.

Methods: We infected male and female weanling (3 weeks old) and adult (8 weeks old) BALB/c mice with influenza A and measured lung function, hyper-responsiveness to methacholine (Mch) and inflammatory responses during the acute infectious stage (4 days after inoculation) and after recovery (day 21).

Results: During the acute infectious stage, there were significant effects of influenza infection on airway resistance ($R_{aw}$), tissue damping (G), tissue elastance (H), and number of inflammatory cells in the bronchoalveolar lavage (BAL) for both males and females of both ages when compared to media controls. Greater responses were seen in adult females than in adult males (e.g. $R_{aw}$: p = 0.030; H: $p = 0.016$; macrophages: $p = 0.003$; neutrophils: $p = 0.003$), and in weanling females compared to weanling males, especially in the lung parenchyma. Most parameters had returned to baseline levels 21 days after influenza inoculation in both age groups and sexes.

Conclusions: We’ve shown increased lung hyperresponsiveness and inflammatory responses in female mice exposed to influenza A compared to male mice. These results are contrary to most previous research, which indicate that males are generally more susceptible to respiratory viral infections. Supported by the NHMRC.

HAEMOPHILUS INFLUENZAE INFECTION INDUCES FEATURES OF NEUTROPHILIC ASTHMA

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Approximately 20% of asthmatics have neutrophic asthma. These patients have intense neutrophilic inflammation, reduced airways hyperresponsiveness (AHR) and high levels of interleukin (IL)-8. Haemophilus influenzae (H) colonisation is common in neutrophilic asthmatics however it is not known if colonisation induces neutrophic asthma or if these patients are predisposed to colonisation. We investigated the nature of this association using mouse models of Hl lung infection and ovalbumin (OVA)-induced allergic airway disease (AAD).

Method: AAD was induced by intraperitoneal sensitisation and intranarial challenge with OVA. At the time of OVA sensitisation, Prevenar or Pneumovax were delivered intranasally either with or without CpG.

Results: Prevenar, but not Pneumovax, suppressed the hallmark features of AAD, including eosinophil influx, OVA-specific TF helper (Th) 2 cytokine release in lung draining lymph nodes and spleen, mucus hypersecretion, total serum IgE and airways hyperresponsiveness. We then investigated whether regulatory T cells (Treg) were important in the suppression of AAD. Prevenar increased the number of CD4+ CD25+ FoxP3+ expressing Tregs in the lungs, lymph nodes and spleens. The release of immuno-suppressive cytokines IL-10 and TGF-β from lymph nodes was reduced. Proliferation assays demonstrated that Tregs suppressed allergic effector T cell proliferation regardless of Prevenar treatment, suggesting that IL-10 and TGF-β concentrations are not limiting for suppressor function.

Conclusion: A currently available human vaccine increases the infiltration of Tregs and suppresses AAD, and may be useful as a novel therapy for asthma. Supported by Asthma NSW and HMRI.

Conflict of Interest: No.

PREVENAR SUPPRESSES ALLERGIC AIRWAYS DISEASE THROUGH THE EXPANSION OF REGULATORY T CELLS

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Current therapeutics for asthma treat the symptoms but not the underlying cause of disease. Our recent finding that exposure to Streptococcus pneumoniae may suppress pro-inflammatory responses led us to investigate whether the current human S. pneumoniae vaccines, Pneumovax and Prevenar, may be used to suppress asthma using mouse models of ovalbumin-(OVA)-induced allergic airways disease (AAD).

Methods: AAD was induced by intraperitoneal sensitisation and intranasal challenge with OVA. At the time of OVA sensitisation, Prevenar or Pneumovax were delivered intranasally either with or without CpG.

Results: Prevenar, but not Pneumovax, suppressed the hallmark features of AAD, including eosinophil influx, OVA-specific TF helper (Th) 2 cytokine release in lung draining lymph nodes and spleen, mucus hypersecretion, total serum IgE and airways hyperresponsiveness. We then investigated whether regulatory T cells (Tregs) were important in the suppression of AAD. Prevenar increased the number of CD4+ CD25+ FoxP3+ expressing Tregs in the lungs, lymph nodes and spleens. The release of immuno-suppressive cytokines IL-10 and TGF-β from lymph nodes was reduced. Proliferation assays demonstrated that Tregs suppressed allergic effector T cell proliferation regardless of Prevenar treatment, suggesting that IL-10 and TGF-β concentrations are not limiting for suppressor function.

Conclusion: A currently available human vaccine increases the infiltration of Tregs and suppresses AAD, and may be useful as a novel therapy for asthma. Supported by Asthma NSW, Asthma CRC.

Conflict of Interest: No.

EARLY LIFE CHLAMYDIAL LUNG INFECTION ENHANCES ALLERGIC AIRWAYS DISEASE THROUGH AGE-DEPENDENT DIFFERENCES IN IMMUNOPATHOLOGY

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Rationale: Asthma typically originates in early-life and the impact of infection during immunological maturation is a critical factor in disease pathogenesis. Exposure to specific pathogens such as Chlamydia may alter immunological programming leading to predisposition.

Methods: We investigated the effect of early life infection on hallmark features of asthma in later-life using an acute mouse model of Ovalbumin-induced allergic airways disease (AAD). Groups were infected with C. muridarum at neonates (~2-4 hrs), infants (3 wks) or adults (6 wks) and subjected to AAD 45 days after infection.

Results: Early-life chlamydial infection enhanced the development of hallmark features of AAD in later-life. Notably infection (both neonatal and infant) increased mucus-secreting cell hyperplasia, airways hyper-responsiveness and IL-13 expression in lungs of adult mice after antigen inhalation. Importantly, these effects correlated with differential alterations in T-cell and dendritic cell responses and lung structure. Infection of neonates suppressed pulmonary inflammatory responses with attenuated eosinophil influx, T-cell and DC responses but without substantially altering lung structure. By contrast, infant infection augmented allergic inflammation with increases in eosinophil influx, OVA-specific T helper (Th) 2 cytokine release and induced substantial alterations in lung structure. Adult infection had no effect on AAD in later life.

Conclusion: Early life infection enhances pivotal features of AAD through age dependent, differential and permanent affects on immune responses and lung structure.

Supported by the National Health and Medical Research Council, Australia.

Conflict of Interest: Supported by Asthma NSW, Asthma CRC.
EPILOGICAL DATA SUGGESTS A LINK BETWEEN VIRAL EXPOSURE AND INFLAMMATION IN THE EARLY LIFE OF BALB/c MICE

RESULTS

Both neonatal exposure to flu (RV, p = 0.017; H, p < 0.001) and antigen (Raw, p = 0.008; H, p = 0.003) individually induced HR in adult mice. However, there was neither an additive or synergistic effect of the two exposures (Raw, p = 0.531, H, p = 0.311).

Conclusions

These findings demonstrate that exposure to Influenza A virus or OVA during the neonatal period alters lung mechanics when challenged with MCh in adult mice. The addition of viral infection in early life did not exacerbate allergen-induced HR.

Supported by NHMRC.

NEUTROPHIL INFUX DURING CHLAMYDIAL LUNG INFECTION DETERMINES THE PHENOTYPE OF ALLERGIC AIRWAYS DISEASE (AAD)

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C. pneumoniae is linked with asthma, however, it is unknown how a Th1-inducing infection is associated with Th2-mediated asthma. We investigated the association using models of chlamydial lung infection and ovalbumin (Ova)-induced AAD.

Adult mice were infected 45 or 7 days before intraperitoneal (IP) Ova sensitisation. AAD was induced by intranasal Ova challenge 12–15 days after sensitisation. Therefore, mice had a resolved or ongoing infection at sensitisation. The affect of pulmonary neutrophil influx on changes induced by an ongoing infection was also examined by treating mice IP with anti-Keratinocyte Chemokine and anti-Macrophage inflammatory protein 2 antibodies during infection. Seven days after infection, antibody-treated mice were sensitised and challenged with Ova. Features of AAD were compared with un-infected and non-sensitised controls.

Ongoing, but not resolved, infection induced Ova-specific Th1 responses that promote neutrophilic and suppress eosinophilic inflammation. During this neutrophil-dominated AAD, mucus secreting cell (MSC) numbers and AHR were reduced. Depletion of pulmonary neutrophil influx reversed increases in Th1 responses and decreases in MSC numbers and AHR during infection-associated AAD. Significantly, infected, antibody-treated mice no longer mounted robust pulmonary or systemic neutrophil responses upon the induction of AAD, despite cessation of antibiotic treatment 10 days earlier. These changes correlated with decreased IL-12 and IL-17 expression, increased thymus and activation-regulated chemokine and augmented antigen presenting cell activation compared to infected, isotype-treated controls.

Support by the NHMRC.

BOTH SEX AND TYPE OF VIRUS INFLUENCE LUNG INFLAMMATORY RESPONSES IN BALB/C MICE

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Background

The roles of host-specific versus viral-specific factors in determining inflammatory responses in the lung to acute viral infection remain unclear. We examined the role of age, sex and type of virus in determining the inflammatory responses to acute viral infection using a mouse model.

Methods

We infected BALB/c mice of both sexes with 10¹⁵ pfu flu (A/Memphis/71(H3N2)) or 5 x 10⁶ TCID₅₀ RV (RV1b serotype). Bronchoalveolar lavage (BAL) samples were taken from groups of mice through the acute phase of infection and following recovery. BALs were used to ascertain total cell counts (TCC) and differential cell counts (macrophages: mac, neutrophils: neut) under light microscopy.

Results

Inflammatory responses were more severe and prolonged in mice inoculated with flu compared to those inoculated with RV. Both male and female flu inflammatory responses peaked at day 4, but females had significantly higher responses (TCC, p = 0.001; mac, p = 0.003; and neut p = 0.006). In contrast, the peak of TCC differed between sexes inoculated with RV (female D2; male D4), whereas the pattern of neutrophilic inflammation was the same. The magnitude of the response was the same between sexes (TCC, p = 0.71; mac, p = 0.52; neut, p = 0.3).

Conclusions

These data clearly demonstrate that host-specific and virus-specific effects are important in the inflammatory responses in the mouse lung. Supported by the NHMRC.
EXTRACELLULAR MATRIX WITHIN THE AIRWAY SMOOTH MUSCLE LAYER IN ASTHMA

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The reported increase in the amount of airway smooth muscle (ASM) in asthma may be due to hypertrophy and/or hyperplasia of ASM cells or increased extracellular matrix (ECM) between ASM cells within the ASM layer.

Aim To estimate the volume fraction of ECM within the ASM layer using ultra-thin (0.5 μm) sections and to calculate and compare the volume of ECM per airway length (mm) in post-mortem tissues from control subjects (C, n = 42); nonfatal (NFA, n = 39) and fatal (FA, n = 29) cases of asthma.

Methods Point counts of ECM were made within the ASM layer on transverse airway sections stained using the Masson’s trichrome technique and the area fraction of ECM (fECM) was estimated. The volume of ECM per airway length was then calculated (V_{ECM} = A_{ASM layer} \times f_{ECM} \times 1 \text{ mm}). Basement membrane perimeter (Pbm) was used to indicate airway size.

Results Table shows results (case means) for large airways.

| Sex | Airway | Pbm | ASM layer/Pbm | fECM | V_{ECM}/1 \text{ mm} |
|-----|--------|-----|---------------|------|---------------------|
| M/F | n (total) mm | mm² |                  |      | (mm³)               |
| C   | 28/14 | 123 | 15 ± 6        | 0.035 ± 0.016 | 0.21 ± 0.17 | 0.13 ± 0.10 |
| NFA | 19/20 | 133 | 14 ± 6        | 0.043 ± 0.023* | 0.18 ± 0.16 | 0.14 ± 0.12 |
| FA  | 19/10 | 92  | 16 ± 5        | 0.065 ± 0.026* | 0.17 ± 0.12 | 0.18 ± 0.13 |

Mean ± SD. (one-way ANOVA) *p < 0.05 for C v FA and **NFA v FA.
The volume fraction of ECM and the absolute volume of ECM were not significantly different between case groups, although there was a trend for increased ECM volume in cases of fatal asthma. Results were similar for small airways.

Support NHMRC Australia (Grants #343601, #446800).
Nomination Nil.
Conflicts Nil.
PRO-FIBROTIC MEDIATORS INCREASE REMODELLING OF COLLAGEN GEYS BY HUMAN AIRWAY SMOOTH MUSCLE CELLS

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Cell-mediated remodelling of three-dimensional collagen gels has been used to assess regulation of pro-fibrotic interactions between cells and their surrounding extracellular matrix. We have previously demonstrated reductions in gel area (‘contraction’) associated with condensation of collagen fibrils in gels seeded with airway smooth muscle (ASM) cells. In this study, we addressed the regulation of this remodelling by transforming growth factor β (TGFβ) and endothelin-1 (ET-1).

Methods Serum-deprived human ASM was cast in Type I collagen gels (1.25 × 10^6 cells/0.5 ml). The effects of TGFβ (0.1–100 pM) and ET-1 (0.1–100 nM) on ASM-mediated reductions in area were determined over 72 h, in the absence and presence of TGFβ blocking antibody, selective ETα and ETβ receptor antagonists, and the protein synthesis inhibitor cycloheximide.

Results Changes in ASM gel area were evident at >4 h, with maximum reduction observed by 72 h (by 33 ± 10%, mean ± SEM, n = 6). The rate and extent of contraction was increased by TGFβ, with a threshold response of 0.3 pM. ET-1, acting via ETα receptors was less potent, with maximal area reduction at 10 nM (by 58 ± 11%, P < 0.05 cf unstimulated). Although CHX did not affect ASM-mediated gel contraction in the absence of TGFβ and ET-1, the augmented response to both mediators required protein synthesis (reduction in area for ET-1+CHX, 33 ± 10%, n = 6, P < 0.05 cf unstimulated). However, ET-1-mediated contraction was not associated with increased TGFβ release.

Conclusions Further studies are required to clarify common or divergent signalling pathways implicated in TGFβ and ET-1-induced collagen gel remodelling. Under the influence of these pro-fibrotic mediators elevated in asthma, ASM has greater potential to increase collagen density in muscle bundles and in turn, to increase internal resistance in the airways.

Grant Support NHMRC, Asthma Foundation of Victoria.

MAST CELL PRODUCTS REGULATE AIRWAY SMOOTH MUSCLE CELL CXCL10 RELEASE

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CXCL10 (IP-10) attracts mast cells (MC) to the airway smooth muscle (ASM) function contributing to MC localization to the asthmatic airway. To examine the effect of variable tissue depth on the estimation of ASM cell volume.

Methods Post-mortem airways from control subjects (C n = 21); nonfatal (NFA n = 20) and fatal (FA n = 21) cases of asthma were studied. On 30 μm sections stained with haematoxylin, the volume density (%v) of ASM cell nuclei was estimated using the optical dissector method and stereological software. ASM cells were counted within each optical dissector volume by scanning through the tissue depth. Partial high power fields (HPF) in which the ASM occupied only part of the tissue depth were recorded. The mean cell volume (Vc = 1/Nv) was calculated both including and excluding partial HPF.

Results The mean ASM cell volume was similar in all groups (Table), but for all groups was significantly reduced when partial depth HPFs were excluded.

| Estimated mean ASM cell volume (μm^3 × 10^4) |
|---------------------------------------------|
| Large Airways (n = 213) | Small Airways (n = 130) |
|--------------------------|---------------------|
| p < 0.05 | All HPF | Partial HPF Included | All HPF | Partial HPF Included |
| C | 6.4 ± 2.6 | 5.5 ± 2.4* | 5.4 ± 1.3 | 4.2 ± 1.2* |
| NFA | 5.8 ± 1.5 | 5.1 ± 1.3* | 5.4 ± 1.5 | 4.7 ± 1.4* |
| FA | 6.4 ± 1.7 | 5.7 ± 1.6* | 5.5 ± 1.5 | 4.8 ± 1.6* |

Conclusion The discontinuous nature of asthmatic airways both along and around the length of airways necessitates correction for varying tissue thickness (space between muscle bundles) within the ASM layer when estimating ASM cell volume.

Support NHMRC Australia (Grants #343601, #446800).

Conflicts Nil.

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MOLECULAR MECHANISMS OF RHINOVIRUS INFECTION OF PRIMARY BRONCHIAL EPITHELIAL CELLS

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Rationale The majority of asthma exacerbations are associated with rhinovirus infection, however the molecular mechanisms of this remain unclear.

Aim To investigate changes in gene expression caused by rhinovirus infection of primary bronchial epithelial cells in vitro.

Methods Bronchial brushings were obtained from participants with asthma (n = 3) and healthy controls (n = 3). Primary bronchial epithelial cells were treated with or without RV43 (MOI 10), RV1B (MOI 2), or UV inactivated RV43 and RV1B, and collected at 24 hours post-infection. RNA was extracted, amplified and genome wide gene expression profiles were generated using Illumina HumanRef 8 expression microarrays. Data was analysed using GeneSpring 10 where differentially expressed genes were defined by tests for both significance (p < 0.05) and a 1.5 fold change.

Results From this study suggest that the RAGE -374A allele, previously associated with severe and aspirin-sensitive asthma, may be contributing to chronic inflammatory asthma phenotypes by increasing RAGE expression, leading to increased pro-inflammatory signalling. In addition, decreased esRAGE expression in severe asthma may indicate a loss of the anti-inflammatory effects of this decoy receptor, further enhancing RAGE signalling in this condition.

MOLECULAR MECHANISMS OF AIRWAY NEUTROPHILIA FOLLOWING A LOW ANTIOXIDANT DIET

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Rationale Withdrawal of antioxidants through consumption of a low antioxidant diet has been reported to increase airway neutrophilic inflammation and worsen symptoms of asthma; however the mechanisms of this are unknown.

Objective To investigate differential gene expression induced by low antioxidant diet.

Methods Induced sputum samples were collected at baseline and after 10 days on a low antioxidant diet. Uregulated genes were involved in the innate immune response and included the innate immune receptors TLR2, IL1R2, CD93, the signaling molecules IRAK2, IRAK3 and neutrophil proteases MMP25 and CPD. Downregulated genes included those involved in endogenous antioxidant defences (GSTA1, GSTA2) and protease inhibition (SLPI, SERPINB3).

Conclusion Withdrawal of dietary antioxidants in asthma induces significant alterations in airway gene expression characterised by upregulation of genes involved in the innate immune response. These results indicate that diet influences airway inflammation in asthma through potentiation of innate immune gene expression.

INCREASED EXPRESSION OF RAGE, AND DECREASED EXPRESSION OF SOLUBLE RAGE, MAY BOTH CONTRIBUTE TO SEVERE ASTHMA

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Activation of the receptor for advanced glycation endproducts (RAGE) leads to prolonged NF-κB signalling and has been associated with chronic inflammation. We have previously identified an association between the RAGE -374T > A polymorphism and both severe and aspirin-sensitive asthma. The effect of this polymorphism on RAGE expression in asthma has not previously been determined. Further, RAGE activation may be offset by an endogenous soluble ‘decoy’ receptor (esRAGE) that binds ligand but lacks signalling capabilities. The role of esRAGE in asthma has not previously been examined.

Objective Determine RAGE and esRAGE expression levels and correlate with asthma severity and patient genotype at the RAGE -374 loci.

Methods Serum was collected from asthmatic and non-asthmatic subjects previously genotyped for the -374T > A polymorphism. Levels of circulating RAGE were assessed using an enzyme-linked immunosorbent assay (ELISA). Preliminary results revealed an almost 1.5-fold increase in RAGE expression levels associated with the -374T > A homozygous mutant genotype. We have previously shown this genotype to be associated with both severe and aspirin-sensitive asthma. Further, decreased levels of esRAGE expression were observed in severe asthmatics relative to healthy control subjects.

Conclusions Results from this study suggest that the RAGE -374A allele, previously associated with severe and aspirin-sensitive asthma, may be contributing to chronic inflammatory asthma phenotypes by increasing RAGE expression, leading to increased pro-inflammatory signalling. In addition, decreased esRAGE expression in severe asthmatics may indicate a loss of the anti-inflammatory effects of this decoy receptor, further enhancing RAGE signalling in this condition.
TLR8 UP-REGULATION DURING ACUTE ASTHMA IN CHILDREN, IDENTIFIED BY MICRO-ARRAY AND CONFIRMED BY QRT-PCR, IS ASSOCIATED WITH TLR8 GENOTYPES

IA LAING1,2, JA BIZZINTINO1, LS SUBRATA1, CJ MCALEAN1, SK-KHOO1, CM HAYDEN1, J GOLDBLATT1, PG HOLT2, PN LE SOUEF1

Supported by compliance with medication (76%) and in monitoring medication use (78%). (84%) with the MDIc than the MDI, and that the counter helped in assessing confidence in knowing that patients were able to determine how much medication the MDIc took a high percentage of the prescribed dose (86%). Clinicians’ (89%) and informed them when to replace the inhaler (90%). Patients using monitor medication use (86%), gave added assurance about medication use rose from 62% (MDI) to 85% (MDIc). A majority felt the MDIc allowed them to and led to a higher level of satisfaction in medication use. Patients’ satisfaction questionnaire.

Use of the MDIc raised confidence in knowing how much medication remained, and led to up-regulation and expression during childhood acute asthma. This failure to upregulate TLR8 may contribute to asthma susceptibility through an inadequate innate immune response to viruses. Supported by the NHMRC, Nomination for Japanese Respiratory Society Early Career Development Award.

Conflict of Interest

PATIENT AND CLINICIAN SATISFACTION WITH FLUTICASONE/SALMETEROL MDI WITH COUNTER

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Introduction Until the introduction of the Metered Dose Inhaler with counter (MDIc), there was no accurate and practical way of estimating how much medication was remaining in the canister of an MDI.

Methods An open-label study was done to evaluate, in out-patients, the Fluticasone/Salbutamol (Seretide®) MDIc. 132 subjects ≥18 yrs old on ICS/ LABA for asthma or COPD were enrolled after written consent. They were then given a Seretide® MDI and instructed to use 2 puffs twice daily for 4 weeks. They then were given a Seretide® MDI and were asked to use it also for 4 weeks. After each treatment period, subjects and clinicians completed a satisfaction questionnaire.

Results 104 patients (age av. 54 yrs, disease duration av. 20 yrs) were enrolled; 99 completed. With the MDI >70% could not establish if they were running out of medication, causing anxiety for 28%. Various sub-optimal methods were used by 84% to determine how much medication remained. Use of p MDIc raised confidence in knowing how much medication remained, and led to a higher level of satisfaction in medication use. Patients’ satisfaction rose from 62% (MDI) to 85% (MDIc). A majority felt the MDIc allowed them to monitor medication use (86%), gave added assurance about medication use (89%) and informed them when to replace the inhaler (89%). Patients using the MDIc took a higher percentage of the prescribed dose (86%). Clinicians’ confidence in knowing that patients were able to determine how much medication remained in the inhaler rose from 4.6 to 9.2 on a scale of 1–10 when the MDIc was used. Clinicians’ responses indicated that they were more satisfied (84%) with the MDIc than the MDI, and that the counter helped in assessing compliance with medication (76%) and in monitoring medication use (78%).

Conclusions The Seretide® MDI with counter led to a higher level of satisfaction for both the patients and the clinicians. The counter in the MDI provides an additional tool to help monitor medication use and improve patient management.

Supported by GlaxoSmithKline.

THE RELATIONSHIP BETWEEN FE NO AND ATOPIC STATUS IN PREGNANT WOMEN WITH ASTHMA

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Forced exhaled nitric oxide (FeNO) is used as a marker of eosinophilic inflammation, but is also modified by atopy and pregnancy. The relationship between FeNO and total and specific immunoglobulin E (IgE) in pregnancy is not known and was evaluated in this study.

Methods Pregnant women with (n = 65) and without asthma (n = 60) were recruited prior to 20 weeks gestation. Participants performed FeNO and serum was collected. A fluoroenzymeimmunoassay using the ImmunoCAP250 was conducted on the serum to quantify total IgE and specific allergens (house dust, mould, weed, domestic animal and grass mixes).

Results Median FeNO, total IgE, and specific IgE to house dust, mould and domestic animal mix were significantly higher for pregnant women with asthma compared to pregnant women without asthma (p < 0.0001, p = 0.001, p < 0.001, p = 0.008, p = 0.0001 respectively). For all subjects FeNO was significantly correlated to total IgE (r = 0.506), and specific IgE to house dust (r = 0.612), weed (r = 0.248), domestic animal (r = 0.443) and grass (r = 0.282) mixes. For pregnant women with asthma FeNO was significantly correlated to total IgE (r = 0.449), and specific IgE to house dust (r = 0.632), domestic animal (r = 0.357) and grass (r = 0.367) mixes. While FeNO was significantly correlated to total IgE (r = 0.348) and house dust mix IgE (r = 0.283) in pregnant women without asthma.

Conclusion In pregnancy, FeNO is related to both asthma and atopic status. The main specific allergen sensitisation driving this relationship is house dust sensitisation, with lesser effects for grass pollen and domestic animal sensitisation in asthma. Supported by the NHMRC.
A COMPARISON OF THREE METHODS FOR MEASUREMENT OF FE\textsubscript{E}\textsubscript{NO}

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Assessment of airway inflammation by exhaled nitric oxide (FE\textsubscript{NO}) can be a useful tool in clinical and epidemiological studies, but simple portable equipment is required. Two new commercially available portable devices, the HypAir FeNO and the Niox Mino®, have been developed that use a chemical sensor to measure FE\textsubscript{NO}. The Woolcock eNO technique (WeNO) uses a calibrated chemiluminescence analyser (ThermoEnvironmental 42c) to measure FE\textsubscript{NO} collected offline. It is not known if these techniques are comparable.

**Methods** FE\textsubscript{NO} was collected and measured from 15 adult subjects (11 non-asthmatic, 4 asthmatic) at an expiratory flow rate of 50 ml/sec using the HypAir FeNO, the Niox Mino® and the WeNO. FE\textsubscript{NO} values are expressed as geometric mean (95% confidence intervals) and compared using a paired Student t test. The repeatability of FE\textsubscript{NO} values was calculated as 95% limits of agreement (95% LoA). Differences between repeat measures were compared between devices by ANOVA.

**Results** FE\textsubscript{NO} measured by the HypAir FeNO (26.9 ppb (20.3–35.5)) and the Niox Mino® (25.7 ppb (20.0–33.0)) were not significantly different but both devices measure FE\textsubscript{NO} significantly higher than the WeNO (15.8 ppb (10.9–22.8); p < 0.0001). Repeatability of the HypAir FeNO (95% LoA: –7.1–4.7 ppb), Niox Mino® (95% LoA: –3.4–2.7 ppb) and WeNO (95% LoA: –3.6–4.2 ppb) was not significantly different between devices (p = 0.62).

**Conclusion** There were no differences between the FE\textsubscript{NO} measured by the HypAir FeNO and the Niox Mino®, but both measure FE\textsubscript{NO} significantly higher than the WeNO. Repetability of the HypAir FeNO, the Niox Mino® and the WeNO was similar to values reported previously. The three devices can be used in both clinical and epidemiological studies, but the different methods used to measure FE\textsubscript{NO} can result in higher or lower FE\textsubscript{NO} values.

**Nominations** None. **Conflict of Interest** None.
A HIGH FAT, HIGH ENERGY FOOD CHALLENGE INDUCES AN EXAGGERATED INFLAMMATORY RESPONSE IN ASTHMA

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Dietary fat has been shown to activate the innate immune response, which has been shown to cause asthma in some individuals. The aim of this study was to examine the effect of dietary fat on inflammation in asthma.

Methods Non-obese (BMI < 20) subjects with asthma were randomized to receive a high fat/high energy (AHFHE) (n = 8) or low fat/low energy (A LoFLE) (n = 10) food challenge. Non-obese healthy controls (n = 10) also underwent a high fat/high energy (ChFHE) food challenge. Subjects on the AHFHE and CHFHE challenge consumed 200% daily energy requirement in 24 hours, including 50% energy from fat. Subjects on the A LoFLE challenge consumed 75% daily energy requirement in 24 hours, including 20% energy from fat. Clinical assessment and blood samples were collected at 0, 2, 3, 4 and 24 hours. Inflammatory markers, including plasma TNFα, CRP and IL-6, were analysed by high sensitivity ELISAs.

Results At 4 hours after the commencement of the food challenges, subjects on the AHFHE challenge, had a significantly higher increase in plasma CRP concentrations, compared to subjects on both the A LoFLE and CHFHE challenge (p = 0.021). In subjects on the AHFHE challenge, there was also a significantly higher increase in plasma TNFα concentrations at 3 hours, compared to subjects on A LoFLE challenge (p = 0.034).

Conclusions A high fat/high energy intake causes an exaggerated systemic inflammatory response in subjects with asthma. This suggests that subjects with asthma are more susceptible to fat-induced innate immune activation.

Supported by an NHMRC Project Grant.

Conflict of Interest No.

TOLL-LIKE RECEPTOR AGONISTS STIMULATE CYTOKINE RELEASE FROM BLOOD BUT NOT AIRWAY CELLS

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The innate immune system has a key role in detecting pathogens and priming protective immunity. Toll-Like Receptors (TLRs) are important in sensing pathogens and directing immune responses. Dysfunction of the innate immune system may be a feature of neutrophilic airways disease, and may be important for resolution of infection and inflammation. Our aim was to investigate innate immune responses of blood and airway cells to TLR2 and 4 activation.

Methods Blood was collected from healthy volunteers (n = 9) and sputum was collected from subjects with airway disease (n = 7). Granulocytes and monocytes were isolated from peripheral blood by Percoll separation and cells from sputum were recovered after processing with dithiothreitol. Cells were cultured at 1 x 10⁶ cells/mL (blood) or 0.5 x 10⁶ cells/mL (sputum) in RPMI1640 and stimulated with either LPS (TLR4 agonist) or Pam3CYSK4 (TLR2 agonist) at a range of concentrations (10 to 10 000 ng/mL). Cells were cultured at 37°C and cell free supernatants were collected at 24 hours. Cytokine and protease levels were measured by ELISA.

Results Both LPS and Pam3CYSK4 stimulation of granulocyte cultures resulted in increased release of IL-8, IL-6 and MMP-9 (p < 0.05). Neither LPS nor Pam3CYSK4 increased neutrophil elastase release from granulocytes. Similarly IL-6 and IL-8 release was significantly higher in monocyte culture after stimulation with LPS and Pam3CYSK4 compared to unstimulated cells (p < 0.05). In sputum cell cultures there was no increase in release of IL-8 or IL-6 in response to either LPS or PamCYSK4 treatment.

Conclusion TLR agonists (2,4) cause differential activation of peripheral blood granulocytes and monocytes, whereas airway cells appear refractory to TLR stimulation.

Supported by NHMRC.

Conflict of Interest No.

DIETARY FAT AND AN ACTIVATED INNATE IMMUNE RESPONSE ARE ASSOCIATED WITH REDUCED FEV1

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Preservation of lung health with aging is an important health issue in the general population, as loss of lung function with aging can lead to the development of obstructive lung disease. Inflammation is increasingly linked to loss of lung function and evidence suggests that consumption of dietary fat exacerbates inflammation. The aim of this study was to examine the contribution of dietary fat to reduced lung function in an older population.

Methods Participants, aged between 55 and 85 years, were recruited from the Hunter Community Study, a population-based cohort, during 2004 and 2005. All participants received a clinical assessment, including baseline spirometry and provided a blood sample. Diets were analysed using food frequency questionnaires. Plasma IL-6 concentrations were measured by ELISA.

Results Smoking, % energy intake from dietary fat, IL-6 and obesity were all found to be inversely associated with reduced forced expiratory volume in 1 second (FEV1) in a linear regression model. Using backward stepwise linear regression, former smoking, % energy from dietary fat and plasma IL-6 remained as negative predictors of FEV1.

Conclusions An increased proportion of dietary fat and innate immune activation are associated with reduced lung function. Dietary fat restriction may be useful in preserving lung function with aging.

Supported by Hunter Medical Research Institute Project Grant.

Conflict of Interest No.

STEROID RESPONSIVENESS IN RELATION TO HISTOLOGICAL PHENOTYPE IN ASTHMA

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Thoracic Society of Australia and New Zealand Annual Scientific Meeting 2009

Airway inflammation in asthma is heterogeneous. Cell types include eosinophilic, neutrophilic, paucigranulocytic and mixed cellularity. Studies have often been confounded by cigarette smoking or inhaled corticosteroid (ICS) treatment. We aimed to ascertain the prevalence of inflammatory subtypes in the absence of confounders and clarify whether steroid responsiveness is exclusive to eosinophilic asthma.

Methods 78 non-smoking adults with current asthma were recruited. Inclusion criteria: hyper-responsiveness to hypertonic saline OR methacholine OR ≥ 12% increase in FEV1, post-bronchodilator. ICS was withdrawn until loss of control (LOC) or one month if no LOC. Patients were classified as eosinophilic (EA: ≥ 2% sputum eosinophils), or non-eosinophilic (NEA: < 2%). Steroid responsiveness was assessed after 4-weeks fluticasone 500 mcg bd.

Results Baseline characteristics for EA and NEA were similar except ICS dose (872 vs. 403 mcg/day, p < 0.05). After steroid withdrawal, 50 patients (64%) were eosinophilic, 26 (33%) paucigranulocytic, and 2 (3%) mixed cellularity. With steroid, the before/after outcomes for EA/NEA were (mean ± SD):

ACQ: EA 1.9 ± 0.9/0.7 ± 0.6; NEA 1.0 ± 0.6/0.7 ± 0.5, p-values < 0.05; FEV1: EA 2.20 ± 0.76/2.86 ± 0.79; NEA 2.65 ± 0.83/2.83 ± 0.88, p-values < 0.05; IcPC20AMP doubling doses; EA 4.2 ± 2.9; NEA 1.6 ± 2.2, p < 0.001. Cell type changed from eosinophilic to mixed cellularity in 2/48 (4%) and neutrophilic in 2/48 (4%); and from paucigranulocytic to neutrophilic in 3/25 (12%). Overall a significant increase in sputum neutrophilia was seen after steroid (19 ± 17% to 29 ± 23%, p < 0.01).

Conclusions Steroid responsiveness occurred almost exclusively in EA and was minimal in NEA. In our population, neutrophilic asthma was absent, but inhaled steroid resulted in an increase in sputum neutrophilia. Whether steroid induced sputum neutrophilia is important is unclear.

Supported by Lottery Health New Zealand.

Conflict of Interest No.
THE EFFECT OF CIGARETTE SMOKING ON ASTHMA CONTROL AND EXACERBATIONS IN PREGNANT WOMEN

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Smoking is more prevalent among pregnant women with asthma than pregnant women without asthma; however no studies have assessed the clinical implications of smoking on asthma exacerbations in pregnancy.

Methods Pregnant women with asthma (n=80) were prospectively assessed from recruitment (14 weeks [3 SD]) to delivery at clinic visits (18, 30, 36 weeks and during exacerbation), and by fortnightly phone calls. There were 27 current smokers (4.0 median pack years), 27 ex-smokers (2.1 median pack years) and 26 never smokers (self-report). The Juniper asthma control questionnaire (ACQ6) was administered at each contact and exacerbations classified as severe (requiring medical intervention) or mild (self-managed).

Results There were 56 exacerbation events in current smokers (23 severe, 33 mild), 59 in ex smokers (26 severe, 33 mild) and 43 in never smokers (11 severe, 32 mild). Current smokers experienced more severe exacerbations per person (median 1, interquartile range [0, 1]) compared to ex smokers and never smokers (0, [0, 0.1]); however this did not reach statistical significance (P = 0.25). ACQ6 during exacerbation (mild or severe) was significantly higher in current smokers (median 2.0, [1.7, 3.0]) compared to never smokers (1.67, [1.2, 2.3]), while the ACQ6 during exacerbation in ex smokers was intermediate (1.8, [1.3, 2.8]) (P = 0.018). The best ACQ6 score recorded when stable by tPA was 0.09 (0, 0.146) and ex smokers (0.09, [0, 0.50]) was not significantly different from never smokers (0, [0, 0.42]) (P = 0.49).

Conclusions During pregnancy, asthma exacerbations are common and are more severe in current smokers than in never smokers. The implications of this may be that the risk of maternal asthma on the baby is greater among smokers.

Supported by the NHMRC, Asthma Foundation of NSW, Hunter Medical Research Institute, Port Waratah Coal Services, University of Newcastle.

Conflict of Interest No.

COAGULATION FACTORS IN THE AIRWAYS IN MODERATE AND SEVERE ASTHMA AND THE EFFECT OF INHALED STEROIDS

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Rationale There is evidence for up-regulation and activation of the extrinsic coagulation cascade in the airways in asthma, and that both plasma and locally-derived factors may be involved. Our objective was to test the hypothesis that the normal haemostatic balance of the healthy airway sampled by sputum induction changes in favor of fibrin formation in asthmatic airways, and that inhaled corticosteroids (ICS) and plasma exudation influence this balance.

Methods 30 stable subjects (10 controls, 10 moderate & 10 severe asthmatics) were recruited and underwent sputum induction using 4.5% hypertonic saline, with analysis of alpha-2 macroglobulin and coagulation factors in sputum using ELISA and activity assays. Additionally, the moderate cohort were weaned off their ICS, followed by further sputum induction 5 days after cessation of steroids.

Results Weaning of ICS was associated with a significant rise in plasminogen (median [IQR]: 13.92 (6.12–16.17) vs. 4.82 (2.14–13.32) ng/ml; p < 0.05) and tissue-plasminogen activator (tPA) (5.57 (3.57–14.35) vs. 3.88 (1.74–4.05) ng/ml; p = 0.026) levels in sputum, such that tPA in moderate asthma post steroid withdrawal was significantly (p < 0.0015) higher than controls (2.14 (0.0–2.53) ng/ml). Severe asthmatics had significantly more alpha-2 macroglobulin (p < 0.001), tissue factor (p < 0.05), plasminogen activator inhibitor (PAI-1; p < 0.05), tPA (p = 0.029) and thrombin activatable fibrinolysis inhibitor (TAI) (p < 0.01) in their sputum than control subjects.

Conclusion Moderate asthma may be associated with increased fibrinolysis that is corrected by ICS. Severe asthma is associated with a pro-fibrinogenic, anti-fibrinolytic environment in the airways. Our study suggests that inhibition of coagulation in severe asthma may be a therapeutic approach.

WHAT ARE THE PRIORITIES OF OLDER PEOPLE WITH ASTHMA?

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Asthma-related mortality and morbidity increase with age and recent Australian Bureau of Statistics data show a continuation of this trend. In 2006, 356/402 (88%) of asthma deaths occurred in those >50 years of age. We designed, validated and then trialed a questionnaire to identify concerns of older people with asthma.

Methods 152 people over 55 years with asthma were recruited from a random sample of 60 pharmacies in regional, rural and metropolitan Victoria and a cluster sample from 17 metropolitan and regional pharmacies in NSW.

Results 87% of participants have both preventer and reliever treatments prescribed and self-reported preventer adherence is high. Although most participants reported good asthma control only 10% reported having no asthma symptoms over the last month. Issues identified by patients included: cost of medications (47%), worry about side effects (38%) while 27% report experiencing side effects. Two-thirds (68%) report frustration over asthma stopping them doing all they want to do. Provision of action plans was relatively high at 37% but another 37% stated they would find own one useful. Less than half of participants reported their GPs had tested their lung function in the past two years, observed their device technique or undertaken a medication review.

Findings also suggest that a high proportion of older people with asthma thought more information about asthma would be helpful.

Co-conclusions A simplified version of our questionnaire used in general practice could assist GPs to identify and address the needs of older people. Supported by the Co-operative Research Centre for Asthma and Airways.

Nomination None.

Conflict of Interest No.
SEASONAL PATTERNS (2004–2007) OF RESPIRATORY VIRUSES ISOLATED WITH ACUTE AIRWAYS DISEASE

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Respiratory virus infections are important triggers of acute airways disease. Seasonal variation of these viruses have been seen in the northern hemisphere, but not described in Australia.

Aim To characterise the viruses associated with acute asthma and COPD.

Methods From 2004 to 2007 we recruited subjects over 6 years admitted to hospital with acute exacerbations of Asthma, COPD or Cystic fibrosis. Sputaneous sputum, throat and nasal swabs were collected. Samples were assayed by real-time PCR for rhinovirus (RV), enterovirus (EV), non-SARS coronavirus (CoV), human metapneumovirus (hMPV), respiratory syncytial virus types A and B (RSV) and influenza virus types A and B (Flu).

Results There were 201 acute episodes were specimens were collected, viruses were detected in 102 (51%) of these. RV was the most frequent virus isolated in 52% of positive samples, followed by EV (18%), CoV (14%), RSV (9%), Flu (7%), and hMPV (7%). The lowest virus detection occurred in summer. Peak RV detection occurred in autumn, but was the most prevalent virus in all seasons. Both Flu and RSV detection were confined to winter.

Conclusion RV is the most prevalent virus associated with acute asthma and COPD all year round. This occurs even in winter though the proportion of Flu and RSV increase during this time.

Conflict of Interest None.

Funding NHMRC Australia, Biota Australia.

THE PROFILE OF SPUTUM EOSINOPHILIA, EXHALED NITRIC OXIDE AND PERCEPTION OF DYSPNEA IN OLDER ASTHMATICS

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Introduction Poor perception of dyspnoea together with under-reporting of the severity of breathlessness contributes to suboptimal management of asthma in adults over 65. The Fraction of exhaled Nitric Oxide (FeNO) is well established as a research tool to assess airway inflammation but its role in clinical practice is unclear. Despite this, it has recently been recommended by the ATS/ERS for use in clinical settings to assess the nature and severity of airway inflammation.

Aim In this observational study we assessed the relationships between FeNO, sputum eosinophilia and other biomarkers of asthma controls in older asthmatics.

Methods 18 participants over the age of 55 were recruited. At visit 1, FeNO samples, Juniper Asthma Control Questionnaire (ACQ) and Marks Asthma Quality of Life Questionnaire (AQLQ) were conducted. Perception of dyspnoea was assessed using the difference between Visual Analog Scale (VAS) both before and after pre and post salbutamol spirometry to measure subjective breathlessness against quantitative changes in spirometry. Sputum induction was performed and sent for analysis of sputum eosinophils. At visit 2, FeNO samples, perception of dyspnoea, ACQ and AQLQ were reassessed. Airway hyperresponsive was tested using methacholine. Both visits were conducted within 2 months of each other.

Results FeNO at visit 1 correlated with AHR (r = 0.573, p = 0.013) and ACQ (r = 0.540, p = 0.021). There were no correlations between FeNO and other biomarkers including sputum eosinophils. There were no correlations between perception of dyspnoea and bronchodilator reversibility. FeNO was non reproducible within the two visits (Mean FeNO of 21.3 ppb and 15.9 ppb at visit 1 and 2 respectively with an error range of 16.9 ppt).

Conclusions FeNO does provide useful clinical information as it correlates with AHR and ACQ. The observed high variability of measured FeNO in this population warrants further investigation.

Conflict of Interest No.

EDUCATION INTERVENTION FOR CHILDHOOD ASTHMA BY INDIGENOUS HEALTH WORKERS IN THE TORRES STRAIT, AUSTRALIA

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The prevalence of childhood asthma in the Torres Strait is high with 30% having persistent asthma and parental asthma knowledge is poor. We conducted a randomised controlled trial of additional education intervention by Indigenous Health Care Workers (HCW) on asthma outcomes.

Methods Children with paediatric respiratory physician diagnosed asthma were enrolled and randomly allocated to: (1) three additional asthma education sessions with a trained HCW or (2) no additional education, and re-assessed at 12 months. Primary endpoint was the difference in the number of unscheduled hospital/doctor visits due to asthma exacerbation between the groups. Secondary outcomes were improvement of quality of life and functional severity scores, asthma knowledge, interpretability of asthma action plans and school days missed due to wheezing.

Results We enrolled and followed up 88 children (81%) aged 1–17 years, 97% Aboriginal and/or Torres Strait Islanders (35 intervention; 53 controls). The groups were mostly comparable at baseline (except for asthma severity which was adjusted for in the analysis). There were no significant differences (p = 0.25) in the number of unscheduled hospital/doctor visits due to asthma exacerbation (intervention group median = 1.0, control group median = 0.0). Compared to the control group, carers in the intervention group were significantly better in knowledge of asthma medication (p < 0.05), possession (p = 0.01) and ability to interpret asthma action plans (p = 0.02). Children in the intervention group missed fewer school days due to wheezing (p = 0.04) compared to the control group. Both groups improved in quality of life and functional severity scores (baseline vs follow up) but there were no significant differences between the intervention and control groups.

Conclusions Additional asthma education sessions conducted by trained local HCW improved some but not all asthma outcomes.

Funding NHMRC, RHSET, Telstra Foundation, Royal Children’s Hosp. Foundation.

TROPICAL PLANT POLLENS AND ALLERGIC RHINITIS

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Background Little has been reported about the allergenicity of pollens from tropical plant families or their relative contributions to allergic disorders in these regions. We investigated associations between daily average fungal spore and pollen counts of several tropical plant families and saliva of four medications commonly used to treat allergic rhinitis in Darwin, Australia, from April 2004 to November 2005.

Methods Five pharmacies provided daily sales data for loratadine/pseudoephedrine and fexofenadine tablets and beclometasone and budesonide nasal sprays. We used Poisson generalised linear and categorical modelling to examine outcomes. All analyses accounted for the potential confounding effects of time trends, season, holidays, respiratory viral illnesses, meteorological conditions and air pollution.

Results The peak total pollen count was 94 grains/m3 while the peak Poaceae (grass) pollen count was just 24 grains/m3. Daily sales of all products increased 5% with each interquartile range rise (3 grain/m3) in Poaceae pollen, greatest at a lag of 1 day (5.07, 95% CI 1.04, 9.25). No associations were observed with fungal spores, the total pollen count or pollen from other plant families.

Conclusions We found an association between tropical grass pollen and allergic rhinitis measurable at low pollen concentrations. High allergenicity and increasing population exposure to pollen from some species of tropical grasses could be contributing an increasing prevalence of allergic rhinitis in tropical regions.

Supported by the Australian Research Council.

No conflict of interest.
**COMPLEMENTARY AND ALTERNATIVE MEDICINE USE IN ASTHMA**

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Complementary and alternative medicines (CAMs) including fish oils and zinc may benefit people with asthma by reducing airway inflammation and hyper-responsiveness. Our aim was to determine the prevalence of CAM use in asthma and its relationship with morbidity.

**Methods** We assessed CAM use in the North West Adelaide Health Study, (n = 3206 adults). Respondents completed surveys and underwent biometrical assessment including spirometry. Asthma was identified by self-reported physician diagnosed asthma or bronchodilator responsiveness. Current CAM use was identified at the clinic visit and included fish oil; other oils (flaxseed, emu); glucosamine; vitamins (multi-, B/C/E/CoQ10); herbal (celery, garlic, ginseng); minerals (magnesium, zinc, ‘minerals’).

**Results** Asthma prevalence was 16.8%. Use of any CAM (29.5%, n = 157), all herbal and all vitamin supplement was not significantly different between people with and without asthma. Compared to those without asthma, males with asthma were more likely to use fish oils (7.1 vs 4.2% OR = 1.71 [0.93–3.87], p = 0.08), and mineral supplements, [4.4 vs 1.6%, OR = 2.40 (1.05–5.47)] specifically zinc, and females with asthma were less likely to use fish oil [5.5 vs 9.2%, OR = 0.51, (0.29–0.91)]. In the asthma population, effects of CAMs on lung function were seen. Males using zinc (n = 7) demonstrated significantly higher mean FEV1, (105.5 vs 90.9, p = 0.03), and FVC (105.3 vs 95.0, p = 0.057) than those not using zinc. Although the differences were not statistically significant, females using fish oils demonstrated increased lung function.

**Conclusions** Sex-specific differences in CAM use occurred in our asthma population. Further investigation of the effects of fish oil and zinc supplements on lung function and respiratory symptoms is warranted.

**Conflict of Interest** None.

**HIGH FLOW OXYGEN CAUSES CARBON DIOXIDE RETENTION IN SEVERE ASTHMA: A RANDOMISED CONTROLLED TRIAL**

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The use of high flow oxygen in acute exacerbations of COPD can result in CO2 retention. High flow oxygen is often used in acute severe asthma, but it is uncertain whether this causes an increase in PaCO2. In this randomised controlled study we investigated the effects of high flow versus titrated oxygen therapy on PaCO2 in acute asthma.

**Methods** 80 patients with severe exacerbations of asthma (FEV1 ≤ 50% predicted) presenting to the Wellington Hospital Emergency Department were randomised to high flow oxygen (8 l/min via a medium concentration mask) or titrated oxygen (to a saturation of 93 to 95%) for 60 minutes, along with routine treatment. Transcutaneous carbon dioxide measurements (tCO2) were made at 0 and 60 minutes. The primary outcome variable was the proportion of patients with a rise in tCO2 ≥ 4 mmHg at 60 minutes. The secondary outcome variable was the proportion of patients with a rise in tCO2 ≥ 8 mmHg.

**Results** Three subjects withdrew from the high flow group leaving 36 for analysis and 41 in the titrated group. A rise in tCO2 ≥ 4 mmHg was seen in 15/36 (41.7%) of the high flow group and 6/41 (14.6%) of the titrated group, a relative risk of 2.8 (CI 1.2 to 6.6, p = 0.008). A rise in tCO2 ≥ 8 mmHg was seen in 5/36 (13.9%) of the high flow group and 3/41 (7.3%) of the titrated group, a relative risk of 1.9 (CI 0.5 to 7.4, p = 0.35). The mean (SD) FEV1 percent predicted was 33.4% (10.5) in the high flow group and 35.4% (9.7) in the titrated group (P = 0.36).

**Conclusion** High flow oxygen therapy results in an increase in tCO2 when delivered to patients with severe exacerbations of asthma, and excessive oxygen delivery should be avoided.

**Supported by** The Health Research Council.

**Conflict of Interest** No.

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**THE RELATIONSHIP BETWEEN PATIENT PERCEIVED RISK OF INHALED CORTICOSTEROIDS IN PREGNANCY AND MEDICATION ADHERENCE**

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Asthma affects 12% of pregnancies in Australia. Variable changes in asthma during pregnancy have been well documented, and it is important to continue using preventer medications (inhaled corticosteroids, ICS) in pregnancy to maintain adequate asthma control. We investigated the relationship between women’s perceived risks of medication and their use of asthma medication.

**Methods** Subjects with current asthma (n = 40) were recruited prior to 20 weeks gestation and had monthly visits. Women completed a 10 cm visual analogue scale indicating their perceived risk of salbutamol and ICS on the baby, with a score of 0% indicating no side effects (healthy baby) and a score of 100% indicating severe side effects (e.g. deformity). Asthma self-management education was provided at each visit and self-reported ICS adherence assessed.

**Results** The median perceived risk of ICS medication was 24% (range 0–70%) at visit 1, 15% (0–61%) at visit 2, 13% (0–61%) at visit 3 and 12% (0–46%) at visit 5 (non-parametric repeated measures ANOVA, P = 0.005). By comparison, the median perceived risk of salbutamol was 10% (range 0–80%) at visit 1 and 5% (range 0–45%) at visit 5. At visit 1, 30% of women perceived low risk (<10%) of ICS on the baby, while at visit 5, 43% of women perceived low risk. There was a significant relationship between ICS non-adherence and perceived risk of ICS at visit 2 (Spearman r = 0.592, P = 0.012), however, this relationship was no longer significant at visit 5 (r = 0.180, P = 0.411).

**Conclusion** Pregnant women with asthma perceive that there is some risk to their baby of the use of ICS. Higher levels of perceived risk were associated with ICS non-adherence. Their perception of risk was improved following asthma education, and provision of such information may improve adherence rates.

Supported by the NHMRC.

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**PAPER WITHDRAWN**
### Refining National Asthma Indicators Using a Delphi Survey

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**Background:** Currently, there are 24 indicators recommended for monitoring to guide policy about the prevention and management of asthma in Australia. There is a consensus that this number is too great for an efficient monitoring program.

**Aim:** A Delphi survey was used to identify a smaller set of core indicators as the focus of future asthma monitoring activities in Australia and elsewhere.

**Methods:** Practising respiratory physicians, paediatricians, general practitioners, asthma researchers, epidemiologists, and representatives of other relevant stake-holders were identified at a national level to conduct interviews on each indicator. A web-based survey was conducted in three rounds. For the 2nd and 3rd rounds, panelists were given feedback regarding their previous responses, pooled results, and anonymous comments from other participants. A Delphi survey was used to identify these indicators.

**Results:** Sixty-two asthma experts from different disciplines were invited to participate. Thirty-two panelists (52%) completed the 1st survey, and 72% of these (preliminary results) successfully completed the 2nd survey. Current asthma (defined as doctor diagnosis plus symptoms or treatment in the last 12 months) and hospital separations for asthma were consistently ranked by the panelists as indicators of asthma in children. On the other hand, Asthma Cycle of Care uptake and airway hyperresponsiveness were identified as potential indicators for exclusion.

**Conclusions:** The Delphi survey has helped to obtain consensus about the most important asthma indicators for monitoring asthma at a national level. This core set of standardized indicators should be used to gain population-based information on asthma in Australia and other countries.

**Support:** ACAM is a collaborating unit of the AIHW and is funded by the Australian Government Department of Health and Ageing.

### Risk Factors for the Development of Asthma Between Age 4 and 7 Years in a National Cohort Study

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**Background:** The risk of developing asthma is associated with genetic, environmental, and lifestyle factors. The aim of this study was to estimate the incidence of asthma and examine risk factors for developing asthma using data from the child cohort of the Longitudinal Study of Australian Children.

**Methods:** The child cohort (aged 4–5 years at baseline) was recruited in 2004 and re-assessed two years later via face-to-face interviews with the primary carer. Asthma diagnosis was ascertained from the question 'Has a doctor ever told you that your child has asthma?'. Multivariate logistic regression was used to examine associations between risk factors and asthma diagnosis.

**Results:** At baseline, 20% of children aged 4–5 years had ever-diagnosed asthma and the estimated incidence of newly diagnosed asthma over the next two years was 8.6%. Independent risk factors significantly (p ≤ 0.013) associated with new asthma diagnosis among 6–7 year olds were wheeze (OR = 3.0); food/digestive allergies (OR = 2.3); and neonatal intensive care after birth (OR = 1.6). No association was observed for eczema, passive smoke exposure, ever breastfed, no siblings, 1+ pets in household, English-speaking primary carer, socioeconomic disadvantage, sex or overweight/obesity.

**Conclusions:** While several of the observed associations are similar to those reported in comparable populations elsewhere, the lack of association with sex, passive smoke exposure, and breastfeeding status suggests that these factors do not have an impact on the incidence of asthma after early childhood.

**Support:** ACAM is a collaborating unit of the AIHW and is funded by the Department of Health and Ageing.

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### Early Life Risk Factors and Incidence of Allergic Rhinitis

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**Background:** Allergic rhinitis (AR) is an increasingly common condition. AR may predispose to asthma and early aggressive treatment might prevent asthma. Understanding risk factors associated with AR is important. We examined the association between early life factors and development of AR using European Community Respiratory Health Study (ECRHS) data.

**Methods:** In 1992–94, community-based samples of 20–44 years old people were recruited from 48 centres in 22 countries. On average, 8.9 years later, 28 centres re-investigated their samples using similar methods. Onset of AR was reported in interviewer-led questionnaires. Cox regression was used to assess independent predictors of AR risk in childhood (0–10 yrs), adolescence (11–20 yrs) and adult life (21+ yrs).

**Results:** Out of the 10,839 participants in ECRHS II n = 5353 (Prev = 32.6%; 95% CI 31.7–33.5%) had ever-diagnosed AR but there was significant heterogeneity in the estimates across countries (p = 0.0001). Data on age at onset of AR was available for 10,373 participants. Males more often got AR in childhood (HR 0.80, 95% CI 0.69–0.93), while females more often got AR in adulthood (1.48, 1.33–1.65). Siblings were associated with a reduced risk of AR in childhood (0.86, 0.82–0.91), adolescence (0.89, 0.86–0.93) and adulthood (0.88, 0.95–1.01), whereas being at pre-school/nerd/day care before 5 years (0.84, 0.76–0.90) and sharing bedrooms with older children (0.86, 0.80–0.92) were associated with a reduced risk of AR; this did not vary with age. Cats and dogs in the first year of life were associated with a significantly reduced risk of AR only in adolescence. A serious respiratory infection before 5 years and parental allergies were associated with increased risk of AR.

**Conclusion:** Early life factors (siblings, day care and bedroom sharing) have the strongest effect in childhood consistent with the ‘hygiene hypothesis’. The apparent protective effects of pets appear to be restricted to adolescent onset AR.

**Support:** European Commission, NHRMC.
INCIDENCE OF ASTHMA AND WHEEZE IN INDIGENOUS CHILDREN LIVING IN URBAN AND REGIONAL AREAS

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Background There is a large disparity in asthma and asthma-related outcomes in Aboriginal and Torres Strait Islander Australians compared with other Australians.

Aim The purpose of this study was to compare the incidence of asthma and wheeze over a two year interval among indigenous and non-indigenous children.

Methods In 2004, the Longitudinal Study of Australian Children recruited two cohorts aged 0–1 years (infant cohort, n = 5107) and 4–5 years (child cohort, n = 4983). Asthma and wheeze were diagnosed by questionnaire and indigenous status was assessed by self-report. Prevalence rates at baseline and incidence rates over two years follow-up period were compared between indigenous and non-indigenous children by calculating rate ratios.

Results In the child cohort, the prevalence of wheeze at baseline was 1.86 times (95% CI 1.52–2.27) higher in indigenous than non-indigenous children but no significant difference was found in the incidence of wheeze over the following two years (IRR 1.21; 95% CI 0.93–1.58). In the child cohort, of whom 3.9% were indigenous, there was no difference in the prevalence of wheeze at baseline among indigenous (19.5%) and non-indigenous children (15.0%) (IRR 1.30; 95% CI 0.96–1.75). In this cohort, the prevalence of asthma at baseline was 1.62 times (95% CI 1.18–2.21) higher in the indigenous children but the incidence of newly-diagnosed asthma over the next two years did not differ between the indigenous and non-indigenous children (IRR 0.7; 95% CI 0.33–1.44).

Conclusions The findings confirm a higher prevalence of reported asthma and wheeze in indigenous compared with non-indigenous children and show that the disparity diminishes with age during childhood. This suggests that the prevalence of wheeze illness in indigenous children is affected by events in early childhood.

Support ACAM is a collaborating unit of the AIHW and is funded by the Australian Government Department of Health and Ageing.

GEOGRAPHIC VARIATIONS IN HOSPITAL RE-ADMISSION FOR ASTHMA

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Background Re-admission to hospital within 28 days has been used as an indicator of health system performance in the care of patients with asthma. However, socio-demographic factors may confound its interpretation at a local level.

Aim The aim of this study was to use national hospital admission data in estimating expected rates of hospital re-admission for asthma at a statistical local area (SLA) level, adjusted for socio-demographic factors.

Methods Nationwide hospitalisation data (excluding Queensland) between 1996 and 2005 were used to identify hospital re-admissions for asthma within 28 days for the same individual using a linkage key. Expected re-admission rate was calculated for each SLA by logistic regression using data on age and sex distribution, state/territory and socio-economic index for areas (SEIFA) as predictors. Observed-to-expected ratio was then calculated for each SLA.

Results The overall rate of re-admission within 28 days for asthma was 4.7%. Age group, sex, state/territory and SEIFA were significant predictors of re-admission rates. The median of the observed-to-expected ratio was 0.93 and the 10th, 25th, 75th and 90th percentiles were 0.0, 0.64, 1.22 and 1.59 respectively.

Conclusions This analysis has identified important local variation in re-admission rates. The median of the observed-to-expected ratio was 0.93 and the 10th, 25th, 75th and 90th percentiles were 0.0, 0.64, 1.22 and 1.59 respectively.

Support ACAM is a collaborating unit of the AIHW and is funded by the Australian Government Department of Health and Ageing.

SINUSITIS IN AUSTRALIANS: IS PEAKED BETWEEN 18 AND 35 YEARS OF AGE?

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Background Sinusitis is one of the most common reasons for attendance in general practice and hospital outpatients. It is usually considered to be self-limiting and of no clinical consequence. However, the true burden of sinusitis is difficult to quantify due to the lack of population-based data.

Aim The aim of this study was to document the prevalence of sinusitis in a representative sample of adults aged 18 years and over.

Methods A cross-sectional survey of a randomly selected sample of adults aged 18 years and over was undertaken. In total, 2567 adults were recruited from the general population and 2446 completed the study. The prevalence of sinusitis was defined as sinusitis in the previous 12 months.

Results The prevalence of sinusitis was 4.7%. Age group, sex, state/territory and socio-economic index for areas (SEIFA) were significant predictors of sinusitis.

Conclusions The prevalence of sinusitis is higher among children and young adults. This suggests that sinusitis may be a cause of school or work absenteeism.

Support ACAM is a collaborating unit of the AIHW and is funded by the Australian Government Department of Health and Ageing.

THE ATOPIC MARCH: GENETIC, SHARED ENVIRONMENT OR DIRECT EFFECT?

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Background The ‘atopic march’ hypothesis – eczema precedes the development of allergic rhinitis and asthma – is controversial. Little is known about whether the influence of eczema on hay fever and asthma is direct or mediated by other factors such as genes and/or shared environment. We sought to examine the contributions of genes and/or shared environment, to the atopic march hypothesis.

Methods We used data from the baseline survey of the Tasmanian Longitudinal Health Study. In 1968, 8583 7-year old school children and their siblings (21,000) were investigated for asthma and other allergies. A novel twin-sibling regression model was used to examine the association between infantile eczema and hay fever and asthma separately.

Results 182 dizygotic (DZ) twin pairs and 3696 sib pairs were included in the study. The association between infantile eczema and hay fever was mediated by parental phenotype (p < 0.001) and infantile eczema in the sibling (p = 0.002). Hay fever was strongly associated with asthma (p < 0.001). In the sib model examining the association between hay fever and asthma the effect of hayfever in a sib was no longer significant (p = 0.9) after adjusting for parental phenotype (p < 0.001). Infantile eczema was significantly associated with asthma. There was no effect of infantile eczema in a sib (p = 0.86) on the association between infantile eczema and asthma.

Conclusion Our findings suggest that different mechanisms are triggered at different stages of the atopic march. There seem to be strong genetic and shared environment components for the infantile eczema – hay fever associations and a stronger genetic component for the hay fever – asthma associations. Conversely, there seems to be a direct effect of infantile eczema on asthma.

Grant Support NHMRC.

SKIN PRICK TESTS USING A TWO MILLIMETRE CUT POINT ARE BEST AT IDENTIFYING ELEVATED SPECIFIC IGE CONCENTRATIONS

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In epidemiological studies of children, using a skin prick test (SPT) cut point of 2 mm or 3 mm for most allergens, attracts controversy due to a lack in evidence based guidelines. The Childhood Asthma Prevention Study (CAPS) provided an opportunity to assay the wheal size cut point offering the best trade-off between sensitivity and specificity in identifying elevated specific IgE concentrations.

Methods Subjects were eight year old children who were born in Sydney and had at least one parent or sibling with asthma. SPTs were performed using extracts of D. pteronyssinus (HDM), cat hair and epidermis (cat), A. alternata (Alternaria) and L. perenne (Rye grass) pollen. Serum specific IgE against the same allergens was determined using the Pharmacia ImmunoCAP 250 system. Levels ≥ 0.35 kUA/L were classified as positive. ROC curves were used to examine the relation between wheal size and positive ImmunoCAP for each allergen. The agreement of SPTs using cut-points of ≥ 2 mm and ≥ 3 mm with ImmunoCAP was assessed by kappa (κ).

Results

| Allergen   | ROC AUC | 95% CI | Kappa |
|------------|---------|--------|-------|
| HDM n = 331 | 0.96    | 0.99 – 0.98   | 0.86  |
| ≥ 2 mm K   | 0.87    | 0.83 – 0.90   | 0.72  |
| ≥ 3 mm K   | 0.82    | 0.81 – 0.87   | 0.70  |

1Area under ROC curve.

Conclusions Amongst 8-year olds, there is good agreement between SPT and serum-specific IgE for the four inhaled allergens examined. A SPT threshold of ≥ 2 mm yields results that are in close agreement with specific IgE in this population.

Supported by the NHMRC.
USE OF MEDICINES IN CHILDREN WITH ASTHMA: THE AUSTRALIAN ASTHMA EDUCATOR PERSPECTIVE

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The global burden of childhood asthma is significant. Health care systems are faced with increasing financial costs due to childhood asthma, while children and their carers are affected through reduced quality of life and reduced emotional and physical health. Despite the availability of effective treatment, the quality use of asthma medicines in children remains suboptimal. An investigation was undertaken to explore issues related to children’s asthma medicine usage from the perspective of the health care professional. Literature evidences problems from the patient’s perspective, but an informed reality is expected from health care professional’s views about ‘issues’ in medicines usage and this has been relatively unexplored in the past. Semi-structured qualitative interviews were conducted with a convenience sample of 21 Australian asthma and respiratory educators. Interviews were audiotaped, transcribed verbatim, and transcripts thematically analysed with the assistance of NVivo 7. Emergent themes associated with health care professionals, parents, medicines and children were found. Major issues included a lack of information provided to parents, poor parental understanding of medicines, the high cost of medicines and devices, child self-image, the need for more child responsibility over asthma management and the lack of standardisation, access to and funding for educational resources on childhood asthma. There are therefore a multitude of key issues that may affect asthma medicines usage in children. This research will help inform the development of educational tools on the use of medicines in childhood asthma that can be evaluated for their effectiveness in getting key messages to their target audience (children, carers, and teachers). The research was funded through a University of Sydney International Program Development Fund Grant.

Conflict of Interest None.

RESISTIN AND AIRWAY INFLAMMATION IN CHILDREN WITH ALLERGIC ASTHMA

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Background A relationship between obesity and asthma has been evidenced by numerous studies on large populations. However, little is known about the linking mechanism. Products of adipose tissue, known as adipokines, including leptin, resistin, TNF-α, PAI-1 and IL-6, have been found to be associated with inflammatory states. This study aimed to determine the relationship between adipokines and respiratory inflammation in a cohort of children with persistent allergic asthma.

Methods Thirty-one children (20 with allergic asthma (AA) and 11 non-allergic healthy control (HC)) aged 6.0–17.9 years of age were recruited. Thirty-one children (20 with allergic asthma and 11 non-allergic healthy control (HC)) aged 6.0–17.9 years of age were recruited.

Results FeNO was significantly higher (mean 7.38 ± 3.91), and a significant negative correlation was found between FeNO and resistin (r = -0.46, p = 0.04), but not with other adipokines, which was not significant from health care professional’s views about ‘issues’ in medicines usage and this has been relatively unexplored in the past. Semi-structured qualitative interviews were conducted with a convenience sample of 21 Australian asthma and respiratory educators. Interviews were audiotaped, transcribed verbatim, and transcripts thematically analysed with the assistance of NVivo 7. Emergent themes associated with health care professionals, parents, medicines and children were found. Major issues included a lack of information provided to parents, poor parental understanding of medicines, the high cost of medicines and devices, child self-image, the need for more child responsibility over asthma management and the lack of standardisation, access to and funding for educational resources on childhood asthma. There are therefore a multitude of key issues that may affect asthma medicines usage in children. This research will help inform the development of educational tools on the use of medicines in childhood asthma that can be evaluated for their effectiveness in getting key messages to their target audience (children, carers, and teachers). The research was funded through a University of Sydney International Program Development Fund Grant.

Conflict of Interest None.

DOES VENTILATION HETEROGENEITY PREDICT AIRWAY HYPERRESPONSIVENESS IN COPD OR OLDER ASTHOMATIC SUBJECTS?

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Ventilation heterogeneity in the conducting airways (Scond) measured by the multiple breath nitrogen washout (MBNW) predicts airway hyperresponsiveness (AHR) in asthmatic subjects. We hypothesise that this is an underlying mechanism for AHR, independent of disease. To test this we compared the relationship of AHR to ventilation heterogeneity in COPD and age matched asthmatics.

Methods 12 COPD and 15 asthmatic subjects (60–86 yrs) underwent base-line spirometry, MBNW, and methacholine (MCh) challenge. AHR was expressed as dose response ratio (DRR = %fall FEV1/mul MCh). Ventilation heterogeneity of the conducting (Scond) and acinar (Sacin) airways were calculated from the MBNW.

Results Values are mean ± SD or geometric mean (95% CI).

| FEV1 (% pr) | Scond | Sacr | DRR |
|------------|-------|------|-----|
| COPD       | 69.9 ± 7.1 | 0.60 ± 0.13 | 0.05 ± 0.02 | 2.3 (1.3–3.5) |
| Asthma     | 71.7 ± 9.6  | 0.21 ± 0.04 | 0.07 ± 0.02 | 9.5 (3.1–22.6) |
| p-value    | 0.32     | <0.01 | 0.79 | 0.12 |

In COPD, DRR correlated with Scond (r = 0.63, p = 0.03), but not with Sacr (r = –0.25, p = 0.44). In asthmatic subjects, DRR correlated with Sacr (r = 0.66, p = 0.008) but not with Scond (r = –0.08, p = 0.77).

Conclusions Scond is related to airway responsiveness in COPD, but most subjects in this study did not have AHR. In contrast to younger asthmatics, AHR is predicted by Sacr, not Scond in older asthmatics, suggesting more peripheral disease processes. Thus, increased baseline Scond does not predict AHR in either COPD or older asthma. Supported by the National Health and Medical Research Council.

Nomination Nil.

Conflict of Interest No.

REFERENCE EQUATIONS FOR IMPEDANCE PARAMETERS MEASURED BY THE FORCED OSCILLATION TECHNIQUE

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Previous studies to determine reference equations for forced oscillatory parameters are limited either by small sample sizes, inclusion of only a single sex, or selection of ‘normal’ subjects from people presenting at clinics or hospitals.

Aim To determine normal predictive equations for respiratory system resistance (Rrs) and reactance (Xrs) in a large randomly selected sample from a general population.

Methods Prospective respiratory health survey of the general population in Busselton, WA, between 2005 and 2007. Subjects had measures of spirometry, atopy by allergen skin prick tests, and Rrs and Xrs (6, 11, 19 Hz) by forced oscillation technique. Eligible subjects were never smokers, with no history of respiratory disease, no symptoms of cough, shortness of breath or chest tightness in the previous 12 months, and no respiratory tract infections in the previous 4 weeks.

Results 459 eligible subjects (167 male) aged 18 to 93 yrs had technically satisfactory FOT measurements. Rrs6 (95% CI) was 2.94 (2.8 to 3.1) in males and 3.91 (3.8 to 4.0) in females. The predictive normal equations were:

\[
\text{Rrs}_6 = 4.19 - 0.0017 \times \text{Age} + 0.0088 \times \text{Wt.kg} - 0.0211 \times \text{Ht.cm},
\]

\[
\text{Rrs}_6 = 5.02 + 0.03, \text{but not with Scond (r = –0.08, p = 0.77).}
\]

Conclusions Scond is related to airway responsiveness in COPD, but most subjects in this study did not have AHR. In contrast to younger asthmatics, AHR is predicted by Sacr, not Scond in older asthmatics, suggesting more peripheral disease processes. Thus, increased baseline Scond does not predict AHR in either COPD or older asthma. Supported by the CRC for Asthma and Airways, NHMRC ID 353532.

Nomination Nil.

Conflict of Interest None.
THE EFFECT OF INHALED CORTICOSTEROIDS ON AIRWAY DISTENSIBILITY IN ASTHMA

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Airway distensibility has been proposed as a potential marker of airway remodeling and is reduced in asthma. The contribution of current inflammation to distensibility is unknown. The aim of this study was to determine the effect of inhaled corticosteroids (ICS) treatment on airway distensibility in asthma.

Methods Twelve asthmatic patients (7 males, 20–60 yrs) underwent 18 weeks of treatment with fluticasone propionate 500 μg bd. Exhaled nitric oxide (FeNO), spirometry, methacholine challenge, and distensibility between 75% TLC and TLC by FOT were measured at baseline, 4, 8, 14 and 18 weeks.

Results At baseline, FEV1 was 87.1 ± 17.8% of predicted and distensibility was 0.20 ± 0.19 L s⁻¹ cmH₂O⁻¹ L lung volume, indicating reduced distensibility in this group. Baseline distensibility correlated with disease duration (p = 0.005), but not with age (p = 0.78). DRS (p = 0.22), FeNO (p = 0.64) or spirometry (p = 0.85). After 18 weeks of treatment, FeNO mean (95% ci) decreased from 8.5 (6.8–10.5) ppb to 6.3 (95% ci 5.0–7.4) ppb (p = 0.04). DRS decreased from 8.38 (6.4–10.4) to 5.25 (3.6–6.9) %/μmol (p = 0.0003). There was no change in distensibility (p = 0.46) or spirometry (p = 0.54).

Conclusion 18 weeks of ICS treatment did not change distensibility in this group of well-controlled asthmatics, despite improvements in FeNO and DRS. This suggests that current inflammation does not contribute to distensibility. The relationship between distensibility and disease remission duration implies that reduced airway distensibility in asthma is related to long-term structural changes, such as airway remodelling. Supported by the CRC for Asthma and Airways.

Conflict of Interest None.

SIMILAR BETWEEN-DAY REPEATABILITY OF FORCED OSCILLATION MEASUREMENTS IN ASTHMA PATIENTS COMPARED WITH NORMALS

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Introduction FOT measurements of resistance (Rrs), conductance (Grs) and reactance (xrs) are measures of airway function that are effort independent and therefore may be used for asthma monitoring by patients.

Aims Compare the day-to-day variability in FEV1, Rrs and xrs in asthmatics and non-asthmatics in the laboratory.

Methods Ten asthmatics (6 males) and 9 normals (4 males) performed repeated spirometry and FOT over 10 consecutive days in the laboratory. Subjects were tested at the same time each day and were asked to continue all usual medications, including bronchodilators. The within subject day-to-day variability was measured from the mean variances.

Results Asthmatic subjects mean ± SD age of 38 ± 12 years was similar to 31 ± 3 years for non-asthmatics. FEV1 was lower in asthmatics (3.22 ± 0.67 L vs 3.64 ± 0.88 L, p < 0.001), while Rrs was higher (3.30 ± 1.00 vs 2.44 ± 0.76 cmH₂O/L/s, p < 0.001) and xrs was lower (−0.95 ± 0.42 vs −0.75 ± 0.28). For Rrs, the within subject day-to-day variability (mean within subject SD) was similar between asthmatics non-asthmatic subjects for FEV1 (0.26L vs 0.15L), Grs (0.04 vs 0.03L/s/cmH₂O) and xrs (0.21 vs 0.17 cmH₂O/L/s).

Conclusion Day to day variability in Grs and xrs measurements in asthmatics are comparable to those in non-asthmatics. Variability of Rrs between days is not a useful measure of variability in lung function since it is strongly related to mean Rrs. This has implications for the use of FOT in monitoring lung function in asthmatics.

Support the CRC for Asthma and Airways, Project 2.1.
UPREGULATION OF MITOGEN-ACTIVATED PROTEIN KINASE PHOSPHATASE 1 BY CORTICOSTEROIDS/β2-AGONISTS: UNCOVERING THE UNDERLYING MOLECULAR MECHANISMS

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Background We and others recently discovered that the repressive effects of corticosteroids on the pro-remodelling phenotype of airway smooth muscle (ASM) cells occur via upregulation of the endogenous MAPK deactivator – MAPK phosphatase 1 (MKP-1). Corticosteroid/β2-agonist combinations enhance MKP-1 mRNA expression. Further investigations into the regulation of MKP-1 are required as these findings may lead to the development of novel anti-inflammatory and corticosteroid-sparing therapies.

Aims We aim to increase MKP-1 to reduce MAPK-mediated pro-remodelling pathways in asthma. We examine the molecular mechanisms underlying upregulation of MKP-1 by corticosteroids/β2-agonists in ASM cells.

Methods ASM cells were treated with vehicle, dexamethasone (100 nM), or fli conscane protopine (1 nM), in the presence of salmeterol (100 nM) or fmitomterol (10 nM), for up to 24 h. MKP-1 protein and the phosphorylation of p38, ERK, JNK, CREB and MKP-1 at Ser202 were quantified by Western blotting and MKP-1 mRNA expression was measured by real-time RT-PCR.

Results β2-agonists alone induced upregulation of MKP-1 protein and corticosteroids induced a sustained increase in protein expression for up to 24 h. In combination, corticosteroids and β2-agonists increased MKP-1 protein in an additive manner. This was supported by MKP-1 mRNA expression, where dexamethasone-induced MKP-1 expression at 1 h was significantly increased by formoterol. To date, our results indicate that activation of ERK at 10 and 30 min by corticosteroids/β2-agonist may lead to phosphorylation of MKP-1 at Ser202, a regulatory motif that controls protein stability, and that CREB phosphorylation may underlie transcriptional regulation.

Conclusion We are beginning to uncover the molecular mechanisms responsible for the upregulation of the MAPK-deactivator MKP-1.

INCREASED LEVELS OF T-CELL GRANZYME B MAY PREDICT BRONCHIOLITIS OBLITERANS SYNDROME

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We have previously reported increased apoptosis of bronchial epithelial cells in transplanted lungs. Granzyme b induces apoptosis in target cells; we therefore evaluated granzyme b in lung transplant patients and as a predictor of BOS/OB. We investigated intracellular T-cell granzyme b in blood, BAL and large airway brushing [23 controls, 29 stable transplants, 23 BOS, 28 acute rejection, 31 infection]. Soluble granzyme b was measured in a cohort from each group. Granzyme b was significantly increased in all compartments of all transplant groups. Surprisingly, granzyme b was even higher in patients with BOS than in patients with acute rejection. For one patient, blood levels of granzyme b were consistently high for 12 m prior to diagnosis of BOS. A further two patients demonstrated increased production of granzyme b by blood T-cells coincident with a decrease in lung function and diagnosis of BOS. Increased T-cell granzyme b production may contribute to a loss of epithelial integrity and dysregulated epithelial repair in BOS. Longitudinal investigation of granzyme b in blood may provide an adjunctive non-invasive method for predicting BOS/OB.

Sources of Support NHMRC Project Grant, NHMRC Clinical Career Development Award and Practitioner Fellowship, Royal Adelaide Hospital Clinical Project Grant.

CELLS OF EPITHELIAL LINEAGE ARE DETECTABLE IN PERIPHERAL BLOOD AND ARE INCREASED IN LUNG TRANSPLANTATION

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Our previous studies have identified CXCR4+ exogenous epithelial cells which have engrafted the transplanted human bronchial epithelium from the circulation. The aim of this study was to identify similar cells in peripheral blood.

Methods Peripheral blood was collected from healthy controls (n = 5, aged 23–40, 3 female) and transplant patients (n = 8, aged 42–62, 3 female, (COPD 4, UIP 1, CP 1, Bronchiectasis 1, CHD 1) 2–66 months post-transplant, all BOS 0). Peripheral blood mononuclear cells (PBMC) were incubated with surface markers (CXCR4–PE; CD45–PerCP and CD14–APC) and then the intracellular epithelial marker pan-Keratin-AlexaFluro488 prior to flow cytometry. Monocytes (CD14+) were excluded and CD45+ and – populations were analysed for epithelial lineage cells.

Results Cells of epithelial lineage were detectable in very low numbers in healthy controls (0.08 ± 0.01% of CD14+ PBMC), but were 7-fold higher in transplant patients (0.57 ± 0.17%, p < 0.05). Almost all cells expressed CD45 and 79% were CXCR4+. The highest number of cells was found in the only patient with residual native lung parenchyma (UIP).

Conclusions For the first time we have identified cells of epithelial lineage in peripheral blood in humans with no history of pregnancy or malignancy. Whether their differentiative and regenerative potential are under investigation, surface protein expression suggests a bone marrow source and implicates the CXCR4/CXCL12 axis in engraftment of target organs. Future studies will focus on the role of this cellular population in diseases of epithelialised organs including the lung.

DENDRITIC CELLS (DC) SUSCEPTIBILITY TO SYNucleIN-INDUCED APOPTOSIS DEPENDS ON DC MATURATION STATUS

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A delicate balance between programmed cell death (PCD or apoptosis) and cell survival is a key mechanism for regulating the immune response. The mechanisms involved in the difference in immature and mature DC response to apoptotic agents are poorly understood. Our recent findings that α-synuclein (α-syn) decrease viability of mature DC prompted us to further examine its effects on DC apoptosis.

Methods Cell viability was measured using Methyl-Tetrazolium Reduction (MTT) assay, whereas annexin-V Apoptosis Detection Kit was used to assess PCD. Expression of the members of Bcl-2 family was assessed using real-time PCR.

Results Exogenous α-syn induces apoptosis but not necrosis in LPS-matured DC. In contrast, immature DC (un-stimulated or stimulated with inflammatory desArg5-Brad) or semi-mature DC (stimulated with TNFα) are resistant to α-syn-induced apoptosis. Although, α-syn increases ceramine-induced apoptosis of both immature and mature DC, α-syn-prestimulated immature DC seemed to be less sensitive to ceramine-induced apoptosis, suggesting α-syn may have some protective effects on these cells. Similarly to ceramine, α-syn induces apoptosis through intrinsic apoptotic pathway and up-regulation of Bad expression.

Conclusion Our findings implicate α-syn involvement in a highly controlled process of apoptosis. It seems that α-syn effect on DC viability depends on DC maturation and activation status (such as engagement of different signalling pathways in DC activated by TNFα, desArg5-Brad or LPS). The dramatic increase in apoptosis of α-syn+ ceramine treated DC, suggests that this two apoptotic agents share the same apoptotic pathway (Bad pathway).

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High numbers of activated mast cells infiltrate airway smooth muscle cells from LAM and control cells. TIMP-1 was further increased by doxycycline (d5, with the disease. In this study we investigated whether doxycycline, an MMP

The altered expression of matrix metalloproteinases (MMPs), such as MMP-2, and their inhibitors (TIMPs) in lymphangioleiomyomatosis (LAM) may contribute to the abnormal proliferation of LAM cells and cystic destruction associated with the disease. In this study we investigated whether doxycycline, an MMP inhibitor, can modulate cell proliferation and secretion of MMPs, TIMPs, and VEGF.

**Methods**

Confluent ASM cells from 6 non-asthmatic donors were serum deprived for 48 h. Cells were then treated with antisense C/EBPα or C/EBPβ oligonucleotides or their respective control oligonucleotides (10 μM), prior to and during stimulation with IL-1β, TNFα and/or IFNγ (10ng/ml each) for up to 24 h. C/EBPα and C/EBPβ proteins were analysed by western blotting and secreted IP-10 and IL-6 were quantified by ELISA.

**Results**

C/EBPα and C/EBPβ expression was significantly reduced by their respective antisense oligonucleotide. Reducing C/EBPβ significantly reduced cytokine induced IP-10 production to: 67.5 ± 6.6% of IL-1β control (p < 0.024); 59.3 ± 6.3% of IFNγ control (p = 0.005); 72.8 ± 5.7% of cytokine control (p = 0.034); whereas it only increased TNFα induced IL-6 release to 117.3 ± 2.1% (p < 0.0001). Reducing C/EBPβ inhibited cytokine induced IL-6 production to 81.0 ± 7.6% (p = 0.0222), but not IP-10 production.

**Conclusions**

The transcription factor C/EBPα is involved in regulating ASM cell IP-10 and IL-6 production. It is unlikely that the absence of C/EBPα is involved in the increased IP-10 production by asthmatic ASM cells. Therefore modulation of C/EBP-isomers expression may be an important regulatory mechanism of ASM-mast cell interactions.

**Funded by** NHMRC.
TP 069

ALTERNATIVE ALVEOLAR MACROPHAGE PHENOTYPE IN COPD PATIENTS WITH/WITHOUT LUNG CANCER – IMPLICATIONS FOR TUMOUR SUSCEPTIBILITY AND PROGRESSION

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Introduction COPD is associated with an increased risk of developing lung cancer. Alveolar macrophages [AM] display phenotypic and functional polarisation in response to host mediators. Alternatively activated M2 AM [in contrast to classically activated M1'] contribute to the resolution of inflammation but may also promote tumour growth. We hypothesised that COPD subjects would display an M2 phenotype and function that could contribute to their increased risk of developing cancer over and above the risks of smoking per se.

Methods We investigated phenotype [M1: CD16, HLA, HLA-DR, CD11C, CD11B, M2: CD1B, CD209, CD163, mannose receptor], arginase, and function [phagocytic ability and basal and LPS induced secretion of inflammatory cytokines] of BAL-derived AM from healthy controls, COPD subjects with/without lung cancer and cancer patients without COPD.

Results AM from COPD subjects with/without cancer showed reduced expression of most M1 markers. Arginase and M2 markers were increased with the exception of mannose receptor that was reduced in all patient groups. Phagocytic ability was decreased in COPD and cancer groups [Controls 22%; COPD/no cancer 11%; COPD/cancer 14% and cancer/no COPD 16%]. CD11b and CD51 were unchanged. Basal and induced secretion of inflammatory cytokines was increased in COPD.

Conclusions AM from COPD subjects display a mixed, mostly alternative phenotype that may contribute to tumour susceptibility and progression. Functional capacity was mixed, with reduced phagocytic ability [M2] but capability of producing high levels of pro-inflammatory cytokines [M1]. Treatment strategies that act by switching macrophage phenotype or by improving phagocytic function may have the potential as cancer preventative in COPD.

Support ALF, NHMRC Career Development Award.

TP 070

LOCAL PRODUCTION OF SAA OCCURS IN RESPONSE TO BACTERIAL LPS AND MAY DRIVE STEROID RESISTANT INFLAMMATORY PROCESSES IN COPD

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Introduction SAA represents a family of acute phase proteins classically secreted by the liver that has potent pro-inflammatory properties. Its blood levels are highly induced by inflammation and infection (100-1000 fold) that also tracks with the severity of COPD exacerbations (Bozinovski et al. AJRCCM 2008). Since SAA is differentially expressed to CRP and is steroid insensitive, we explored i) whether SAA can be directly produced in COPD lung and ii) whether local production contributes to inflammation.

Methods BAL and sputum samples were collected from the Melbourne Longitudinal Community Cohort (MLCC) with Moderate-Severe COPD. SAA protein levels in BALF and sputum samples were measured by ELISA (Anogen). Lung resection samples were selected for SAA by IHC.

Results Preliminary screen of BALF and sputum has detected SAA at levels significantly higher than those previously published (106-107 vs 104-105). SAA staining in the BALF and sputum samples was detected in neutrophils, monocytes and macrophages. ELISA of sputum samples confirmed SAA levels significantly increased in COPD compared with controls (4.4 ± 5.3 x 104 vs. 2.2 ± 4.4 x 105 p < 0.01, n = 3).

Conclusions SAA is present in BALF and sputum from COPD patients and is up-regulated in COPD. It is produced locally in COPD and is not confined to the liver. SAA may play a role in mediating COPD in response to bacterial LPS.

TP 071

REDUCED TOLL-LIKE RECEPTOR 7 FUNCTION IS ASSOCIATED WITH ASThma, BUT INDEPENDENT OF ATOPY

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Background Anti-viral innate immunity may be impaired in asthma, though the mechanisms are not well understood. Toll-like receptor (TLR) 7 recognizes single-stranded viral RNA. This study aimed to investigate TLR7 function in 14-year-old adolescents with asthma, and to determine whether this is influenced by the Th2 cytokines IL-4 and IL-13.

Methods Blood mononuclear cells obtained from atopic asthmatic (n = 17), atopic, non-asthmatic (n = 29) and healthy, non-atopic individuals (n = 21), were stimulated with the TLR7 agonist imiquimod. Expression of interferon regulatory factor 7 (IRF7) and the anti-viral molecules myxovirus resistance (Mx) protein A and 2’5’ oligoadenylate synthetase (OAS) were measured by real-time PCR.

Results TLR7-induced IRF7, MxA and OAS mRNA were significantly lower in asthma compared to healthy subjects (p = 0.048, p = 0.041 and p = 0.003 respectively), and these responses did not vary with atopy in the absence of asthma. Exposure to IL-4 or IL-13 in vitro did not alter expression of IRF7, MxA and OAS.

Conclusions TLR7 function was reduced in those with asthma. However, this appeared to be independent of atopy per se, as expression of anti-viral molecules was similar in healthy individuals regardless of atopic sensitization, and was not affected by short term exposure to Th2 cytokines in vitro. These findings may partly explain why people with asthma are more susceptible to respiratory viral infections.

TP 072

AIRWAY EPITHELIAL CELLs DOWN-REGULATE LEUCOCYTE PRO-INFLAMMATORY RESPONSE IN THE AIRWAYS VIA THE COX-2 PATHWAY AND PGE-2 PRODUCTION

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Introduction Anti-viral innate immunity may be impaired in asthma, though the mechanisms are not well understood. Toll-like receptor (TLR) 7 recognizes single-stranded viral RNA. This study aimed to investigate TLR7 function in 14-year-old adolescents with asthma, and to determine whether this is influenced by the Th2 cytokines IL-4 and IL-13.

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Conclusions TLR7 function was reduced in those with asthma. However, this appeared to be independent of atopy per se, as expression of anti-viral molecules was similar in healthy individuals regardless of atopic sensitization, and was not affected by short term exposure to Th2 cytokines in vitro. These findings may partly explain why people with asthma are more susceptible to respiratory viral infections.
Adoptive transfer of macrophages re-engineered from embryonic stem cells to deliver SOD3 ameliorates lung injury in mice

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Macrophage activation and accumulation in the lung during sustained lung injury permits the opportunity to use macrophages as cellular vehicles to deliver therapeutic genes intimately to sites of lung injury. We have derived and characterised functional and phenotypically distinctive macrophages (esM) from mouse embryonic stem cells that overexpress the potent antioxidant superoxide dismutase 3 (SOD3) from the tetracycline-regulated ROSA26 knock-in locus. The aim of the study is to assess the therapeutic potential of these cells to ameliorate lung injury after adoptive transfer into recipient mice.

Methods Mice received either SOD3- or wild type (Wt)-esM or saline via intravenous administration and were given 10µg lipopolysaccharide (LPS) transnasally 1 hr later. 24 hrs post LPS, bronchoalveolar lavage (BAL) fluid was collected and lungs were removed for assessment of multiple inflammatory indices.

Results Western blot confirmed an approximate 2-fold increase in SOD3 protein in the lung tissue of SOD3-esM treated mice. Adoptive transfer of SOD3-esM reduced BAL neutrophilia by 30% in LPS treated mice (SOD3-esM: 3.5 ± 0.46 × 10⁶ vs. Wt-esM: 5.2 ± 0.47 × 10⁶ vs saline: 5.0 ± 0.37 × 10⁶, p < 0.05). Analysis of pooled lung homogenate from SOD3-esM treated mice also revealed a dramatic 45% (vs. saline) and 35% (vs. Wt-esM) reduction in IL-6 mRNA levels.

Conclusions The adoptive transfer of macrophages overexpressing the antioxidant SOD3 was able to ameliorate LPS-induced lung inflammation. This suggests a crucial role for superoxide in promoting neutrophilic lung injury, potentially via the regulation of IL-6. This study also highlights the potential of novel cell-based therapies for clinical lung disease.

Supported by NHMRC and GSK Post Graduate Support Grant.

Conflict of Interest No.

Therapeutic role for mannose binding lectin in cigarette smoke-induced lung inflammation? Evidence from a murine model

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Objectives Defective efferocytosis in the airway may perpetuate inflammation in smokers with/without COPD. Mannose binding lectin (MBL) improves efferocytosis in vitro; however, the effects of in vivo administration are unknown. MBL circulates in complex with MBL-associated serine proteases (MASPs), and efferocytosis has been shown to involve activation of cytoskeletal-remodeling molecules including Rac1/2/3. We hypothesized that MBL would improve efferocytosis in vivo, and that the mechanisms would include up-regulation of Rac1/2/3 or MASPs.

Methods In vivo: We applied a smoking mouse model to investigate the effects of MBL on efferocytosis. MBL (20 µg/20 g mouse) was administered via nebulizer to smoke-exposed mice. In lung tissue (disaggregated) and BAL we investigated leukocyte counts, apoptosis, and the ability of alveolar and tissue macrophages to phagocytose apoptotic murine epithelial cells. In vitro: We applied flow cytometry, ELISA and rtPCR to investigate the effects of MBL on Rac1/2/3 and MASPs in human alveolar macrophages.

Results In vivo: Smoke exposure significantly reduced efferocytosis in BAL and tissue. Efferocytosis was significantly improved by MBL (BAL: control 26.2%, smoke-exposed 17.66%, MBL + smoke-exposed 27.8%; Tissue: control 35.9%, smoke-exposed 21.6%, MBL + smoke-exposed 34.5%). Leukocyte/macrophage counts were normalized in smoke-exposed mice treated with MBL. Human studies: MASPs were not detected in BAL and not produced by alveolar or tissue macrophages. MBL significantly increased expression of Rac1/2/3 in alveolar macrophages.

Conclusion We provide evidence for Rac1/2/3 involvement in the MBL-mediated improvement in efferocytosis and a rationale for investigating MBL as a supplement to existing therapies in smoking-related lung inflammation.

Support NHMRC.
OSTEOPONTIN-DEFICIENT MICE EXHIBIT LESS CIGARETTE-SMOKE-INDUCED ACCUMULATION OF INFLAMMATORY CELL

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Osteopontin (OPN) is abundantly expressed in lung cancer, inflammation and repair. It is a multifunctional cytokine and cell adhesion protein that binds to integrins and CD44 variants on cell surface. As OPN is upregulated in COPD, the aim of this study was to examine the effect of OPN and CD44 deficiency on lung inflammation and long-term cigarette smoke exposure.

Methods OPN−/−, CD44−/− and wild type (WT) C57BL6 mice (n = 6) were exposed to cigarette smoke for 4 weeks (9 cigarettes/day; 5 days/week). Bronchoalveolar lavage fluid (BALF) and lung tissue were collected for inflammation profiling and analysis for cytokines and chemokines expression.

Results WT mice showed significant accumulation of macrophages and neutrophils in lung after 4 weeks smoke exposure as compared to no smoke control (P < 0.001). OPN−/− and CD44−/− mice had significantly lower macrophage and neutrophil counts in BALF (P < 0.05), but similar lymphocytes number as compared to WT after smoke exposure. Paradoxically, OPN deficiency in lung shows up-regulated expression of neutrophil specific chemokine (KC) and monocyte chemoattractant protein-1 that were significantly greater than WT, despite having lower neutrophil and macrophage numbers. Lungs of OPN−/− mice also showed induction of IL-6 gene and protein expression that was not observed in WT. There was no significant difference in the transcriptional profile of pro-inflammatory genes between CD44 and WT.

Conclusions These data indicate that while the OPN-CD44 axis is important for inflammatory cell trafficking it must also activate an unknown negative feedback mechanism that ordinarily constrains pro-inflammatory mediator induction. By inference, local targeting of OPN-CD44 might reduce lung inflammation at the cost of enhanced systemic burden and co-morbidities. Funded by NHMRC.

Conflict of Interest No.

IMPARED MACROPHAGE PHAGOCYTOSIS IN NON-EOSINOPHILIC ASTHMA

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Introduction Patients with non-eosinophilic asthma have increased numbers of neutrophils in the airways. Persistence of airway neutrophils may be due to impaired phagocytosis of apoptotic cells. The aim of this study was to examine macrophage phagocytosis in patients with eosinophilic and non-eosinophilic asthma and compare this with healthy controls and patients with COPD.

Methods Participants with stable asthma and COPD (n = 10 and 7 respectively) and healthy controls (n = 7) underwent a clinical assessment, skin allergy test, hypertonic saline challenge, and sputum induction. Sputum cells were dispersed using dithiothreitol then resuspended in RPMI with 10% FCS. Phagocytosis of apoptotic bronchial epithelial cells by sputum-derived macrophages was determined using flow cytometry.

Results Participants were similar in age, gender and smoking histories. Those with airways disease had a significantly lower FEV1/FVC compared to healthy controls. Phagocytosis was significantly impaired in patients with non-eosinophilic asthma (mean (SD); 11.0% (4.9)) as compared to eosinophilic asthma (20.5% (4.0)) and to a similar degree to participants with COPD (12.2% (2.4)). A negative correlation was observed between the proportion of sputum lymphocytes and macrophage phagocytosis. Sputum neutrophils were significantly higher in patients with COPD compared to healthy controls and eosinophilic asthma but were not different to non-eosinophilic asthma. There was a significant trend towards increased numbers of neutrophils and lymphocytes in patients with COPD.

Conclusion Macrophage phagocytosis is impaired in non-eosinophilic asthma and may explain the persistent airway neutrophilia that characterises this asthma subtype. Supported by NHMRC.

INCREASED BACTERIAL LOAD AND COLONISATION IN COPD

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Introduction Increased airway infection with bacterial pathogens is an important feature of COPD. Ageing is also associated with increased susceptibility to bacterial infection, and colonisation with a variety of normal flora in both COPD and ageing. It is not known if the bacterial colonisation occurs in both COPD and ageing. It is not known if the bacterial colonisation identified in each participant was 4.5 (1.6). There was no difference in the number of species identified in each participant group. Participants with COPD had a non-pathogen load twice that of older healthy controls (5.3 × 105 versus 2.6 × 105, p = 0.036). The mean (SD) number of different organisms identified in each participant was 4.5 (1.8). There was no difference in the number of species identified in each participant group. Participants with COPD had a non-pathogen load twice that of older healthy controls (5.3 × 105 versus 2.6 × 105, p = 0.05). Participants with COPD had significantly more pathogens isolated compared to healthy controls (31%, 7%, 1% p < 0.05). Participants with COPD had a non-pathogen load twice that of older healthy controls (5.3 × 105 versus 2.6 × 105, p = 0.05). Participants with COPD had significantly more pathogens isolated compared to healthy controls (31%, 7%, 1% p < 0.05). Participants with COPD had a non-pathogen load twice that of older healthy controls (5.3 × 105 versus 2.6 × 105, p = 0.05). Participants with COPD had significantly more pathogens isolated compared to healthy controls (31%, 7%, 1% p < 0.05). Participants with COPD had a non-pathogen load twice that of older healthy controls (5.3 × 105 versus 2.6 × 105, p = 0.05).

Conclusion COPD is associated with increased bacterial load that comprises both known pathogens and non-pathogenic species. This suggests that bacterial colonisation in COPD results from a local immune deficit resulting in a reduced ability to clear microflora. Supported by NHMRC.

PEPSIN, A MEASURE OF PULMONARY MICROASPIRATION IN COPD AND BRONCHIECTASIS

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Gastro-oesophageal reflux (GOR) in COPD and bronchiectasis is a potential contributor to lung disease severity. Pepsin in airway samples is a possible non-invasive marker of pulmonary microaspiration. The aim of this study was to determine the presence of pepsin in airway samples in COPD and bronchiectasis and its association with GOR and lung function.

Methods Patients with COPD or bronchiectasis completed dual-probe 24 hr oesophageal pH monitoring, measuring number of reflux episodes (NRE) and reflux index (RI). Lung disease severity was assessed using spirometry. Four samples of sputum and saliva were collected over the 24 hr period, with the concentration of pepsin measured using an ELISA.

Results Thirty patients with bronchiectasis and 27 with COPD were recruited. A total of 36 (23%) sputum samples and 71 (40%) saliva samples were positive for pepsin (concentration > 1.953 ng/ml). NRE and RI were not associated with pepsin in sputum or saliva in COPD or bronchiectasis (all p > 0.05). There was a trend towards lower FEV1, % predicted in those with positive sputum (pepsin present) in COPD (p = 0.08) but not bronchiectasis (p = 0.41). In COPD, patients with positive sputum only (not diagnosed with GOR) had a lower FEV1, % predicted compared to those with GOR only (sputum negative for pepsin) (p = 0.005).

Conclusion Pepsin in airway samples in COPD and bronchiectasis is not reliant on a diagnosis of GOR. Pulmonary microaspiration of GOR may contribute to reduced lung function in COPD.

Support NHMRC, Physiotherapy Research Foundation, Monash University.
PATIENTS MISCLASSIFIED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) HAVE SIGNIFICANT MORBIDITY

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COPD is known to be under-diagnosed in primary care. We had the opportunity to assess misclassification in a study that recruited patients with a diagnosis of COPD.

Methods GPs in 160 Tasmanian practices were invited to participate. 21 respondents carried out practice database searches by: COPD diagnosis and tiotropium use. 168 patients with > 10 smoking PYH completed spirometry testing and questionnaires. COPD was confirmed and classified according to GOLD.

Results 110 (65.5%) met COPD criteria [62M (56.4%), 46 smokers (41.8%), mean age 61], 14 (24%) respectively did not report a COPD diagnosis. Of 58 who did not meet COPD criteria [27M (46.6%), 27 smokers (41.8%), mean age 61], 14 (24%) reported a COPD diagnosis.

Conclusions A high proportion of COPD patients in general practice are misclassified but are nevertheless treated as if having COPD and do have significant respiratory and psychological morbidity.

Supported by NHMRC and ALF/Boehringer Ingelheim COPD Fellowship.

STATINS MAY REDUCE MORBIDITY AND MORTALITY IN COPD PATIENTS

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Statins have anti-inflammatory and immunomodulating properties which could possibly influence inflammatory airways disease. We assessed evidence for disease modifying effects of statin treatment in patients with chronic obstructive pulmonary disease (COPD).

Methods A systematic review was conducted of studies which reported effects of statin treatment in COPD. Data sources searched included MEDLINE and EMBASE (up to October 2008) and reference lists of identified papers.

Results Eight papers reporting nine original studies were eligible. Only one study was a randomized controlled trial. The other studies were analyses of observational data and included one nested case-control study, five historical cohort studies of which one was linked with a case-control study, and one ecological study. Reported outcomes included decreased all-cause mortality, decreased COPD deaths, reduction in incidence of respiratory-related urgent care, reduction of COPD exacerbations and required intubations secondary to COPD exacerbations and attenuated decline in pulmonary function parameters in statin users. The only interventional study reported improvement in exercise capacity and dyspnea after exercise associated with decreased levels of C-reactive protein and Interleukin-6 in statin users, but no improvement of lung function.

Conclusions There is evidence from retrospective studies and one randomized controlled trial that statins may reduce morbidity and/or mortality in COPD patients. Further interventional studies are required to confirm these findings.

Support NHMRC CCRE in Respiratory and Sleep Medicine.

COPD EXACERBATIONS AND THE ‘WEEKEND EFFECT’

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Weekend versus weekday admissions have been associated with poorer health outcomes (the ‘weekend effect’). This phenomenon has only been studied on neonates in Australia. We examined the weekend effect on inhospital deaths of COPD admissions. To compare with overseas research we also studied the weekend effect on myocardial infarction, intracerebral haemorrhage, and acute hip fracture patients.

Methods This was a state-wide retrospective study using administrative data from the Queensland Hospitals Admitted Patient Data Collection. Patients included emergency department admissions to QLD public hospitals during the 2002/03–2006/07 financial years. Outcomes included 30 day in-hospital mortality (primary) and 2 day in-hospital mortality (secondary). Logistic regression was used to adjust for confounders.

Results The total patient cohort was 54,396. There was no weekend effect on 30 day mortality for COPD (adjusted risk ratio [ARR] = 0.92, 95% CI: 0.81–1.04, P = 0.222) or intracerebral haemorrhage (ARR = 1.01, 95% CI: 0.86–1.16, P = 0.935). There was a significant weekend effect for myocardial infarction (ARR = 1.15, 95% CI: 1.03–1.26, P = 0.007). Weekend acute hip fracture admissions trended to lower mortality (ARR = 0.78, 95% CI: 0.54–1.03, P = 0.13), 2 day mortality results were similar.

Conclusions There was no weekend effect for COPD which was consistent with overseas research. Future research should look at the regional variation (tertiary versus non-tertiary) of outcomes of weekend versus weekday COPD admissions.

Supported by the University of Queensland School of Medicine.

Conflict of Interest No.
Results

The audit examined the records of all inpatients during 2007 with the ICD10 discharge code J 44 (AECOPD) to establish suitability for inclusion in HITH. Patients were not suitable if they were geographically isolated, lived alone, had a pH < 7.35 or presented with more than one acute medical problem. Cost analysis compared the inpatient management costs with the projected costs of establishing a HITH program. The audit examined the records of all inpatients during 2007 with the ICD10 discharge code J 44 (AECOPD) to establish suitability for inclusion in HITH. Patients were not suitable if they were geographically isolated, lived alone, had a pH < 7.35 or presented with more than one acute medical problem. Cost analysis compared the inpatient management costs with the projected costs of establishing a HITH program.

Methods

The audit examined the records of all inpatients during 2007 with the ICD10 discharge code J 44 (AECOPD) to establish suitability for inclusion in HITH. Patients were not suitable if they were geographically isolated, lived alone, had a pH < 7.35 or presented with more than one acute medical problem. Cost analysis compared the inpatient management costs with the projected costs of establishing a HITH program.

Aims

To audit inpatient admissions for AECOPD to the Royal Hobart Hospital for 2007, establish the proportion of patients that would have been suitable for HITH management and to estimate the cost effectiveness of establishing a HITH program.

Results

418 inpatient episodes were coded as AECOPD. 281 (67%) had no other acute medical problems. Of these 281 episodes, 119 (42%) presented after hours (6 pm to 8 am) and 22 were geographically isolated, leaving 56 (20%) suitable for inclusion in a HITH program. The average length of stay for these patients was 5.75 days, estimated to cost $270,000.

The HITH program would cost approximately $80,000 to establish and run for the first 12 months.

Conclusions

Approximately 20% of admissions for AECOPD would be suitable for HITH management. HITH for AECOPD in Southern Tasmania would be cost effective and relieve pressure for inpatient beds.

Supported by the Australian Institute of Health and Welfare.

Conflict of Interest

Nil.

TRENDS IN COPD DISABILITY, MORBIDITY AND MORTALITY IN AUSTRALIA

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Chronic obstructive pulmonary disease (COPD) is a prominent contributor to the burden of disease in Australia, in terms of disability, morbidity and mortality. It was the underlying cause of 4,761 deaths, or 4% of all deaths, in Australia in 2006. There were 52,560 hospital separations with COPD as the principal diagnosis in 2006–07. Following trends in COPD morbidity and mortality allows insights into the factors that are contributing to its burden.

Methods

Prevalence, hospitalisation, disability and mortality data were extracted from various national administrative and non-administrative collections. While disease prevalence and disability estimates were obtained from the ABS health surveys (National Health Surveys and Surveys of Disability, Ageing and Care), morbidity and mortality data were extracted from the National Hospital Morbidity Database and National Mortality Database, respectively. Time series were plotted to study underlying trends in various epidemiological aspects.

Results

The burden of COPD may be on the decline in Australia. The hospital separations for COPD are declining. Mortality among males has been declining since 1970 and the peak in female mortality was reached in 1996. Declines in smoking rates have probably been the major contributors to this downward trend. The disability associated with COPD however has shown no marked changes over the last two decades.

Conclusions

Considerable declines in mortality but limited declines in associated disability raise interesting issues as to the impact of COPD on the burden of disease in Australia.

Supported by the Australian Institute of Health and Welfare.
NON-PLEURITIC CHEST PAIN IN EXACERBATIONS OF BRONCHIECTASIS

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Background and Objective Chest pain has been described as occurring in the context of bronchiectasis but has not been well characterized. This study was performed to describe the characteristics of chest pain in adult bronchiectasis and to define the relationship of this pain to exacerbations.

Methods One hundred and fifty-three patients with bronchiectasis were interviewed by one of the investigators and asked about the presence of chest pain over the past year.

Results Sixty one (40%) described respiratory chest pain over this period and in the majority of cases 54/81 (66%) occurred with an exacerbation and two distinct types of chest pain could be described, pleuritic (n = 5) and non-pleuritic (n = 52) with 3 subjects describing both forms. The non-pleuritic chest pain occurred most commonly over both lower lobes, was mild to moderate in severity and came on as an early symptom in an exacerbation. The pain subsided as patients recovered.

Conclusion Awareness of this symptom of non-pleuritic chest pain may be useful in facilitating early diagnosis of bronchiectasis exacerbations.

COMMUNICATION WITH GENERAL PRACTITIONERS (GP) ENHANCES THE MANAGEMENT OF EXACERBATIONS IN PEOPLE WITH COPD

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Action plans are recommended in the management of acute exacerbations of COPD (AECOPD) but the usage rates of action plans in people with COPD is low according to a retrospective study conducted in 2007. This was a follow up study and the aim was to investigate the usage rates of action plans after implementing strategies in the pulmonary rehabilitation program at CRGH.

Methods In addition to self-management education, each rehabilitation attendant was given a letter addressed to their GP with a blank action plan. The letter included a description of the COPD program, suggested management of AECOPD based on the COPD-X guidelines and the contact details of the COPD nurse for additional support. Furthermore, each attendant received a follow-up phone call four weeks after the education session to review the response from the GP and reinforce the importance of early intervention at the onset of AECOPD. People were excluded if they lived in an aged care facility or were unable to follow instructions in English.

Results Consecutive rehabilitation attendants were interviewed and the results were compared to the study conducted in 2007. 54 people (54 males) were interviewed, 32% of the participants had a completed action plan in place compared to 22% in the last study. 70% of participants (including those without an action plan) had prescriptions for prednisone and antibiotics for early intervention in AECOPD compared to 60% in the last study. For those who did not have an action plan and/or prescriptions, the majority (81%) were advised to contact the GP at the onset of AECOPD.

Discussion Even though the usage rate of the action plan remains relatively low, it has increased through written communication to the GP. Furthermore, the percentage of people with prescriptions for early intervention in AECOPD has also increased. This improvement is vital as early detection and prompt intervention reduce the severity and recovery time of the exacerbation.

MENTORING BY COMMUNITY NURSES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) DECREASES MORTALITY

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1Leung R, Spencer L and Greer T. Respirology (2008) 13 (supple 2); A14.

COPD is a leading cause of mortality and morbidity, and a frequent cause of hospitalisation. Whether comprehensive programmes for patients with COPD alter outcomes remains unclear. We enrolled participants hospitalised with acute exacerbations into a controlled trial of mentoring by community health nurses to improve self-efficacy.

Aim To reduce healthcare use and increase quality of life (HRQOL).

Methods Admissions to the Royal Hobart Hospital were allocated to according to domicile, matched for rurality and socio-economic status. Outcomes, included healthcare utilisation and HRQOL (SF-36), measured 3-monthly for one year.

Results Of 319 admissions, 105 (33%) were excluded and 63 (20%) declined participation, leaving 55 in the intervention (I) and 51 in the control (C) group. Mean age was 69.1 years, and duration of COPD 9.5 years. There were significantly more deaths in the control (n = 11; 21.6%) than intervention (n = 4; 7.3%) group (p = 0.009). There were more hospital admissions in the year following compared to preceding entry (C = 38 vs 107, I = 52 vs 110), but no significant difference between groups. HRQOL changes varied between sub-scales, with no significant difference between interventions.

Conclusions Mentoring by community health nurses reduced mortality but did not significantly change healthcare resource use or HRQOL.

Support Department of Health & Human Services, Tasmania.

REMOTE MONITORING IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) DOES NOT REDUCE HOSPITAL ADMISSIONS OR IMPROVE QUALITY OF LIFE WHEN COMPARED TO STANDARD BEST PRACTICE CARE

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Remote in-home monitoring (RM) of physiological and symptom-related variables may allow early detection and treatment of exacerbations in patients with COPD. It is unclear whether RM improves patient outcomes or reduces healthcare resource utilisation.

Aim To determine whether RM in moderate-severe COPD reduces hospital admissions and length of stay (LOS) or improves quality of life (QOL) (SF-36, Chronic Respiratory Disease Questionnaire-CRQ).

Methods Forty-four patients having at least one hospital admission in the previous 12 months were randomised to standard best practice care (SBP) (n = 22) or SBP+RM (n = 22). SBP included clinical management according to COPD-X guidelines with availability of pulmonary rehabilitation and provision of outreach nursing. RM involved daily measurement of spirometry, inspiratory capacity, weight, temperature, blood pressure, oximetry, ECG, sputum colour and volume, symptoms and medication usage. RM data were reviewed five days weekly to determine need for intervention.

Results There were no differences (mean ± SD, SBP vs. SBP+RM) in age (68 ± 8 vs. 70 ± 9), gender (M/F: 10/12 both groups) or previous computer-familiarity (59% vs. 50%) between groups. The SBP group had a lower FEV1 (0.66 ± 0.24 vs. 0.91 ± 0.34, p < 0.01). There were no differences in number of COPD-related admissions/year (1.5 ± 1.8 vs. 1.3 ± 1.7, p = 0.76), COPD-related LOS days/year (15.6 ± 19.4 vs. 11.4 ± 19.6, p = 0.66), total admissions/ year (2.2 ± 5.1 vs. 2.0 ± 2.3, p = 0.86), total LOS days/year (22.1 ± 29.9 vs. 21.6 ± 30.4, p = 0.88) or QOL between the two groups.

Conclusion The addition of RM to SBP did not reduce healthcare utilization or improve quality of life in this group of patients already receiving regular nursing outreach.

Supported by Department of Human Services (Vic).
TP 094

HIGH-ACUITY RESPIRATORY PATIENTS CAN BE SAFELY MANAGED IN A HIGH DEPENDENCY SETTING OUTSIDE OF THE ICU

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The Princess Alexandra Hospital Respiratory High Dependency Unit (RHDU) was established in 2001 and consists of four allocated, monitored beds within the Respiratory ward. The purpose of the RHDU is to provide specialised medical and nursing care for patients with acute or chronic, complex respiratory conditions.

Methods
Prospective data audit of admissions to the RHDU between 1 October 2007 and 30 September 2008.

Results
226 patients (120 male) were admitted, median age 67 (18–89). Indications for admission included COPD (101), sleep disordered breathing (65), pneumonia (44), asthma (35) and lung malignancy (18). 69% of patients had respiratory failure (16% Type 1, 53% Type 2). 128 patients were treated with non invasive ventilation (NIV), which was successful in 88% of cases.

Conclusions
Two to five year survival is poor in patients with COPD after the first exacerbation with type II respiratory failure requiring the use of NIV. Survivors have high risk of readmissions and subsequent NIV use. Supported by Department of Respiratory Medicine, Royal Perth Hospital.

Nomination: No Conflict of Interest Nil.

TP 095

SELECTED PATIENTS WITH RESPIRATORY FAILURE CAN BE SUCCESSFULLY MANAGED IN A WARD-BASED RESPIRATORY HIGH DEPENDENCY UNIT (RHDU)

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The Respiratory High Dependency Unit at Princess Alexandra Hospital consists of four beds within the Respiratory Ward with facilities for respiratory monitoring and non-invasive ventilation (NIV). It provides specialised medical and nursing care to patients with significant respiratory illness. This study assessed the characteristics and outcomes of patients admitted to RHDU with respiratory failure.

Methods
Prospective data audit of patients with respiratory failure (RF) admitted to the RHDU between 1 October 2007 and 30 September 2008.

Results
158 patients (83 male) with RF were admitted, median age 68 (18–88). Average length of stay was 5.1 days. 64 patients were not considered suitable for ICU admission. 130 patients had type 2 respiratory failure (T2RF). 52 acute, 71 acute on chronic, 7 chronic. pH in patients with acute T2RF was (mean ± SD) 7.28 ± 0.09. Mean FEV1 was 0.93 ± 0.4L. Main diagnoses included pneumonia (8), COPD (6), asthma (4) and lung cancer (4). 119 patients received NIV. Mean duration of NIV was 2.4 ± 1.9 days in T1RF and 5.82 ± 5 days in T2RF patients. NIV was successful in 93% of T2RF patients, but only 3/9 patients with T1RF. 8 patients required transfer to ICU (5 T1RF), HDU and in-hospital mortality were 14.3% and 21.4% respectively in T1RF, and 6.9% and 11.5% in T2RF.

Conclusions
Patients with RF can be successfully managed in a ward-based RHDU. Despite the fact that many had very poor lung function and significant co-morbidity and were not considered candidates for ICU, the vast majority survived. Response to NIV was better and mortality was lower in T2RF vs. T1RF.

TP 096

VARIABILITY IN THE RATE OF PRESCRIPTION AND COST OF DOMICILIARY OXYGEN THERAPY IN AUSTRALIA

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Domiciliary oxygen therapy (DOT) provides mortality & morbidity benefits for some patient groups with hypoxaemia but it is expensive. Service provision is reported to vary between jurisdictions but the extent and impact of this variability is unclear.

Aims
To determine the rate of prescription and government expenditure for domiciliary oxygen therapy (DOT) in Australia and to identify interstate differences in rates, costs and service provision.

Methods
Retrospective observational study of government departments and health services (state and federal) that funded domiciliary oxygen therapy in Australia in 2005 (includes Department of Veterans Affairs and Department of Human Services [Aging].

Results
In 2005, 20,127 patients were using DOT (national prevalence of 100 per 100,000 of population) at a total cost of approximately $31 million. State health departments, DVA and DoHA fund 69% (13899), 20% (4084) and 11% (2144) respectively. Prescription rates varied three fold between states ranging from 133 (Tasmania) to 44 (Northern Territory) per 100,000 of population and cost per patient year varied four fold between DVA and DoHA. All jurisdictions funded oxygen according to clinical criteria based on the TSANZ Position Statement, however considerable variability in service provision was identified.

Conclusion
DOT prescription rates and costs varied considerably between jurisdictions. Australia urgently requires a national DOT register to enable the current variability to be understood and to enable service planning and benchmarking of clinical outcomes interstate and internationally. Project funded by the Medical Aids Subsidy Scheme.
INTRANASAL SESAME OIL (NOZOIL™) REDUCES NASAL SYMPTOMS DUE TO OXYGEN THERAPY

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Introduction Use of supplemental oxygen therapy is often associated with nasal symptoms particularly in the acute setting. This study examines the effectiveness of Nozoil™ in alleviation of nasal symptoms due to oxygen therapy.

Methods This is a single-blinded placebo-controlled randomized control trial of patients admitted to hospital with respiratory illness requiring oxygen therapy (for at least 12 hours per day). Allocation was to Nozoil™ or placebo (isotonic saline). Primary endpoint is change in nasal symptoms (dryness, irritation, stuffiness and crusting) as measured by a daily visual analogue scale (0 to 10). Symptom scores were compared on an intention to treat basis using student’s t-test.

Results 36 patients with mean age 69 (± SD11.7) years. Mean length on the trial was 6 (± 2.5) days. There was a significant improvement in mean nasal symptom score at Day 2 and 4 (compared to Baseline) for all measured parameters with Nozoil™. The placebo arm had improved symptoms of stuffiness on Day 4, but this was not reflected in other parameters. There was a non-statistically significant trend for baseline score to be higher with Nozoil™ which was not seen at Day 4.

| Symptom | Baseline (Mean) | Day 4 (Mean) |
|---------|----------------|--------------|
| Nozoil™ | Placebo | Nozoil™ | Placebo | p | p |
| Dryness | 4.95 ± 1.13 | 3.78 ± 1.48 | 2.23 ± 0.93 | <0.05 | 2.57 ± 0.91 | 0.13 |
| Irritation | 5.09 ± 0.99 | 4.21 ± 1.37 | 2.95 ± 1.14 | <0.05 | 2.92 ± 1.55 | 0.11 |
| Stuffiness | 5.19 ± 1.34 | 3.64 ± 1.59 | 2.09 ± 0.98 | <0.05 | 2.46 ± 1.13 | 0.04 |
| Crusting | 5.43 ± 1.42 | 4.14 ± 1.50 | 2.40 ± 1.12 | <0.05 | 3.03 ± 1.41 | 0.48 |

Conclusion Nozoil™ improves nasal symptoms due to oxygen therapy. This effect was not replicated with placebo. Recruitment is ongoing.

MAXIMAL TREADMILL AND CYCLE EXERCISE TESTS IN PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Cycle and walking tests are used to measure exercise capacity in people with COPD. Performance may be limited by dyspnoea and/or leg fatigue, and oxygen saturation (SpO2) may decrease. However, cycling and walking differ in terms of the muscle mass involved.

Aim To investigate the ventilatory, metabolic and symptom responses to maximal cycling and supported treadmill walking tests in subjects with COPD.

Methods 14 subjects (3 females) aged 67.1 ± 8.1 yrs with moderate or severe COPD (FEV1 41 ± 13.4% pred) exercised to a symptom-limited maximum during incremental treadmill and cycle ergometry tests. Dyspnoea, heart rate, SpO2 and breath-by-breath metabolic and ventilatory variables were collected (Metamax 3B, Cortex Ltd). Blood lactate concentration and inspiratory capacity (IC) were measured before and after each test.

Results Table shows peak values and change in IC (mean ± SD):

| Test | Dyspnoea (Borg score/10) | SpO2 (%) | Oxygen uptake (L/min) | Blood lactate (mmol/L) | Δ IC (ml) |
|------|--------------------------|----------|-----------------------|------------------------|-----------|
| Treadmill | 5.5 ± 1.7 | 85.5 ± 5.1 | 1.51 ± 0.6 | 2.9 ± 1.1 | 567 ± 189 |
| Cycle | 4.4 ± 1.1 | 88.9 ± 5.0 | 1.37 ± 0.6 | 4.7 ± 1.4 | 548 ± 146 |

Discussion and Conclusion A smaller muscle mass is recruited when cycling compared to walking and this is likely to explain the higher blood lactate and lower oxygen uptake recorded at the end of the cycle test. The lack of significant difference in the magnitude of change in IC indicates that development of dynamic hyperinflation is likely to have been similar with both exercise modalities. Testing exercise capacity on a cycle may underestimate the extent of oxygen desaturation occurring in COPD subjects during activities of daily living that include walking.

THE POSITIONAL ACTIVITY LOGGER 2 IS A VALID MEASURE OF PHYSICAL ACTIVITY IN INDIVIDUALS WITH COPD

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Regular physical activity is a vital aspect of managing chronic obstructive pulmonary disease (COPD) yet few valid quantitative measures exist. This study investigated the validity of the Positional Activity Logger 2 (PAL2) – a small accelerometer-based device which provides highly configurable quantitative data of physical activity duration, intensity and body position.

Method Ten subjects (age range 56–78 years) with COPD (GOLD II-IV) completed a one-hour physical activity protocol with simultaneous recording via the PAL2 and video. Filmed activity and posture duration was calculated via digital chronometer by a blinded observer. Time spent upright, non-upright and moving was compared between the PAL2 and video using Bland and Altman plots. To test the feasibility of home-based physical activity monitoring, participants also wore the PAL2 and completed an activity diary for 12 hours the following day at home.

Results Bland and Altman plots revealed high agreement between the PAL2 and video. For moving tasks, the mean difference was small (1.82 mins) and limits of agreement were narrow (± 1.39 mins). The PAL2 mildly overestimated physical activity compared to video and diary. Most subjects (70%) returned complete data sets from the 12-hour period.

Conclusion The PAL2 is a valid measure of physical activity in individuals with COPD and can be self-applied in the home setting.
THE RELATIONSHIP BETWEEN THE PHYSICAL ACTIVITY LEVEL SIX MINUTE WALK DISTANCE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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The six minute walk distance (6MWD) is a widely accepted outcome measure of pulmonary rehabilitation (PR). Recent advances in actigraphy have led to a renewed interest in the estimation of Physical Activity Level (PAL), particularly as an outcome measure of PR. However, it remains to be seen if there is a relationship between 6MWD (as an estimate of physical capacity) and the daily PAL. While the 6MWD and PAL are separate independent measures it could be argued that individuals with a greater 6MWD (and potentially a greater capacity for exercise) would have a greater daily level of physical activity. Hence the aim of this study was to examine the relationship between 6MWD and PAL in COPD patients prior to undertaking PR.

Methods Twenty eight COPD patients (67.5 ± 8.0 yr; FEV1/FVC = 63 ± 21%) undertook two six minute walk tests according to ATS guidelines, PAL was then estimated using a multi-sensor device (SenseWear, Healthcare Bodymedia) worn for a 7 day period. An index of PAL was derived by dividing total daily energy expenditure in metabolic equivalents (METS) by whole night sleeping energy expenditure (average of 3 nights sleeping). A PAL of 1.70 was defined as being active. Relationships between data were analysed using correlation coefficients.

Results The mean 6MWD for the group was 436 ± 69 m while the mean PAL was 1.54 ± 0.18. On average the group spent 5.04 ± 1.27 hours per day when they were classified as being active (i.e. PAL > 1.70). We found no significant relationship between 6MWD and PAL (r = 0.2, P = 0.26) or 6MWD and time spent with PAL > 1.70 (r = 0.18, P = 0.33).

Conclusion These data suggest that while individuals with a greater 6MWD may have a greater capacity to perform exercise, this does not necessarily translate into a greater PAL per se prior to undertaking PR.

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Correlation between 6MWD and PAL in COPD patients prior to undertaking PR. The magnitude of change was similar in males and females (Table, mean, 95% CIs):

| Variable | Males (n = 117) | Females (n = 69) | p-value |
|----------|----------------|----------------|---------|
| 6MWD (m) | 44 (35, 53) | 43 (31, 55) | 0.9 |
| CRDQ Dyspnoea | 0.9 (0.7, 1.1) | 1.1 (0.8, 1.3) | 0.2 |
| CRDQ Emotional function | 0.5 (0.3, 0.6) | 0.6 (0.4, 0.8) | 0.3 |
| CRDQ Fatigue | 0.9 (0.7, 1.1) | 1.0 (0.7, 1.3) | 0.6 |
| CRDQ Mastery | 0.8 (0.5, 1.0) | 0.9 (0.7, 1.1) | 0.4 |

Conclusions Females were referred to PR earlier in their disease process. Gender does not appear to influence outcomes to a short-term PR program.

QUALITATIVE STUDY OF SUPERVISED EXERCISE WITH THE CHRONIC DISEASE SELF-MANAGEMENT PROGRAMME (CDSMP)

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Supervised exercise is recommended as part of pulmonary rehabilitation, but the CDSMP, used in a metropolitan tertiary hospital, has no supervised exercise. The experience of supervised exercise with the CDSMP was explored as part of a randomised controlled trial using mixed methods. Qualitative data are reported.

Methods Qualitative data were collected by semi-structured interviews with a purposeful sample following the CDSMP with or without supervised exercise (CDSMP ± Exercise). Data were subjected to thematic analysis.

Results Of 84 participants, 14 men and 6 women were interviewed over 2 years about their experiences of COPD, the CDSMP and supervised exercise. Major findings were: 1) The meaning of COPD was described in terms of CRDQ Dyspnoea 0.5 (0.3, 0.6) 0.6 (0.4, 0.8) 0.3

CRDQ Emotional function 0.9 (0.7, 1.1) 1.0 (0.7, 1.3) 0.6

CRDQ Mastery 0.8 (0.5, 1.0) 0.9 (0.7, 1.1) 0.4

Conclusions Females were referred to PR earlier in their disease process. Gender does not appear to influence outcomes to a short-term PR program.

Cystic Fibrosis SIG

BACTERIAL DENSITY INFLUENCES PSEUDOMONAS SEROLOGY IN PRESCHOOL CHILDREN AND INFANTS WITH CYSTIC FIBROSIS

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Effective eradication of Pseudomonas aeruginosa (Psa) in young children is dependent on accurate and early detection of infection. The value of serology as a marker of early respiratory infection with Psa remains uncertain in young children. We aimed to assess antibodies formed against different Psa antigens as markers of early/intial Psa infection. Serum IgG levels to multiple Psa antigens were determined using a commercially available ELISA, while those for Psa exotoxin A were determined using a custom in-house assay. Bronchoalveolar lavage (BAL) was performed and fluid cultured to provide evidence of Psa infection. Antibody levels were determined in blood collected at the same time in a discovery population (AREST CF) to determine optimal cut-off levels, which were then applied in a blinded fashion to a test population (ACFBAL). These antibody titres were then compared with varying bacterial density cut-off levels. Sensitivity of both assays improved with higher bacterial density while specificity remained unchanged. The exotoxin A assay was more sensitive than the commercial multiple antigen assay, especially at lower bacterial densities, with sensitivities of 0.92 and 0.69, respectively at a bacterial density of > 1,000 cfu/ml. These data suggest that exotoxin A serology may be more suitable to detecting early respiratory infection with Psa that the commercially-available multiple antigen assay.

Supported by Australian Cystic Fibrosis Research Trust.

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OUTCOMES OF HEALTH-MENTOR TRAINING TO IMPROVE SELF-MANAGEMENT BY PEOPLE WITH CYSTIC FIBROSIS (CF)

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The beneficial role of ‘mentors’ in chronic disease management is becoming increasingly recognised. As group support is difficult for people with CF, training was evaluated for telephone-delivered self-management support augmenting information technology (IT) tools for this group.

Methods Volunteer health professionals undertook 12 hours of training addressing CF, health-mentoring, and IT tools, a database and a mobile phone programme with symptom-monitoring through daily text messages. Health-mentoring was incorporated into daily workloads over six months. Understanding of mentoring, self-management, self-efficacy, goal setting, action planning and mentoring self-efficacy were measured pre/post training on a five-point Likert scale by self-administered questionnaires. Qualitative data were collected by self-report.

Results 29 of 34 mentors completed mentor training. Pre/post training there were significant improvements in understanding of mentoring (p < 0.001), self-management (p = 0.002), self-efficacy (p < 0.001), action planning (p = 0.001) and mentoring self-efficacy (p = 0.006). Training met the needs of 78.6% (22/29). At focus groups, mentors reported translating skills learned to other work areas. Transition from face-to-face contact to telephone-mentoring was challenging for some.

Implications Health-mentor training meets the needs of trainees and can alter health professionals’ understanding and practices.

Conflict of Interest Nil.

Support Australian Cystic Fibrosis Research Trust and ‘Pathways Home’ Commonwealth Government grant.

INCREASED IN VIVO SENSITIVITY FOR TRANSGENE EXPRESSION IN MURINE NASAL AND LUNG AIRWAYS USING LUCIFERASE IMAGING

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Noninvasive bioluminescence imaging has allowed for rapid in vivo quantification of long-lasting gene transfer in experimental animals. Luminescence assays can be performed repeatedly on the same individual throughout its lifetime. We are testing the longevity of a single nasal delivery of our lentiviral (LV) gene transfer system in mouse airways.

Methods C57Bl/6 mice were instilled nasally using our standard lysophosphatidylcholine (LPC) or a control (PBS) pretreatment one hour prior to delivery of an LV vector containing the reporter-gene luciferase. Imaging to detect luminescence was via the IVIS system (Xenogen) 10 minutes after an intranasal bolus of the substrate D-luciferin, at 1 week, 1 & 3 months post LV.

Results LPC pretreated LV gene transfer resulted in significantly greater gene transfer compared to PBS pretreatment at all time points (p < 0.05, ANOVA). Unexpectedly, luciferase activity was also detected in the lung in both groups of mice. A statistically significant reduction occurred in nasal and lung luminescence at the 3 month time point (p < 0.05, RM ANOVA).

Conclusions Lentiviral luciferase gene expression persisted for at least 3 months after a single dose. Since luciferase gene expression could be observed in both the primary target organ (nasal airway) and in the lung; and since we have not seen LacZ gene expression in lung using this dose volume, the luciferase reporter gene appears to offer higher sensitivity than provided by reporter genes whose presence relies on histochemical detection. Supported by the NH&MRC.

THE ROLE OF RHINOVIRUS IN THE INFLAMMATORY RESPONSES OF HEALTHY AND CYSTIC FIBROSIS AIRWAY EPITHELIAL CELLS

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Introduction Cystic Fibrosis (CF) lungs are essentially normal at birth and prior to bacterial colonization are more prone to respiratory viral infections (VRIs). Rhinovirus (RV) is the most common type of VRI to target the airway epithelium and could potentially trigger inflammatory responses in CF patients. The aim of this study was to investigate the responses of airway epithelial cells (AECS) to major (RV14) and minor (RV1b) RV serotypes in an in vitro and ex vivo model of healthy and CF epithelium.

Methods In vitro healthy (16HBE14o-) and CF (CFBE41o) AEC lines were established in culture while ex vivo primary AECS were collected from healthy non-atopic (pAECnon) and CF (pAECCF) patients < 3 years of age. Cells were exposed to various titres of RV14 and RV1b (MOI: 3-100 viral particles/cell) over 72 hours. After exposure, levels of cell cytotoxicity and inflammatory cytokine release were measured by MTS assay and ELISA/TRF assays.

Results The cell lines did not exhibit any cytotoxic effect over 72 hours at any MOI, but a greater time and MOI-dependent effect was observed in pAEC non when compared to pAEC CF cells. In addition, RV14 was shown to induce the production of IL-8 and IL-6 in both 16HBE14o- and CFBE41o- (p ≤ 0.05). In contrast, exposure to RV1b led to greater cytotoxicity and marked productions of IL-8 and IL-6 in pAECS compared to RV14. Overall, IL-8 and IL-6 responses in pAECS were found to be greater than those measured in cell line models (p ≤ 0.05).

Conclusions There may be fundamental differences in cellular mechanisms that exist between transformed immortalized cell lines and pAECS in response to viral exposure which prime pAECS to be more susceptible to early inflammation. Therefore, cell lines and pAECS may have RV serotype-specific responses, emphasizing the importance of using pAECS in examining inflammatory responses associated with CF exacerbations.

THE FORCED OSCILLATION TECHNIQUE IS NOT ASSOCIATED WITH SPIROMETRY IN SIX YEAR OLDS WITH CYSTIC FIBROSIS

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Introduction The forced oscillation technique (FOT) can be used from an early age to track lung function in young children. Spirometry is the conventional method of lung function in children, although young children find it difficult to perform. Spirometry may not be sensitive to changes in the peripheral lung where lung damage begins.

Aim The aim of this study was to determine if there were any associations between lung function using spirometry and the FOT in children with cystic fibrosis (CF), and if lung function using FOT at 4 and 5 years was predictive of spirometry at age 6.

Methods Lung function using FOT was measured 21 children with CF at the time of their annual bronchoalveolar lavage (BAL) assessment. Spirometry was measured within four months of FOT (15 ± 64 days).

Results The 21 children (6.21 ± 0.66 years) had normal Z scores for FEV1, FVC and FEF25–75. z score Rrs8 was abnormal (p < 0.02), while xrs8 was = 0.02), RM ANOVA. Unexpectedly, luciferase activity was also detected in the lung in both groups of mice. A statistically significant reduction occurred in nasal and lung luminescence at the 3 month time point (p < 0.05, RM ANOVA).

Conclusions Lentiviral luciferase gene expression persisted for at least 3 months after a single dose. Since luciferase gene expression could be observed in both the primary target organ (nasal airway) and in the lung; and since we have not seen LacZ gene expression in lung using this dose volume, the luciferase reporter gene appears to offer higher sensitivity than provided by reporter genes whose presence relies on histochemical detection. Supported by the NH&MRC.
RESPIRATORY BURST RESPONSE OF CIRCULATING GRANULOCYTES ARE ELEVATED IN CYSTIC FIBROSIS

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Whether inflammation observed in CF arises in the absence of infection is still a matter of debate, though it is certain that episodes of infection do exacerbate inflammation. Ascertainment leukocyte function in early-life CF as part of a comprehensive pulmonary assessment should provide further insights into inflammation progression. Therefore, we investigated respiratory burst responses of circulating granulocytes in children enrolled in the ARESTCF early-surveillance program.

Methods Whole blood (WB) from 42 children with CF (10 w–8 y) at time of annual bronchoalveolar lavage (BAL) and 13 healthy children as control (1 y–7 y). WB was stimulated ex vivo by either opsonised E. coli or PMA respectively; substrate fluorescence in leukocytes was assessed by flow cytometry. BAL also provided inflammation, cytokly and microbiological assessment and low-dose HRCT were assessed for bronchiectasis, bronchial wall thickening and gas trapping.

Results CF, but not control, granulocyte response to PMA decreased with age (p < 0.05). Unstimulated cells exhibited identical activity (MFI 59) between groups, whilst mean CF response was significantly higher to both opsonised E. coli (221 vs 164, p = 0.05) and PMA stimulation (607 vs 370, p < 0.005), even in the absence of current or past infection. Unstimulated activity, adjusted for age, was associated with bronchial wall thickening score (β = 0.04 MFI (0.02 SE, p < 0.05)).

Conclusion Elevated response levels of peripheral blood granulocytes in children with CF, regardless of infection, suggests neutrophils may react excessively to low level stimulation in the lung.

CITRATE EXERTS COMPLEX EFFECTS ON THE HUMAN AIRWAY

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Introduction Ion transport is an important mechanism to maintain the airway epithelium. The importance of correct ion transport can be seen by the disease Cystic Fibrosis which is characterised by decreased Cl− secretion and increased Na+ absorption. These abnormalities can be demonstrated in vivo using the nasal potential difference (NPD) technique. We have previously shown that the CF airway can develop small Cl− responses when the surface is nominally Ca2+ free (Middleton et al AJRCCM 2003; 168: 1223–1226). Further studies in 4 clinically relevant Ca2+ chelators (citrate, oxalate, EGTA, EDTA) showed that only citrate exerted significant effects. This abstract examines the effects of citrate on the airway epithelium.

Methods NPD was measured using standard techniques (Middleton et al ERU 1994; 7: 2050–2056) in 6 non-CF subjects. The effect of citrate (10 mM) on NPD was measured without pretreatment, and in the presence of amiloride to block Na+ channels, and amiloride/low Cl− solution which augments Cl− secretion.

Results Citrate decreased the basal NPD by ∼2 mV, which may reflect decreased Na+ absorption or decreased Cl− secretion. However in the presence of amiloride, citrate now increased the PD by ∼2 mV. With amiloride/low Cl− pretreatment, citrate increased the NPD by 5 mV, which would suggest that citrate increased Cl− secretion.

Conclusion The combination of these responses suggests that citrate exerts complex effects on airway ion transport. This may entail dual effects – decreased Na+ absorption and increased Cl− secretion. Other putative transport mechanisms, such as the Na+-dicarboxyl transporters are currently being investigated. Supported by the National Health & Medical Research Council (NH&MRC), and Cystic Fibrosis Australia. Conflict of Interest No.
IMPROVING SELF-EFFICACY IN ADOLESCENTS AND YOUNG ADULTS WITH CYSTIC FIBROSIS

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Introduction Life expectancy has improved in patients with Cystic Fibrosis (CF), however gains made in childhood may be lost during adolescence because of reduced adherence to treatment regimes. Encouraging patients with a chronic disease to take a more active role in managing their own condition may be effective. The mentorship system seeks to facilitate self-management and decision making. Interventions of this type may prove effective during the transition period from childhood to adulthood in young people with CF. This project aims to develop relationships between patients with CF and health professionals, through a system of mentorship, to improve quality of life and to examine the use of information technology (IT) tools to assist with the development of self-efficacy.

Methods A randomized, controlled pilot study of a program of education and behavioural adaptation in adolescents with CF designed to enhance self-management. 46 Queensland adolescents aged 12 – 19 years, were recruited. Participants were randomised to one of three groups each for 6 months with a further 6 months follow up: standard care (controls; N = 15), standard care + phone mentoring (M; N = 16), or standard care, phone mentoring + IT tool (M + IT; N = 15) which facilitated electronic self reporting of daily symptoms. Primary outcomes included the Stanford Self-Efficacy scale and CFQ-R. Secondary outcomes were spirometry and height and weight z-scores. Outcomes were to be re-assessed at 3, 6, & 12 months following the initial assessment. Qualitative data were also collected from 10 intervention participants and mentor.

Results Preliminary analysis of 27 patients was undertaken. No clinically meaningful improvements were detected between groups.

Conclusions The trial provided an important opportunity for mentor training and refinement of IT tools, but did not produce short-term improvements in these particular outcomes for adolescents measured using these methods.

Supported by CF Australia, & RCH Foundation, Brisbane.

No conflict.

ΔF508 CFTR FUNCTION CAN BE EFFICIENTLY RETORE IN PRIMARY CYSTIC FIBROSIS AIRWAY EPITHELIAL CELLS (AEC)

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Cystic fibrosis (CF) is caused by mutation(s) in the CF transmembrane conductance regulator, with the most common mutation being ΔF508. Studies to date have examined ways to restore expression of ΔF508 CFTR utilizing different methods. Although many of these studies have been conducted in cell lines, very few have examined correction of ΔF508 CFTR function in primary CF cells. The aim of this study was to investigate whether functional activation of the ΔF508 CFTR could be efficiently assessed in primary CF AECs.

Methods AECs were obtained from CF patients by non-bronchoscopic brushing. ΔF508 CFTR activation was examined by adopting the YFP halide reporter assay (Gailletta et al, 2001, AJPCP;281). Cells were overexpressed with yellow fluorescent protein (YFP) adenosine and transduced with shRNA either against STx-8 or BCAP31, in order to knockdown mRNA and/or protein expression of syntaxin-9 (STx-8) or STx-8 B-cell receptor associated protein – 31 (BCAP31). These two molecules are co-chaperones involved in the transport of CFTR to the cell surface. AEC were pre-incubated with 100 μM genistein and 10 μM forskolin, then injected with iodide and YFP signal examined over 12 seconds. Correction of ΔF508 CFTR was determined by quenching of YFP signal.

Results CF AECs were successfully transduced with YFP at ≥80% efficiency and low cytotoxicity. Knockdown of STx-8 and BCAP31 enhances activation of ΔF508 CFTR. Furthermore, incubating the cells at 27°C also resulted in correction of ΔF508 CFTR in AEC.

Conclusions These findings provide proof of principle that restoration of CFTR function in CF AECs can be efficiently assessed using YFP-halide reporter assay. In light of this, restoration of ΔF508 CFTR function can be assessed by use of pharmacological agents. Therefore, this novel technique will provide insights into new therapies for the treatment of cystic fibrosis.

Funding Sources CFTR, CHRF.

INDIVIDUALISED AMINOGLYCOSIDE DOSING IN ADULT PATIENTS WITH CYSTIC FIBROSIS IMPROVES PHARMACOKINETIC PARAMETERS

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In cystic fibrosis (CF) patients, aminoglycoside (AG) pharmacokinetics (PK) are altered when compared to patients without CF.

Aim To optimise in clinical practice AG concentrations in CF patients using computer dose adjustment software and compare this to the current dose adjustment nomogram.

Methods Usual method for adjusting AG dose in our unit is an algorithm based on trough levels. The intervention was the introduction of Bayesian dose individualisation software. Initial PK parameters for each patient were estimated from population data based on height, weight, creatinine clearance and dose. Drug concentrations were entered and subsequent concentration-time curves were projected to estimate required doses. Once commenced on AGs, each clinician determined management, with the exception of the modifications to timing and dose based on the program.

Results There were 6 patients in the pre-intervention group and 5 in the post-intervention group. Groups were similar in age, volume of distribution, clearance, weight, baseline creatinine and change in creatinine during treatment (all had normal renal function). The intervention group had significantly greater maximum AG concentration for each dose (20.7 vs 27.6 mg/L, (difference 6.9, 95% CI 5.1–8.7, p < 0.001)) and area under the curve for each dose (68.9 vs 99.7 mg h/L, (difference 30.8, 95% CI 26.1–35.4, p < 0.001)). There were no serious adverse events in either group.

Conclusion Determining AG dose using Bayesian dose individualisation software results in higher peak concentrations and greater area under the curve when compared to the use of an algorithm based on trough levels.

CONFLICT OF INTEREST None.

COHORT SEGREGATION EFFECTIVE IN REDUCING CLONAL PSEUDOMONAS STRAIN IN A CYSTIC FIBROSIS CLINIC

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We previously described a clonal strain of P. aeruginosa (PA) which appeared to be more virulent than wild-type strains. The high prevalence of this strain within our CF clinic raised suspicion of person-to-person transmission, prompting the introduction of cohort segregation in January 2000.

Aim To evaluate the prevalence of clonal strain PA from 1999 (pre-segregation) to 2007. We identify factors associated with acquisition of the clonal strain and examine the effect of cohort segregation on mortality rates.

Methods Cross-sectional analysis of data obtained in 1999 (baseline), 2002 (initial assessment) and 2007 (current) to ascertain prevalence and incidence of the clonal strain. Data on age of acquisition, lung function, presence of lung disease, hospitalizations, prior pseudomonas infection and mortality rates was analysed.

Results Prevalence of clonal strain PA within our CF clinic has declined from 21% in 1999 to 14% in 2002 and to 6% in 2007. Incidence has also decreased from 3.3 cases/yr (between 1999 and 2002) to 1.4 cases/yr (between 2002 and 2007). 14 of the 22 deaths occurring within the CF population between 1999 and 2002 occurred in patients infected with the clonal strain, as compared to 8 of 9 deaths between 2002–2007. The average age of clonal strain acquisition between 2002 and 2007 was 12 years, all had radiologically proven bronchiectasis.

Conclusion Cohort segregation has been associated with a reduction in the prevalence and incidence of a clonal strain of P. aeruginosa within a Melbourne CF centre. With evidence to suggest increased mortality associated with clonal strain infection, a policy of strict segregation of patients infected with clonal strains of P. aeruginosa is recommended.

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VENOUS THROMBOSIS ASSOCIATED WITH PERIPHERALLY INSERTED CENTRAL CATHETERS IN LUNG TRANSPLANT RECIPIENTS

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Rationale Management of lung transplant (LTx) patients is often complex, necessitating prolonged intravenous therapy both in the inpatient and outpatient settings. Prolonged use of in-dwelling venous catheters for this purpose may be complicated by local and pulmonary thrombotic events.

Aim To evaluate the incidence of catheter associated thrombus in LTx patients.

Method Single-centre retrospective review of all treatment episodes February 2002–February 2007 necessitating a PICC (peripherally inserted central venous catheter) line in the LTx unit at St Vincent’s Hospital. Any patient presenting with symptoms suggestive of PICC related thrombosis (PRT) underwent venous duplex. Patient demographics, site and type of catheter, duration of therapy and history of prior thromboembolism were also recorded as were complication rates.

Results 382 treatment episodes resulted in placement of a PICC. The average age was 42 (range 18–62) and 58% were male. The mean duration of therapy was 12 days (3–21 days); the main indication for PICC line insertion was post transplant infection; 64% were placed in the right arm. 13 (3.4%) patients presented with PICC related thrombosis with a mean duration to presentation of 14 days (7–21 days); 8 of the 13 PRT were in the right arm.

Conclusion PRT remains an important and common source of morbidity for LTx patients.

EXPRESSION OF WILD-TYPE AND A NOVEL SPLICE VARIANT OF GPCR A* IN HUMAN LUNG CELLS

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GPCR A codes for a G-protein coupled receptor that is induced during tissue injury and inflammation. This receptor has been implicated in processes such as cell proliferation and angiogenesis. Characterisation of alternative promoters of GPCR A has lead to the discovery of an alternatively spliced GPCR A mRNA transcript. This study aimed to assess the distribution of wild-type and splice variant transcript within a selection of immortalised lung cell lines and primary lung tissue.

Methods Total RNA was extracted from human adult lung fibroblasts (NHFL), human fetal lung fibroblasts (HFLF), human bronchial epithelium (16HBE), human lung adenocarcinoma (A549), human lung squamous carcinoma (HS20) and primary lung tissue. GPCR A wild-type and splice variant expression levels were measured using two-step RT-PCR.

Results The expected wild-type product was observed in all cell lines except HS20. Interestingly, the splice variant was observed only in lung fibroblast cells and primary lung tissue. Wild-type transcript expression was higher compared to splice variant transcript expression in lung fibroblast cells. In primary lung tissue both transcripts were expressed similarly.

Conclusion GPCR A wild-type and splice variant transcripts are differentially expressed in human lung cell lines. The increased expression of wild-type and splice variant transcript in lung fibroblasts may reflect the need for GPCR A expression in processes involved in wound healing.

*Due to confidentiality agreements, the name of the gene cannot be disclosed.

Supported by UWA, LIWA and CRC for Asthma and Airways.

The Surgical Resection Rate of Stage 1 Non-Small Cell Lung Cancer (NSCLC) at Nepean Hospital is Well Above the NSW State Average

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Introduction The Nepean multidisciplinary lung cancer team was established eighteen years ago. Weekly clinical management meetings review all cases of lung cancer. At the Australian Lung Cancer Conference (2007) O’Connell et al presented a study that quoted the current NSW surgical intervention rate for stage 1 NSCLC at less than 60%.

Methods A retrospective review of our service over the last 3 years examined the management and survival outcomes of stage 1 NSCLC. This audit included patients between January 2005 and February 2008. Demographic information, histopathology results and outcomes were reviewed.

Results Three hundred fifty-nine [391] lung cancer cases were identified: Mean age 70 years (36–93 years), NSCLC 310/391 (79%), small cell lung cancer 58/391 (15%), and mesothelioma 23/391 (6%). 69/391 (18%) cases were defined pre-operative as Stage 1 NSCLC. Surgical intervention with curative intent was performed in 60/69 (87%). 6/60 were upstaged post operatively. One patient died from respiratory failure 20 days postoperative (aged 62 yrs).

Conclusions Stage 1 NSCLC patients should be managed with early surgical resection. We report high rates of surgery with very low rates of operative mortality compared with NSW state average. This data suggests that the rate of surgical intervention state-wide is too low.

Conflict of Interest None.
VENTILATION AND PERFUSION CHANGES FOLLOWING BRONCHOSCOPIC LUNG VOLUME REDUCTION

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Bronchoscopic lung volume reduction (BLVLR) may improve respiratory function, exercise tolerance and quality of life (QOL) in selected patients with severe COPD. The physiological mechanisms behind these improvements have yet to be studied. To evaluate this further, we measured serial changes in regional ventilation (V) and perfusion (Q) in two patients following BLVLR (Patient A and Patient B).

Methods Both patients had BLVLR using Zephyr endobronchial valves targeting their left upper lobe and lingular. Differential VQ scans were performed prior to BLVLR and at one day, one month and three months afterwards. %total V and %total Q were determined for upper and lower zones at each test. Spirometry, lung volumes, six minute walk distance and SGRQ scores were also measured at each visit.

Results Changes in lung function and V/Q in treated LUX are shown.

Patient A Patient B
FEV1 (L) LUZZ%V LUZZ%Q FEV1 (L) LUZZ%V LUZZ%Q
Baseline 0.51 4 18 0.89 27 25
30 days 0.70 9 6 0.99 19 21
90 days 0.83 5 6 0.98 22 23

6MWT distance in Patient A increased from 210 m to 265 m. Patient B was unchanged.

Conclusion Our results suggest improvement from BLVLR occurs with a reduction in ventilation and perfusion mismatching. Baseline and subsequent changes in regional ventilation and perfusion may be different in those who respond well to this procedure. Differential VQ scans may help predict respond-ers to this procedure, which could guide patient selection for this innovative treatment.

Conflict of Interest None.

ENDOBRONCHIAL ULTRASOUND IN AUCKLAND: THE FIRST 50 CASES

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Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has high sensitivity and specificity in diagnosis and mediastinal staging of lung cancer, and is also an increasingly useful tool for diagnosis of medi-astinal lymph nodes in granulomatous disease.

Methods EBUS-TBNA was set up by the Respiratory Service at Auckland District Health Board in November 2007. To date, 50 cases (mean age 50 yrs, range 32–84) have been performed by 2 operators, one of whom had prior experience of the technique. Indications included (1) suspected or biopsy proven lung cancer with mediastinal involvement at accessible lymph node stations; (2) proximal hilar mass without endobronchial involvement and (3) suspected granulomatous disease. 78% of referrals were from respiratory physicians, 26% from other district health boards and 80% for suspected or confirmed malignancy.

Results Conscious sedation with midazolam (median dose 2 mg) and fentanyl (95 mcg) was used. TBNA was undertaken in 44 patients; 41 had nodes accessible to biopsy, 3 had non nodal tissue. More than one site was sampled in 12 patients, median 3 passes at first site, 1.5 at second. Nodal stations comprised station 2–4, n = 15; station 7, n = 26; station 10–11, n = 9. Four patients are awaiting a final diagnosis and thus their results are not included. In malignant disease the sensitivity was 77% and specificity 100%. The sensitivity for granulomatous disease was 86%. Supplemental oxygen was used routinely, and no complications requiring significant intervention were reported.

Conclusion EBUS-TBNA is a well tolerated, safe procedure which has a high sensitivity in malignant and granulomatous disease. Results comparable to international standards can be rapidly achieved by a new service.

Conflict of Interest None.

FLEXIBLE FIBEROPTIC BRONCHOSCOPIC PROCEDURES AND PROCEDURALIST-ADMINISTERED SEDATION REMAINS SAFE

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Background Flexible fiberoptic bronchoscopy has become an essential investigation to directly visualise the airways down to the subsegmental level, and is used for diagnostic purposes as well as for therapeutic intervention. Previously published data on bronchoscopic safety have been predominantly concerned with complications occurring in the immediate peri-procedural period (4 h) and mainly using retrospective methodology. We prospectively explored the delayed complication rate occurring up to 48 h post-bronchosco-py, with some focus on the incidence of complications arising from proce-duralist-administered sedation.

Method Data were prospectively collected on all patients undergoing flexible fiberoptic bronchoscopy over a twelve month period at our tertiary hospital. Patient and procedure details, indication and medications given were recorded. Immediate minor and major complications were collected, with delayed complications assessed by telephone interview 48 h later. The case notes and bronchoscopy records of 558 patients, age range 17 to 92 years, were reviewed.

Results 57.9% (539) had bronchoscopy with or without bronchial biopsies, 38.7% (216) underwent transbronchial biopsy and/or transbronchial nodal aspiration, and 3.4% (19) had therapeutic airways instrumentation. The minor complication rate at 4 h was 4.12% (23). However, at 48 h as many as 26% of total V and 3.4% (19) had therapeutic airways instrumentation. The minor complication rate at 4 h was 4.12% (23). However, at 48 h as many as 26% of patients reported one or more minor complications. These delayed cases were reviewed and all deemed not clinically significant. Major complications occurred in 2.2% (12) of procedures, and exclusively occurred within 4 hours of bronchoscopy, of which only 3 events could be attributed to bronchoscopy itself (all pneumothoraces from transbronchial biopsies). There were no deaths as a result of bronchoscopy. No complications could be attributed to proce-duralist-administered sedation.

Conclusion Our data confirm the overall safety of flexible fiberoptic bronchoscopy within our institution’s practice guidelines. Peri-procedural surveil-lance seems sufficient to capture important adverse events. Our established sedation protocols are sufficient for bronchoscopic procedures without addi-tional anaesthetic or sedation staff.

OUTCOMES WITH EBUS TBNA ARE DETERMINED BY PRESENCE OF MALIGNANT DISEASE RATHER THAN AN OBIVIOUS LEARNING CURVE

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Background Success in obtaining a tissue diagnosis from EBUS TBNA could provide guidance on numbers of cases needed for training in the technique.

Methods Prospective data on consecutive cases by one proceduralist from the time of institution of EBUS TBNA in November 2005. A positive benign result was defined as at least moderate lymphocyte numbers on specimens, and follow-up or surgical excision confirmed benign disease. Where there were inadequate lymphocytes on TBNA the result was negative even if the overall sensitivity for granulomatous disease was 86%. Supplemental oxygen was used routinely, and no complications requiring significant intervention were reported.

Results Of 252 cases adequate follow-up was available on 242 (in 238 patients) of which 150 had malignant nodes and 92 had benign nodes (inflammatory, normal, sarcoid and silicotic). All but 10 cases needed a tissue diagnosis using TBNA, with these other 10 needing nodal staging. Sensitivity overall was 93% for malignancy (139/150) and 74% for benign nodes (68/92), p = N.S. Numbers of positive results by sequential groups of 20 cases were 1st 18,2nd 15, 3rd 13, 4th 16, 5th 18, 6th 16, 7th 17. The 3rd group of 20 cases had an unusual cluster of necrotic malignant nodes which were difficult to diagnose; 2 patients had a positive malignant diagnosis on a repeat biopsy. The most recent group of 20 had 19 positive EBUS TBNA results. Reasons for negative benign nodes included blood stained aspirates. Virtually all nodes were entered so node size per se was not a clear reason for a negative result. Conclusion Overall sensitivity for malignant disease was persistently high. Apart from the 3rd group of 20 cases there were reasonably uniformly favorable results from the outset without clear evidence of a learning curve. It is possible the prior experience of non EBUS TBNA helped in reducing the learning curve. Generally outcomes depended on the presence of benign nodes as opposed to a learning curve. Those learning the procedure could reasonably audit their cases distinguishing benign from malignant disease.
SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AND RISK OF LUNG CANCER IN AN AUSTRALIAN CAUCASIAN POPULATION

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Lung cancer is a leading cause of cancer-related deaths worldwide. Smoking is the principal cause of lung cancer, yet less than 20% of smokers develop the disease, suggesting the role of genetic predisposition. We hypothesised that SNPs predispose susceptible smokers to lung cancer.

Methods Medline, Cochrane and Embase databases were queried to find all reports of SNPs associated with susceptibility to non small cell lung cancer (NSCLC). SNPs studied in Caucasian populations were further prioritised based on t>1000 cases/control and >10% minor allele frequency (MAF). In addition to reported SNPs, tag SNPs including coding non-synonymous, coding synonymous and high MAF were selected. MassArray sequencing was used to genotype the SNPs of peripheral blood genomic DNA from smokers with NSCLC and smokers without NSCLC.

Results Seven high risk (SE2BL, Hypothetical gene LOC123888, CHRNA3, MTRR, SMNT1, MDM2, ERCC2) and four low risk candidate genes (DUSP23, CER1, XPA and AURKA) were prioritised. The cohort contained 1021 smokers with lung cancer and 1113 healthy smokers. As internal controls we used SOD2 and CYP1A1 gene SNPs that have been previously studied in our cohort. Demographics of the cases were age (mean ± SD) 66 ± 10 years, pack yrs 41 ± 33, and controls were age 62 ± 14 years, pack yrs 36 ± 31. The samples are currently being genotyped and the full results will be presented.

Conclusion From the literature, putative candidate genes for susceptibility to NSCLC have been identified. This is one of the largest Australian studies of genetic susceptibility to lung cancer, to date.

Support The Prince Charles Hospital Foundation, NHMRC, Cancer Council Queensland, Smart State, DDB.

Conflict of Interest None.

EBUS BIOPSY: THE FIRST 72 PROCEDURES FROM A TERTIARY CENTRE

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Endobronchial ultrasound guided transbronchial lung biopsy using a guide-sheath (EBUS-GS) is a relatively new diagnostic technique currently in use in five Australian centres. It has the potential for higher diagnostic yield and lower rates of bleeding than traditional image-intensified transbronchial lung biopsy and lower pneumothorax rates than CT-guided percutaneous biopsy. We present our initial experience with EBUS-GS since its inception at our institution in July 2007.

Methods Prospective identification of all EBUS-GS cases from 31/7/07 to 30/9/08. Retrospective analysis of case notes, radiology and pathology results. Radiological interpretation was blinded to outcome. Success was defined as obtaining definitive tissue diagnosis by EBUS-GS without need for further biopsy.

Results 64 patients had 72 procedures by 3 operators. Fourteen (21%) had incomplete data sets. Means (range) were as follows: age 68 yrs (42–83), Male/female ratio 41/23, lesion size (mm) 31 (8–100), FEV1 2.15 L (0.71–4.0). Mean procedure time was 35 minutes. Overall success was 43%. In the unsuccessful (n = 38) 25 patients required at least one further diagnostic procedure, 8 were followed up with radiology alone. 46 patients had malignant neoplasm as the final diagnosis, EBUS-GS successfully diagnosed 25 giving ‘sensitivity’ of 54%, 9 patients had a benign pathology and 9 patients had no tissue diagnosis or missing data (private patients). Factors influencing success included: size of lesion <30 mm (58% vs 31% p < 0.005); lesion localised by EBUS or not (57% vs 15% p < 0.0003); malignant vs benign disease (54% vs 22% p < 0.05). Distance from pleura and traceability of an airway to the lesion on CT scan did not affect success.

Conclusions Our diagnostic sensitivity is lower than published series reflecting our learning curve. Our experience should help us define those cases most likely to benefit from EBUS-GS biopsy in future.

Conflict of Interest None declared.

Acknowledgements The Prince Charles Hospital Foundation, DDB, NHMRC, SmartState, CQQ.

ENDOBRONCHIAL ULTRASOUND GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION COMPARED TO TRANSBRONCHIAL BIOPSY AND ENDOBRONCHIAL BIOPSY FOR DIAGNOSIS OF SARCOIDOSIS

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Rationale Studies have shown endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is clinically useful in the investigation of mediastinal lymphadenopathy and diagnosis of sarcoidosis. We performed a retrospective review of seven consecutive patients referred to St Vincent’s Hospital with evidence of mediastinal lymphadenopathy and suspected sarcoidosis.

Method We performed a retrospective review of seven consecutive patients referred to St Vincent’s Hospital with evidence of mediastinal lymphadenopathy on CT scan and suspected sarcoidosis. Each patient underwent a combined procedure of EBUS-TBNA, BB and TBLB.

Results 4/7 patients were diagnosed with sarcoidosis on EBUS-TBNA. In two of these cases sarcoidosis was also diagnosed on TBLB. All of these cases had normal lung parenchyma on CT chest consistent with Stage I disease. The remaining three cases had nodular infiltrates and mediastinal lymphadenopathy on CT chest and sarcoidosis was diagnosed with TBLB only. The diagnosis of sarcoidosis could not be found on tissue obtained from bronchial biopsies. There were no complications associated with the above procedures.

Conclusion These preliminary results demonstrate EBUS-TBNA has a role in the investigation of mediastinal lymphadenopathy and suspected Stage I sarcoidosis.
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**Objective**
To review our experience with EBUS-TBNA in patients with mediastinal lymphadenopathy.

**Method**
Retrospective analysis was performed. Cases which proceeded to surgery were identified and histopathological results were compared with FNAB findings. Cases which did not proceed to surgery were analyzed for the reasons (non-operable disease, non-malignant diagnosis and non-pulmonary malignancy). Cases which were non-diagnostic at FNAB were analyzed for other diagnostic information and for available outcome data. The case series was also cross-analyzed with the St Vincent's Hospital Lung Cancer Multidisciplinary Team Database to evaluate the influence of FNAB on the primary endpoint.

**Discussion/Conclusion**
This preliminary descriptive review suggests EBUS-TBNA is a clinically useful test and supports the commencement of a randomised controlled trial at St Vincent's Hospital to formally compare EBUS-TBNA and surgical staging in lung cancer patients.

**Conflict of Interest**
No.

**Introduction**
61 cases of percutaneous fine-needle aspiration biopsy (FNAB) between November 2006 and August 2008 were retrospectively analysed for FNAB cytology or histopathology. Subsequent formal surgical pathology and Complications of the FNAB procedure were also recorded and assessed.

**Aim**
The primary endpoint of the study is the diagnostic accuracy of the FNAB procedure.

**Methods**
Retrospective analysis was performed. Cases which proceeded to surgery were identified and histopathological results were compared with FNAB findings. Cases which did not proceed to surgery were analyzed for the reasons (non-operable disease, non-malignant diagnosis and non-pulmonary malignancy). Cases which were non-diagnostic at FNAB were analyzed for surgical diagnosis, for other diagnostic information and for available outcome data. The case series was also cross-analyzed with the St Vincent's Hospital Lung Cancer Multidisciplinary Team Database to evaluate the influence of FNAB on the primary endpoint.

**Discussion/Conclusion**
This project will provide an institutional audit, will place FNAB in the context of an emerging Multidisciplinary Team and provides updated data on contemporary series of cases.

**Conflict of Interest**
No.

**Background**
A stand alone Bronchoscopy suite was designed as part of the overall Royal Brisbane & Women's Hospital redevelopment and procedures began there in January 2003.

**Method**
Statistics from all patient bookings was entered onto the Unit database and a prospective review of procedure types and numbers for the year 2007 January to December was undertaken and compared to the first year 2003 January to December.

**Result**
In 2003 269 standard bronchoscopies were performed and 133 pleural procedures. Day procedural activity doubled within the first twelve months. Bronchoscopy lists increased to four per week and medical staff throughout the hospital utilized the Bronchoscopy suite for pleural procedures under supervision of trained personnel. In 2007 a total of 775 procedures had been performed (a 300% increase over 4 years). These included DAFE bronchoscopy 101, DAFE rigid laryngoscopy 35, EBUS guide sheath technique 113, EBUS balloon technique 7, and TBNA using the linear scope 113. Standard bronchoscopy numbered 207 and the use of diathermy for hot biopsy or Argon Plasma Coagulation was 20. One tracheal stent was placed and 60 pleural procedures were performed.

**Discussion/Conclusion**
No waiting list exists for procedures in the department with many patients seen by Medical staff one day and having their procedure the next. This expansion of services, numbers and complexity, would not have been possible without a stand alone, dedicated bronchoscopy suite.

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**Conflict of Interest**
No.
EXPRESSION AND EPIGENETIC REGULATION OF KALLIKREINS AND KININ RECEPTORS IN PLEURAL MESOTHELIOMA CELLS

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The kallikrein-kinin cascade may be an important signalling pathway in pleural mesothelioma. Tissue (hK1) and plasma (hK1) kallikreins are proteases that convert kinogen to biologically active kinin peptides, which elicit cellular effects by binding to B1 and B2 receptors. The aim of this study was to determine the expression of hK1, hK1B, B1, and B2 receptors in different mesothelioma cell lines and to assess whether these genes are regulated by DNA methylation.

Methods Malignant mesothelioma cell lines (JU77, NO36, LO68) were obtained from pleural effusions of three patients. Cells were fixed and immunoperoxidase labelled using specific antibodies, with semi-quantitative assessment by brightfield microscopy. mRNA expression was assessed by real-time RT-PCR and cells were treated with 5-aza-2'-deoxycytidine (5-aza) for 48 h to assess the effect of DNA demethylation.

Results Both NO36 and JU77 cells expressed hK1, hK1B and B1, and B2 receptors, with 40–80% of cells showing cytoplasmic and/or peripheral staining for these proteins. mRNA expression for hK1, hK1B, B1, and B2 receptors was greater in LO68 than NO36 cells (4.4, 13.5, 15.6 and 19.7 fold, respectively). mRNA expression for hK1, hK1B and B2 receptor was also greater in LO68 than JU77 cells (833, 2.4 and 16.5 fold, respectively). After 5-aza treatment, hK1, B1, and B2 receptor mRNA expression was decreased. In contrast, hK1B mRNA expression was increased.

Conclusions Kallikrein and kinin receptor proteins and genes are differentially expressed in malignant mesothelioma cells. The kallikrein and kinin receptor genes appear to be epigenetically regulated by DNA methylation. Further studies on the function of these proteins in mesothelioma cells may lead to the development of novel drugs and biomarkers for pleural mesothelioma.

Supported by the Cancer Council of Western Australia.

NON-INVASIVE IMAGING FOR MONITORING FGK45 TREATMENT PROGRESS IN AN ORTHOTOPIC MODEL OF MESOTHELIOMA

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Introduction Malignant pleural mesothelioma is not rare, and it is dramatically increasing worldwide. Stimulation of antitumour immunity has long been a subject of intense research, and has the potential major benefit of inducing a generalized systemic response thereby eliminating both primary and metastatic disease. FGK45, the activating anti-CD40 antibody, can replace or augment CD4 helping in priming DCs to activate CD8 T cells. Most animal studies on mesothelioma use subcutaneous nodules. We have established an immunocompetent orthotopic model of mesothelioma which more accurately reflects the human disease.

Methods An AE17 cell line was stably transfected with a construct containing the luciferase reporter gene (AE17-SFG). C57Black6 mice were injected intrahepatically with AE17-SFG cells. When all mice (10 mice per group) developed detectable tumours, 3 intraperitoneal injections of PBS or FGK45 in 1 week were given on following day to determine the therapeutic effect. Tumour growth in the pleural space was detected by systemic administration of luciferin followed by light detection with the xenogen camera. mRNA expression was assessed by real-time RT-PCR and cells were treated with 5-aza-2'-deoxycytidine (5-aza) for 48 h to assess the effect of DNA demethylation.

Results By Day 28 all mice in the PBS group developed massive detectable tumours, and had to be sacrificed. In contrast all mice that received FGK45 showed tumour regression with no detectable tumours in the all animals by day 37. Monitoring is ongoing.

Conclusions An intrapleural model of mesothelioma has been established in C57Black6 mice and non-invasive imaging can monitor treatment progress. FGK45 treatment can effectively inhibit mesothelioma cell growth in the pleural space.

INTEGRATION OF ACGH AND GENE EXPRESSION DATA IDENTIFIES CANDIDATE GENES IN ASBESTOS-RELATED LUNG CANCER

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Asbestos related lung cancer (ARLC) accounts for 4–12% of all lung cancers worldwide. Here, we aimed to identify candidate genes with concordant changes in gene dosage and gene expression in search of ARLC specific genetic alterations.

Methods Expression (22,323 element Operon microarrays) and arrayCGH (Agilent Human Genome CGH Microarray Kit 44B) analysis was performed on lung adenocarcinomas (AC) from 12 patients with >20 asbestos bodies per gram wet weight of lung (AB/gww; ARLC) and 24 patients with 0 AB/gww (NARLC) tissue. Copy number variations (CNVs) were called using the Circular Binary Segmentation algorithm. ACE-IT was used to divide chromosomes into gene dosage groups (loss, normal and gain), based on user-defined thresholds for contamination and balanced representation between groups.

Results Thresholds of 5 for contamination and balance and P-value of 0.8 (ARLC) identified six genes with significant concordance between copy number and expression at raw P-values <0.5 adjusted by Benjamini-Hochberg multiplicity correction and 43 genes for NARLC (P < 0.5 adjusted). Pearson correlations showed r values >0.5 for three genes in ARLC tumours, with one also identified in NARLC (Cathepsin K). The other two genes (VPS72 and PIP5K1A) represent candidate genes of interest with moderate concordance, indicating their over-expression may be driven by increased copy number on chromosome 1q21.2.

Conclusions The two genes identified here may play a role in causation or progression of ARLC, may be specific to AC and could potentially be useful as biomarkers or treatment targets for ARLC.

Supported by The Prince Charles Hospital Foundation, DDB, NHMRC, Smart State, Cancer Council Queensland.
TRENDS IN HOSPITALISATION AND MORTALITY FOR PNEUMOCONIOSIS IN AUSTRALIA

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Pneumoconiosis is a chronic occupational respiratory condition, stemming from a variety of causative agents, described as types. Prominent among these are coal workers’ pneumoconiosis, asbestosis and silicosis. Changes in the burden of disease from various types of pneumoconiosis differ over time. This study reports varying trends in hospitalisation and mortality by type of pneumoconiosis in Australia.

Methods Hospital separations data were obtained from the National Hospital Morbidity Database (AIHW) for years 1998–2006 for all separations where pneumoconiosis (J60 to J64) was the principal diagnosis. Age-standardised rates were plotted by type of pneumoconiosis to study the underlying trends. The cause of death data were extracted from the National Mortality Database for the years 1998 to 2006, for all deaths in which pneumoconiosis (J60 to J64) was listed as an associated or underlying cause of death.

Results Pneumoconiosis was the principal diagnosis for 213 hospital separations in 2006–07 in Australia. Asbestosis was the most common type of pneumoconiosis for hospitalisation. The number of pneumoconiosis hospitalisations in Australia has remained steady overall since 1998–99; however, the rate of asbestosis hospitalisations increased during this period. Deaths from pneumoconiosis on the other hand have increased from 0.3 per 100,000 persons in 1998 to 0.5 per 100,000 persons in 2006, age standardised. This upward trend in mortality is mainly due to asbestosis, which increased in numbers from 43 deaths in 1998 to 91 in 2006. Deaths from other types of pneumoconiosis however have remained steady during this period.

Conclusions The burden of disease from various types of pneumoconiosis is not trending uniformly in Australia. Asbestosis, the most common type of pneumoconiosis, is contributing more to this burden lately as reflected in hospitalisation and mortality.

Supported by the Australian Institute of Health and Welfare.

IN UTERO EXPOSURE TO ARSENIC VIA DRINKING WATER ALTERS POST-NATAL LUNG FUNCTION

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Background Epidemiological evidence has shown a link between in utero exposure to arsenic and the development of obstructive lung disease in later life. One mechanism by which this may occur is through an alteration in lung growth. Using a mouse model we aimed to determine if in utero arsenic exposure alters post-natal lung development.

Methods Pregnant BALB/c, C3H or C57BL/6 mice were given drinking water comprised of ddH2O or ddH2O containing 100 ppb As in the form of NaAsO2 from day 8 gestation to birth. Body weight and size were monitored in offspring from birth to 2 weeks of age. At 2 weeks of age mice were anaesthetised, tracheostomised and mechanically ventilated. Baseline lung volume, lung mechanics (airway resistance – Rm, tissue damping – G, tissue elastance H) and the volume dependence of lung mechanics were measured using plethysmography and the forced oscillation technique.

Results There was no difference in lung function between BALB/c mice exposed to As and controls. C3H mice showed increased lung volume (0.02 mL (0.005 (SE), p = 0.01)) for a given body size and increased Rm (217.8 hPa·L−1 (58.4 (SE), p = 0.001)) for a given lung volume following in utero exposure to As compared to controls. Whereas, As exposed C57BL/6 mice had increased G [4038 hPa·L−1 (1340 (SE) p = 0.003)] and H [19008 hPa·L−1 (5809 (SE), p = 0.002)] compared to controls.

Conclusions These results demonstrated a clear effect of in utero arsenic exposure on post-natal lung development as measured by lung function. The strain dependence of this response provides an excellent opportunity to understand the mechanism by which this occurs and will assist in identifying the potential link between early life arsenic exposure and the development of obstructive lung disease in later life.

Supported by the NHMRC.

EFFECTS OF IRON-CONTAINING PM10 AND URBAN PM10 ON CYTOKINE PRODUCTION BY DENDRITIC CELLS AND MACROPHAGES

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Iron-containing ambient particulate matter (PM10) may activate lung cells when inhaled, and its effects may differ from those of urban PM10. This study assessed the effects of iron-containing PM10 from Port Hedland, as well as PM10 from urban and regional centres, on cytokine production by dendritic cells (DC) and macrophages.

Methods Monocytes were isolated from blood of healthy donors by centrifugation for 5 days with M-CSF and GM-CSF. DC and macrophages were exposed to lipopolysaccharide plus interferon-γ, and monocytes were further stimulated with iron-containing PM10 from Port Hedland and urban PM10 from Perth, as well as PM10 from urban and regional centres. DC supernatants were assayed for IL-10 and IL-12, and macrophage supernatants were assayed for IL-6 and TNF-α.

Results Both iron-containing PM10, from Port Hedland and urban PM10, stimulated the release of IL-10 from DC and IL-6 from macrophages, although statistically significant effects were only observed at PM10 concentrations of 500 μg/mL. All PM10 samples stimulated concentration dependent increases in macrophage TNF-α secretion, which was significantly increased at PM10 concentrations ≥100 μg/mL. Macrophage TNF-α production in response to Port Hedland Harbour and Perth PM10 samples (200 μg/mL) was similar but significantly greater than with a Sydney PM10 sample (p < 0.05). Among the iron-containing samples, PM10 from the Port Hedland Harbour, Hospital and Cargill sites induced significantly greater TNF-α production compared with PM10 from a background sampling site (p < 0.01).

Conclusions When inhaled into the lungs of exposed individuals, iron-containing PM10, as well as urban PM10, is likely to stimulate the release of IL-10 from DC, and IL-6 and TNF-α from resident macrophages, resulting in immune and inflammatory responses in the lungs.

Supported by the Department of Environment and Conservation, Western Australia.

WORK-ASSOCIATED IRRITABLE LARYNX SYNDROME

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Background Work-associated Irritable Larynx Syndrome (WILS) is characterised by a state of chronic hyperkinetic laryngeal dysfunction, induced or exacerbated by workplace exposure(s). Symptoms are attributable to laryngeal tension and are triggered by sensory stimuli such as odours and airborne irritants.

Objective To describe a group of patients with symptoms clinically suggestive of WILS.

Methods Cases were identified from a review of charts at an Occupational Lung Disease clinic between 2002 and 2006. Although required for a formal diagnosis, assessment of laryngeal tension was not part of this preliminary investigation.

Results From 192 alphabetically consecutive files, 17 subjects were identified with a likely diagnosis of WILS. The average age of subjects was 45.9 years (range 38–56) and 88% (15/17) were female. An identifiable triggering event at the onset of symptoms was present in 71%. Chronic work-related symptoms included cough (53%) and dysphonia (76%). A clinical diagnosis of gastroesophageal reflux was present in 71%. A history of asthma was reported in 88% at the time of initial assessment, and of this group 100% (15/15) were regularly using inhaled corticosteroids, long acting beta-agonists, Montelukast or prednisone. 6/13 subjects with a clinical diagnosis of asthma had no evidence of bronchial hyper-responsiveness based on methacholine challenge.

Conclusion This group of workers with symptoms suggestive of WILS has a female predominance and high prevalence of asthma diagnosis. Laryngeal conditions should be considered as differential diagnoses when assessing patients with work-related respiratory symptoms.
ESTABLISHMENT OF A WEB-BASED REGISTRY FOR ORPHAN LUNG DISEASES IN AUSTRALIA AND NEW ZEALAND

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An ‘orphan disease’ is a condition both rare (prevalence <5 per 10,000) and neglected by medical sciences. As a result, an understanding of epidemiology, pathophysiology, outcome and therapies are often lacking. There is a clear need to address this issue in Australasia. Previous web-based registries on rare lung diseases have proven to be a successful resource.

Aims
1) To establish a registry of rare lung diseases in Australasia and facilitate the collection of data on adult and paediatric diseases to inform prevalence and incidence (Phase 1). 2) To establish a website as an information resource for these diseases. 3) Gather detailed information on individual diseases such as Idiopathic Pulmonary Fibrosis and potentially other Interstitial Lung Diseases for which novel therapies are arising (Phase 2).

Methods
TSANZ members will be invited to participate in reporting cases electronically to a dedicated website following a monthly email reminder. Data will be validated and entered into an electronic database and act as an information resource for clinicians and patients.

Results
The Australasian Registry Network for Orphan Lung Diseases (ARNOLD) website (http://www.arnold.org.au) will provide a means by which TSANZ physicians will be able to submit data on rare lung diseases to an electronic database and act as an information resource for clinicians and patients.

Funded by the Australian Lung Foundation.

Conflict of Interest None.

COMPARISON OF PULMONARY HYPERTENSION COMPLICATING LUNG DISEASE AND PULMONARY ARTERIAL HYPERTENSION

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Introduction
It is unclear whether patients with pulmonary hypertension (PHT) complicating lung disease have similarities with idiopathic and connective tissue (c.t.) disease related pulmonary arterial hypertension (PAH).

Methods
Results of imaging tests, pulmonary function tests (PFTs), arterial blood gases (ABGs), six minute walk tests (6MWT), echo and right heart catheter (RHC) for patients seen in the PHT service were reviewed. Patients were divided into those with idiopathic or c.t. disease related PAH, those with emphysema, always disease and interstitial lung disease (ILD).

Results

|                   | AFO n = 15 | Emphysema n = 12 | IAP/H/Scl n = 69 | ILD n = 19 |
|-------------------|------------|------------------|------------------|-----------|
| 6MWT (m)          | 278 (31)   | 387 (21)         | 307 (18)         | 357 (35)  |
| FEV1 (%pred)      | 67 (2)     | 87 (5)           | 91 (2)           | 75 (4)    |
| FVC (%pred)       | 87 (4)     | 100 (5)          | 94 (2)           | 75 (4)    |
| TLC (%pred)       | 98 (7)     | 100 (5)          | 94 (2)           | 75 (4)    |
| DLCO (%pred)      | 52 (7)     | 48 (8)           | 61 (3)           | 46 (4)    |
| Echo PASP (mmHg)  | 61 (6)     | 62 (6)           | 62 (4)           | 57 (6)    |
| mPAP (mmHg)       | 38 (2)     | 38 (4)           | 40 (2)           | 39 (4)    |
| CI (l/min/m2)     | 2.8 (0.4)  | 2.6 (0.3)        | 3.1 (0.2)        | 3 (0.3)   |
| pO2 (mmHg)        | 70 (4)     | 62 (8)           | 70 (2)           | 60 (5)    |
| pCO2 (mmHg)       | 37 (2)     | 32 (3)           | 37 (1)           | 31 (1)    |

Patients with emphysema and PHT had at most mild airflow limitation. Patients with emphysema and ILD tended to have lower pO2 and pCO2 at rest but better exercise capacity. Haemodynamic parameters are similar.

Conclusions
In patients referred to a regional PHT service, the haemodynamics seen in those with lung disease are similar to those with PAH. Studies are required to clarify whether they have similar responses to treatment.

Conflict of Interest None.

COMPARISON OF MODIFIED SHUTTLE WALK TEST AND CARDIOPULMONARY EXERCISE TEST IN SARCOIDOSIS

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The modified shuttle walk test (MSWT) may be a useful test of functional capacity in sarcoidosis. The aim of this study was to correlate MSWT distance with CPET measured VO2 max and lung function in sarcoidosis.

Methods
25 (14 female, mean age 48 yrs) patients with sarcoidosis completed a STEEP protocol cycle ergometer CPET and corridor MSWT in random order on the same day. Oxygen saturation and heart rate were monitored during MSWT using portable oximeter. Demographic and pulmonary function data were prospectively collected. Repeatability of MSWT in 22 sarcoidosis patients had previously been tested (r = 0.95; p < 0.0001).

Results
Average FEV1 2.3 L (72%predicted), FVC 3.27 L (79%predicted), DLCO 18.9 (74%predicted). There was a strong correlation between MSWT distance and max VO2/kg achieved during CPET (r = 0.90; p < 0.0001). FEV1 and FVC showed weak correlation with distance (r = 0.44; p = 0.03, r = 0.65; p = 0.0005) as did DLCO and DLCO %predicted (r = 0.53; p = 0.009, r = 0.46; p = 0.02) but not FEV1 or FVC %predicted. 16 patients had respiratory muscle pressures measured with stronger correlation between MSWT distance and PImax (r = 0.80; p = 0.0002) and PEmax (r = 0.89; p < 0.0001) than between max VO2/kg and PImax (r = 0.61; p = 0.01) and PEmax (r = 0.78; p = 0.0003).

Conclusion
In sarcoidosis max VO2/kg achieved during CPET strongly correlates with MSWT distance. MSWT correlates with respiratory muscle pressures but, like CPET, only weakly with lung function measurements. Funded by Green Lane Hospital Research and Education Fund.

No conflict of interest.
N-ACETYL C YSTEINE IN PULMONARY FIBROSIS: AN AUDIT OF CLINICAL EXPERIENCE

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Introduction  N-acetylcysteine (NAC) combined with azathioprine and prednisone has been shown to preserve lung function better in idiopathic pulmonary fibrosis (IPF) than azathioprine and prednisone alone.

Methods  An audit of all patients commenced on therapy with NAC in our interstitial lung disease clinic between December 2004 and May 2006. Data relating to demographics, diagnosis, survival, pulmonary function and 6 minute walk (6MWD) tests were determined from medical records.

Results  25 patients have been treated with NAC; 22 patients had a diagnosis of IPF, 3 of fibrotic NSIP. The average age was 70 yrs, 76% male, 72% European. 4 patients stopped therapy within 1 month; 2 due to intolerance, 2 due to inability to reliably take prescribed meds.

At baseline those in the ongoing treatment group had lower FVC than those who failed treatment, (52%predicted versus 64%). At 6 months those who failed treatment had an average 0.33 L or 7% reduction in FVC from baseline, 6.6% reduction in DLCO and 49.2 m loss in 6MWD. Those who remain on treatment had an average improvement of 0.27 L or 7.4% in FVC and 1.6% in DLCO from baseline. The 6MWD fell by 4.4 m. At 12 months of ongoing treatment the FVC had improved 0.05 L or 3.8%, DLCO 0.75%.

Conclusion  In selected patients triple therapy with NAC, azathioprine and prednisone is well tolerated and appears to be associated with a stabilisation of lung function. Lower FVC at baseline is not necessarily associated with treatment failure.

Conflict of interest  None.

6MWT USING FOREHEAD OXIMETRY IS A RELIABLE MEASURE OF SEVERITY OF SCLERODERMA LUNG DISEASE

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Background  The six minute walk test (6MWT) is a validated field test in the assessment of patients with interstitial lung disease. The aim of this study was to determine the reliability of the 6MWT in scleroderma (SSc) lung disease and correlate results with morphologic and functional measures of disease severity.

Methods  31 patients (24 female, mean age 47, mean DLCO 65%, VC 77% predicted) with ACR classification of scleroderma performed two 6MWT, using various oximetry sites, 1 week apart. They also had SSc specific disease severity and QOL measures.

Results  There was good reliability between the two 6MWT (distance; ICC 0.96, r = 0.89, Borg; ICC 0.85, r = 0.91, both p < 0.0001 for r). Forehead and finger oximetry were more reliable than earlobe (ICC: 0.64, 0.60, 0.24, r = 0.46, 0.47, 0.14, n = 22,17,7 respectively). Forehead desaturation, but not finger or earlobe desaturation, showed moderate correlation with radiologic extent of disease for the following CT patterns: ground glass density (r = -0.51, p = 0.01) reticular (r = 0.49, p = 0.02), fibrosis (r = -0.48, p = 0.02). Forehead desaturation, but not finger or earlobe, also correlated with FVC (r = 0.49, p = 0.02), DLCO %predicted (p = 0.46, p = 0.04), and patient global assessment. Distance correlated with FVC (r = 0.62, p < 0.002) but not with DLCO or CT extent of disease. Borg correlated only with global assessments and QOL measures.

Conclusion  The 6MWT is feasible, valid and reliable in SSc lung disease, but forehead oximetry should be used. The test measurements correlate reasonably but variably with functional and morphologic measures of disease severity.

Support  Green Lane Research and Educational Trust.

IS EXERCISE TRAINING SAFE FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION?

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Background  Historically, patients with pulmonary arterial hypertension (PAH) have not routinely been referred for exercise training, an intervention with proven efficacy in patients with respiratory and cardiovascular disease. Recent advances in the diagnosis and medical management of PAH have enabled earlier detection, slowing of disease progression and thus improved survival.

Hypothesis  Supervised exercise training is safe in PAH.

Method  Electronic and hardcopy Royal Perth Hospital (RPH) documentation was reviewed for each patient to identify reported outcome measures and the incidence of adverse events in order to ascertain whether supervised exercise training is safe in this population.

Results  Since November 2005, 7 patients (5 females), aged 16–81 years, mean 6 minute walk distance (6MWD) 334 m (range 150 m–460 m), WHO functional class II to IV, have participated in the pulmonary rehabilitation program. Exercise training comprised lower limb endurance training (walking and cycling), upper limb endurance training and functional strength training for the lower limbs. Six patients completed 12 weeks of exercise training. The remaining patient completed 9 weeks due to undergoing a total joint replacement.

Conclusion  The exercise training program delivered at RPH is safe in the PAH population. A randomised controlled trial will commence shortly to determine the physiological, clinical and quality of life responses to exercise training in patients with PAH.
VALIDATION OF THE CAMBRIDGE PULMONARY HYPERTENSION OUTCOME REVIEW FOR AN AUSTRALIAN AND NEW ZEALAND PAH POPULATION

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Background: Historically, quality of life (QoL) in patients with pulmonary arterial hypertension (PAH) has been most often measured using generic QoL tools, commonly the Medical Outcomes Study 36-item Short Form Health Survey (SF-36). A disease-specific QoL measure for PAH (The Cambridge Pulmonary Hypertension Outcome Review – CAMPHOR) has recently been developed in the UK and validated in both UK and American populations with PAH. Our aim was to validate the CAMPHOR for use in an Australian and New Zealand PAH population.

Methods: The CAMPHOR was applied to an Australian cohort of 15 patients (aged 68.9 ± 10.0 yrs; 11 females) with PAH to determine relevance of the questions, the terminology and language used and the clarity of the CAMPHOR. A test-retest reliability study is currently being performed to examine repeatability, internal consistency and construct validity of the CAMPHOR in an Australian and New Zealand population with PAH.

Results: Data from the patient interviews confirm that the CAMPHOR is appropriate for use in an Australian population with PAH. At present, 38% of the proposed subject sample has completed the test-retest reliability study (n = 20; aged 71.4 ± 15.5 yrs; 19 females). The three CAMPHOR scales have good internal consistency (Cronbach’s alpha coefficients = 0.93 to 0.98) and repeatability (correlation coefficients [r] = 0.84 to 0.93, p < 0.01). The CAMPHOR scales also correlate significantly with SF-36 sub-scales ([r] = 0.5 to 0.81, p < 0.05).

Conclusion: Our data suggest that the CAMPHOR is an appropriate and useful instrument for assessing the QoL of Australian and New Zealand patients with PAH. Ongoing research will determine whether the CAMPHOR is superior to the SF-36 in detecting changes in our PAH population.

ASSOCIATION OF CARDIOPULMONARY COMPLICATIONS OF SYSTEMIC SCLEROSIS USING THE AUSTRALIAN SCLERODERMA SCREENING PROGRAM (ASSP) DATABASE

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1St Vincent's Hospital, Vic., 2Princess Charles Hospital, Qld, 3Menzies Institute, Tas., 4Canberra Rheumatology, ACT, 5Royal Perth, WA, 6St George, NSW, 7Queen Elizabeth, SA, 8Royal Prince Alfred, NSW, 9Sunshine Coast Rheumatology, Qld, 10Monash Medical Centre, Vic., and 11Royal Adelaide Hospital, SA

The ASSP was established in 2007 to improve screening for pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). An electronic web-based database was developed to assist with decision-making about further investigation according to a screening algorithm.

Method: Enrolled patients were screened with lung function tests, Doppler echocardiogram, ECG and clinical evaluation. Data are recorded in the electronic database. If abnormalities are detected, an email is sent to the treating physician, and decision-making about further investigation according to a screening algorithm.

Results: To date, 526 patients (87.3%, females; 12.7%, males) have been enrolled from 12 centres. As a result of screening, 29 patients were considered at high risk of PAH with sPAP >50 mmHg on Echo. RHC had been ordered for 28 and completed in 25, in whom 20 were confirmed to have PAH. Seventy-seven patients were considered to be at moderate risk of PAH either because DLCO < 50% with sPAP > 50% or because sPAP was between 40 and 50 mmHg on Echo. A RHC was requested in 22 of these, completed in 20, resulting in a further 10 cases of PAH being detected. All patients with confirmed PAH commenced PAH specific therapy. FVC was > 85% in 25% of patients who commenced lung function tests. ILD was detected in 10/179 (5.6%) of those who had a RHC. In 58%, ILD was rated as moderate or severe on HRCT.

Conclusion: These preliminary data demonstrate the value of the program in identifying SSc patients with cardiopulmonary complications.

RAD IN DPLD ASSOCIATED CTD: 3-YEAR RESULTS OF A PILOT, MULTICENTRE, INVESTIGATOR DRIVEN, RANDOMISED DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF RAD IN CTD

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Rationale: Diffuse parenchymal lung disease (DPLD) is a leading cause of death in connective tissue disease (CTD). Everolimus may represent a therapeutic option.

Objective: To evaluate the efficacy and safety of Everolimus (RAD) in CTD.

Methods: 17 patients with DPLD associated CTD were enrolled in a 3-year pilot investigator driven, placebo controlled, double blind, multicentre study of Everolimus.

Results: Data expressed as M ± SD *p < 0.05 versus placebo arm.

| Group          | n  | M:F  | Age (yrs) | FVC% | TLC%* | DLCO%* |
|----------------|----|------|-----------|------|-------|--------|
| Everolimus     | 11 | 6:5  | 49 ± 18   | 72 ± 25 | 77 ± 18 | 47.7 ± 15.6 |
|                | 28 | 0.03 | log rank  |
| Placebo        | 6  | 3:3  | 51 ± 15   | 56 ± 16 | 58 ± 10 | 29.8 ± 11.1 |
|                | 33 | 0.01 | log rank  |

Intention to treatment analysis demonstrated a significant survival advantage for the Everolimus arm (KM, p = 0.03, log rank). Higher baseline DLCO% correlated with better survival (HR 0.82, CI 0.70–0.95, p < 0.01) as did higher TLC (HR 0.93, CI 0.87–1.00, p < 0.05) and 6-minute walk distance (HR 0.99, CI 0.98–1.00, p < 0.01). There was no difference in time to disease progression between groups (KM, p = 0.34, log rank) or incidence of serious adverse events.

Conclusion: Everolimus used for CTD associated DPLD demonstrated a survival benefit. However, univariable analysis suggested that this may be related to better baseline characteristics in the active arm. This encouraging pilot study strongly supports the need for further randomised controlled trials.

PRIMARY HUMAN PULMONARY MICROVASCULAR ENDOTHELIAL CELLS (HMVEC) UNDERGO ENDOCYSTAL TRANSITION (EMT)

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Pulmonary hypertension is a fatal disease characterized by extensive vascular remodelling resulting from abnormal proliferation of pulmonary vascular endothelial and smooth muscle cells (SMC). Traditionally, it has been thought that the SMC-like cells that accumulate in vascular lesions were derived from the proliferative expansion of resident vascular SMC. Recently TGF-ß1 signalization has been identified as an important driver to maintain vascular EMT (EMT) and is being implicated as an important mechanism in fibrotic lung disease. EnMT has also been investigated for its potential role in vascular disease. Those studies that have shown EnMT in response to TGF-ß1 have used animal primary endothelial cultures from larger blood vessels. We tested whether TGF-ß1 could induce EnMT in a more relevant cell line i.e. HMVEC.

Methods: Cultured HMVEC were treated with TGF-ß1 (5 ng/ml) for 21 days. Cells were examined by phase contrast microscopy, immunofluorescent histology and Western blots for an increased expression of mesenchymal markers and down regulation of endothelial markers.

Results: Phase contrast images of HMVEC following TGF-ß1 demonstrated a change from their ‘cobblestone’ morphology to a more elongated, spindle-shaped fibroblast-like morphology. TGF-ß1 induced EnMT was confirmed by IF imaging as evidenced by loss of endothelial marker expression e.g. VE-cadherin with a gain in expression of mesenchymal markers e.g. fibronectin and S100A4. Immunoblot reconfirmed EnMT by demonstrating decreased VE-Cadherin and a concomitant increase in fibronectin and vimentin expression.

Conclusions: Primary HMVEC are capable of undergoing EnMT in response to TGF-ß1 which may have important implications for the pathophysiology of a wide range of pulmonary vascular diseases. Elucidation of the mechanisms involved is needed to develop specific therapies for the reversal of EnMT.

Supported by NHMRC & NHP.

Nomination: Nil.

Conflict of Interest: No.
IRON TABLET ASPIRATION: HIGH INDEX OF SUSPICION AND EARLY INTERVENTION ESSENTIAL

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There are scattered cases reports of aspiration of iron tablets leading to bronchial stenosis and rarely bronchial perforation and massive haemoptysis. The mechanism is bronchial wall tissue necrosis as a result of local release of cytotoxic oxidant radicals. These complications may be more common in the elderly.

Results We have recently seen three cases of this syndrome in our region and all cases documented resultant bronchial wall damage and stenosis. In all cases there was a delay in bronchoscopic removal and toilet. The initial bronchoscopic appearance were similar in all cases with characteristic of extensive mucosal damage and yellow/orange necrotic coating. Subsequent bronchoscopic finding were of significant scarring and stenosis. Bronchial biopsies showed necrosis, squamous metaplasia and tissue fragments staining positively for iron with Perl’s stain.

Conclusion Even in the absence of airway symptoms or CXR abnormality our experience suggests that in patients with a history of possible aspiration of iron tablets early aggressive investigation and management is mandatory in an attempt to minimize local damage and resultant sequel.

Conflict of Interest Nil.

A SPECIALISED CLINIC FOR LYMPHANGIOLEIOMYOMATOSIS: EXPERIENCE OF AN ORPHAN LUNG DISEASE CLINIC AT ST VINCENT’S HOSPITAL, SYDNEY

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Background Lymphangioleiomyomatosis (LAM) is a rare cystic lung disease almost exclusively affecting women. Few physicians will see more than one case of LAM and clinical experience is therefore limited. A LAM clinic was established at St.Vincent’s Hospital in 2006 to provide specialist advice and to support women with this rare disease, and to promote research in this area.

Results 35 patients had LAM of whom 5 had tuberous sclerosis. 12 patients had renal angiomyolipomas and 3 had abdominal lymphangioleiomyomas. Mean FEV1 was 63% and DLCO 41.2% predicted. Mean 6MWD was 436 m and 8 patients had significant desaturation on exercise.

Conclusions A specialised clinic for an orphan lung disease provides a facility attractive to patients, allows multidisciplinary care and implementation of research. However, it is resource intensive.

Correlation Between Quantitative CT Scans and Functional Parameters in Lymphangioleiomyomatosis (LAM)

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Background CT scans are crucial in the diagnosis and monitoring of the progression of cystic lung diseases such as LAM. Quantitative CT scanning has been used in COPD and LAM to assess correlation between the functional parameters and extent of air trapping as measured by emphysema software.

Aim To correlate the quantitative score of cystic lesions obtained by volumetric CT software with pulmonary function data as well as quality of life data in LAM.

Methods 17 patients with LAM underwent volumetric CT scans, lung function tests as well as six minute walk tests. Quality of life was assessed using a St. George’s Respiratory Questionnaire.

Results There was a significant correlation between the lung volume as computed by CT and TLC on lung function testing (r = 0.84). Residual volume was also correlated with CT lung volume (r = 0.77). There was no correlation seen with other parameters such as FEV1, FVC, diffusion capacity, blood gases or quality of life indices. There was also no correlation between functional capacity as measured by 6 minute walk distance or VAS dyspnoea scores.

Conclusions Quantitative Ct scans may be useful in the evaluation of patients with LAM. Serial measurements may be useful, along with other parameters such as lung function tests, as an indicator of prognosis. However further studies are required to validate this.

An Audit of Thromboprophylaxis Use in Medical Inpatients at Norfolk and Norwich University Hospital

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Introduction Venous thromboembolism (VTE) is responsible for 25,000 hospital related deaths per year in the UK. Prophylaxis with low molecular weight heparin (LMWH) reduces the incidence of VTE. An audit of enoxaparin use at NNUHT was carried out to assess adherence to trust guideline-to assess the safety and suitability of LMWH use. Audit Standards: 7 audit standards were derived to assess adherence to the trust guideline. An eighth standard was included to assess the effectiveness of enoxaparin at reducing VTE and investigate its use in patients in directorates with high and low usage rates.

Methods A ‘snap-shot’ audit was done for all medical in-patients at NNUH in one day in February 2006. Data was collected only for patients receiving LMWH. For analysis of prescription rates, all patients in chosen wards were assessed for indications of LMWH use. Data was collected for VTE rate the year before and after introduction of enoxaparin.

Results Out of 49 patients prescribed LMWH, 10% were fully mobile, 18% did not have VTE risk factors. 12% of the patients were prescribed tinzaparin (non-formulary). 10% had moderate renal impairment but did not receive correct dose LMWH. Most had FBC monitoring. Anti-embolism stockings use in this group was 2%. Of 68 patients who did not receive LMWH, 11 had contraindications, 95% of the remaining patients had one or more VTE risk factors. Introduction of enoxaparin did not affect the rate of VTE.

Discussion and Conclusion Thromboprophylaxis is underused in 22% and over-used in 16% of patients. Risk factors assessment, compliance with formulary, dosing in renal impairment and toxicity monitoring should be improved. LMWH use at NNUHT is inconsistent across specialties. It is crucial to alert prescribers about clinical guidelines and benefits of LMWH.
HLA MATCHING BEFORE LUNG TRANSPLANTATION AND THE RISK OF DEVELOPING BRONCHIOLITIS OBLITERANS SYNDROME

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The link between acute cellular rejection and bronchiolitis obliterans syndrome (BOS) is established. The contribution of antibody mediated rejection to BOS is unclear. We hypothesised that a) Human leukocyte antigen (HLA) matching before lung transplantation (Tx) confers protection against BOS & b) development of donor-specific HLA antibodies after lung Tx is associated with accelerated decline in FEV1, from peak post Tx level.

Methods Lung Tx donors and recipients have HLA typing, but matching is not performed. Recipients are tested for HLA antibodies pre-Tx and with each post-Tx surveillance bronchoscopy. We classified subjects as +HLA (n = 9) if they developed new class I or II HLA antibodies post-Tx or had increased % panel of reactive antibodies. Others were classified as –HLA (n = 17). The % class I and II HLA matches & mean monthly FEV1, decline was calculated for both groups.

Results 31 consecutive lung Tx performed between Nov 2004 and Sept 2008 were analysed; actuarial 2-year survival was 96.5%. 26 subjects >3 months post-Tx (results from >4 bronchoscopies) provided data. Donor-recipient class II HLA match is associated with reduced likelihood of developing HLA antibodies after Tx (p = 0.08, Fisher’s test). Development of HLA antibodies is associated with accelerated FEV1, decline and more episodes of acute rejection. Donor-recipient class II matching prior to lung Tx is associated with a reduced likelihood of developing new HLA antibodies and a slower decline in lung function, supporting the hypothesis that HLA matching before lung Tx may protect against development of BOS.

Conclusions None.

PLEURAL CAVITY IRRIGATION WITH TAUROLIDINE DURING LUNG TRANSPLANTATION MAY REDUCE POST-OPTATIVE EMPYEMA

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Taurolidine, a derivative of the amino acid taurine, has broad-spectrum anti-microbial effects, diminishes bacterial adherence and eradicates biofilms. It has numerous uses, including as peritoneal irrigation fluid. We hypothesised that taurolidine pleural cavity irrigation during bilateral lung transplantation (LTX) may reduce rates of empyema.

Methods 9 patients considered high risk for developing pleural infection after LTx had pleural cavity irrigation (1.25 L of warmed (37°C) 0.5% taurolidine) during bilateral lung transplantation (LTX) to may reduce rates of empyema. Following lung expansion, we compared the number of post-operative pleural fluid samples and episodes of empyema in these subjects to those from 8 other low risk subjects who underwent LTx without taurolidine.

Results Taurolidine was well tolerated without any reported adverse events and no episodes of post-Tx empyema. The mean number of post-Tx pleural aspirations was 1.44 (SEM 0.433) compared with 1.25 (SEM 0.491) among the non-taurolidine group. One subject (54 y, female, UIP) in the non-taurolidine group developed S. warneri empyema 8 days post-LTx.

Conclusions Pleural cavity irrigation with 0.5% taurolidine during bilateral LTx is well tolerated and has the potential to reduce the risk of post-operative empyema.

Conflict of Interest None.
CALCINEURIN INHIBITION CAN BE SAFELY MAINTAINED IN LUNG TRANSPLANTATION COMPLICATED BY REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME (RPLS)

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RPLS is a potentially devastating early complication of calcineurin inhibitor (CNI) therapy in solid organ transplantation. Management centres on cessation of CNI therapy, however this strategy is complicated in lung transplantation due to the threat of allograft rejection and bronchial dehiscence.

Methods Review of all cases of RPLS, confirmed with characteristic cerebral lesions on T2-weighted MRI, at our institution (n = 140 transplants).

Results 4 cases of RPLS were identified (incidence 2.8%, Table).

| Case | 1 | 2 | 3 | 4 |
|------|---|---|---|---|
| Age  | 50 | 26 | 61 | 13 |
| Sex  | M | M | F | F |
| Diagnosis | IPF | CF | α9-AT | CF |
| Days post-transplant | 9 | 68 | 10 | 312 |
| BP | 170/50 | 174/100 | 115/45 | 140/100 |
| Magnesium (mmol/l) | 1.29 | 0.79 | 0.64 | 1.24 |
| CNI level (ng/ml) | CyA 229 | Tac 26.9 | CyA 322 | Tac 31.9 |
| Changed to | Everolimus |

RPLS occurred early post-transplant in 2 cases in patients with CNI in the therapeutic range. In both, RPLS presented with altered sensorium alone with associated difficulty in extubation or a requirement for reintubation. The other 2 cases occurred in the context of CNI toxicity, with grand-mal seizures as the presenting symptom. All cases were successfully managed with a change in immunosuppression and aggressive BP control, with no neurological sequelae.

Conclusions A high index of suspicion is required to make the diagnosis of RPLS early post-transplant as symptoms may be atypical. CNI may be in the therapeutic range, and seizure activity may be absent. RPLS can be successfully managed in the setting of lung transplantation while maintaining calcineurin inhibition.

DEATH WITH A FUNCTIONING GRAFT AFTER LUNG TRANSPLANTATION: LESSONS FROM THE KIDNEY

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Rationale Death with a functioning graft (DWF) is a major cause (9–30%) of secondary graft loss after renal transplantation, DWF is rarely reported after lung transplantation (LTx) where obliterative bronchiolitis (OB), manifesting as severe lymphocytic bronchiolitis (LB) is an accepted major risk factor for chronic allograft dysfunction after lung transplantation (LTx). DWF is likely to become more common, so strategies to manage potential causes of DWF will assume greater importance.

Methods Single centre retrospective analysis of 341 90-day survivors of LTx who had haemorrhage (n = 341) or pneumothorax (n = 146) transplants, 1987–2008. 288/609 (47%) were deceased at 1279 days, 1987–2008. 288/609 (47%) were deceased at 1279 days.

Results 79/196 (40%) with graft failure had BOS 3, 53/196 (27%) had BOS 2, and 5/196 (2%) died with cardiac allograft dysfunction. Groups included: acute graft dysfunction; n = 14, prophylaxis (highly sensitised patients); n = 4, and chronic respiratory failure; n = 6. AMR treatment of acute and chronic allograft dysfunction comprised Rmab plus HD-IVIG or Rmab and PP plus LD-IVIG; prophylaxis comprised Rmab ± HD-IVIG.

Conclusion AMR after LTx should be considered when graft dysfunction occurs with or without associated cellular rejection but especially where refractory to standard therapies. Treatment with PP, IVIG and Rmab is generally well tolerated and may result in stabilisation of lung function if commenced early. Late empiric 'salvage' treatment is not beneficial. Precise diagnostic criteria for AMR are needed to enable effective prophylaxis and early intervention to maintain graft function.

ANTIBODY MEDIATED REJECTION AFTER LUNG TRANSPLANTATION: EMERGING DIAGNOSTIC AND THERAPEUTIC STRATEGIES

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Rationale Antibody mediated rejection (AMR) is now thought to contribute to chronic graft dysfunction after lung transplantation (LTx). AMR is caused by antibodies (Ab), typically against donor HLA antigens and does not respond to T-cell therapies. Treatment options include: (i) high-dose (1–2 gm/kg) intra-venous immunoglobulin (HD-IVIG) to block anti-HLA Ab, (ii) plasmapheresis (PP) plus low-dose (LD-) (0.1 gm/kg) IVIG to remove anti-HLA Ab and (iii) Rituximab (Rmab) (anti-CD20 chimeric Ab) (375 mg/m2) to deplete B cells.

Objective to describe outcome of treatment and prophylaxis for AMR after LTx.

Methods single centre retrospective review of AMR 2005–8. AMR diagnosis was based on presence of circulating anti-HLA Ab ± histopathology ± graft dysfunction. Groups included: acute graft dysfunction; n = 14, prophylaxis (highly sensitised patients); n = 4, and chronic respiratory failure; n = 6. AMR treatment of acute and chronic allograft dysfunction comprised Rmab plus HD-IVIG or Rmab and PP plus LD-IVIG; prophylaxis comprised Rmab ± HD-IVIG.

Results 7/14 acute dysfunctional patients (3 with donor specific Ab and 2 with donor Ab homology) improved or stabilised whereas therapy for chronic allograft dysfunction was ineffective. No prophylaxis patient developed primary graft dysfunction or hyperacute rejection and the single significant adverse event was an anaphylactoid reaction to Rmab.

Conclusion AMR after LTx should be considered when graft dysfunction occurs with or without associated cellular rejection but especially where refractory to standard therapies. Treatment with PP, IVIG and Rmab is generally well tolerated and may result in stabilisation of lung function if commenced early. Late empiric 'salvage' treatment is not beneficial. Precise diagnostic criteria for AMR are needed to enable effective prophylaxis and early intervention to maintain graft function.

SEVERITY OF LYMPHOCYTIC BRONCHIOLITIS AFTER LUNG TRANSPLANTATION: IMPLICATIONS OF THE NEW ISHLT GRADING SYSTEM

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Rationale Severe lymphocytic bronchiolitis (LB) is an accepted major risk factor for bronchiolitis obliterans syndrome (BOS) after lung transplantation (LTx).

Objectives We assessed the utility of the new 3-level ISHLT Grading system for LB to predict risk of BOS and death after LTx compared with the old 4-level system.

Methods Single centre retrospective analysis of 341 90-day survivors of LTx who underwent 1770 transbronchial lung biopsies (TBx) procedures.

Results TBx showed grade B0 (normal) (n = 501), B1R (mild) (n = 938), B2R (moderate-severe) (n = 74) LB and Bx (no bronchiolar tissue) (n = 75). 182 TBx were ungraded (8 inadequate, 142 cytomegalovirus, 32 other diagnoses). LTx recipients were grouped by highest B grade prior to the diagnosis of BOS ≥1: B0 (n = 12), B1R (n = 255) and B2R (n = 51). 23 patients were unclassifiable. Cumulative incidence of BOS and death were dependent on highest B grade (Kaplan-Meier, p < 0.001, log-rank). Multivariable Cox proportional hazards analysis showed significant risks for BOS were highest B grade (RR 1.94, CI 1.31–2.89) (p < 0.001) and longer ischemic time (RR 1.00, CI 1.00–1.00) (p < 0.05) while risks for death were BOS as a time-dependent covariable (RR 20.08, CI 11.56–34.87) (p < 0.001) and highest B Grade (RR 1.91, CI 1.02–2.22) (p < 0.05). Acute vascular rejection (Grade A on TBx) was not a significant risk factor for either BOS or death in multivariable analysis.

Conclusion The new ISHLT Grading system for LB confirms severity of LB is associated with increased risk of BOS and death after LTx independent of acute vascular rejection but has a lower discriminatory power than the old system as most evaluable patients fall into the B1R group.
Oropharyngeal colonization (OPC) was performed on all patients in the BOS group and the control group.

**Results**

**Exercise Induced Desaturation (SpO2)**

- **6MWD:** 6 minute walk distance, SpO2: resting oxygen saturation, RDI: respiratory disturbance index, SGRQ: St. George's respiratory questionnaire.

**Conclusions**

EID continues to improve for at least 3 months after bilateral lung transplantation. Patients with PGD will have a slower recovery in EID, but by 6 weeks post-transplant have reached the EID level attained by their non-PGD peers.
THE CHANGE IN LUNG FUNCTION AND EXERCISE CAPACITY IN THE FIRST SIX MONTHS AFTER LUNG TRANSPLANTATION

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Purpose Improvements in lung function and exercise capacity occur after lung transplantation, however the trajectory of this improvement is not well described. The aim of this study was to provide information on the trajectory of change in lung function, six minute walk distance (6MWD) and functional muscle strength (step test) in the first six months after lung transplantation.

Methods and Materials We prospectively evaluated consecutive lung transplant recipients at our centre from Dec 2006 until Feb 2008. All participants completed an exercise program consisting of both aerobic and strength training which was progressed throughout the first six months post transplant. Lung function (recorded as percentage of predicted FEV1), 6MWD and the number of steps completed during a one minute step test (22.5 cm) were assessed at 2, 6, 13 and 26 weeks after lung transplantation.

Results 13 patients (10 bilateral, 2 heart-lung & 1 single lung transplant; median age 41 years (range 22 to 58 years); 7 female; (5 CF, 3 COPD)) were studied. From baseline FEV1, of 26.7% (3.4% SEM) pre-transplant, there was a progressive improvement to 55.9% (4.0%) at 2, 73.5% (5.4%) at 6, 84.4% (6.3%) at 13 weeks and 84.2% (7.3%) at 26 weeks respectively. Baseline 6MWD of 382.5 metres (m) (39.6 m) pre-transplant, improved by 73.0 m (24.7 m) at 2, 101.6 m (28.7 m) at 6, 134.5 m (21.5 m) at 13 and 151.0 m (35.1 m) at 26 weeks respectively. Baseline step test of 19.0 steps (2.6) pre-transplant, improved by 7.9 steps (2.4) at 2, 12.9 steps (2.9) at 6, 14.4 steps (2.9) at 13, and 17.2 steps (6.3) at 26 weeks respectively. There was significant improvement in FEV1, between pre-transplant to 2 (p < 0.001), 2 to 6 (p < 0.001) and 6 to 13 weeks (p = 0.006), 6MWD between pre-transplant to 2 (p = 0.013) and 6 to 13 weeks (p = 0.006) and step test between pre-transplant to 2 (p = 0.035) and 2 to 6 weeks (p = 0.007).

Conclusion Improvement in exercise capacity after lung transplantation lags improvement in lung function. Our data suggests that this lag is due to slower recovery of functional muscle strength.

ECMO FACILITATES SUCCESSFUL MANAGEMENT OF SEVERE PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

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Rationale Severe primary graft dysfunction (PGD) after lung transplantation (LTx) is associated with significant early and late morbidity and mortality. Extracorporeal membrane oxygenation (ECMO) has been reported infrequently in this setting.

Objectives To review outcomes of ECMO for severe PGD post LTx.

Methods single centre retrospective analysis of LTx patients 2004–2008.

Results 5 bilateral LTx/147 LTx performed 2004–2008 sustained severe PGD (ISHLT Grade 3) and were managed with veno-venous (VV) ECMO within 24 hours.

| Patient | Age/Sex | Dx | PaO2/FIO2 | ECMO* | Intubated* | LOS* | Status FU* |
|---------|---------|----|----------|-------|-----------|------|-----------|
| 1       | 37 F    | OB | 45       | 11    | 40        | 71   | BOS 0 1555 |
| 2       | 15 F    | B  | 43       | 6     | 36        | 66   | BOS 0 825  |
| 3       | 36 F    | PHT| 53       | 6     | 28        | 65   | BOS 0 172  |
| 4       | 21 M    | OB | 32       | 18    | 38        | 78   | BOS 0 118  |
| 5       | 46 F    | PF | 54       | 7     | 36        | 43   | BOS x 43   |

Dx = diagnosis, OB = obliterative bronchiolitis, B = bronchiectasis, PHT = pulmonary hypertension, PF = pulmonary fibrosis, * = days, LOS = length of stay, FU = follow-up. Patient 4 was converted from veno-arterial (VA) to VV ECMO after 6 days. Patients 3, 4 and 5 also received endobronchial surfactant replacement therapy. Complications included digital ischaemia (n = 1), lymphocele (n = 1), deep venous thrombosis (n = 1) and femoral venous cannula site dehiscence (n = 1) but all have recovered.

Conclusion The data support early institution of ECMO in patients with severe PGD post LTx to minimize risk of barotrauma, volutrauma and pulmonary oxygen toxicity and to facilitate complementary therapeutic modalities which may limit graft injury.

DOES MANNOSE-BINDING LECTIN (MBL) DRIVE COMPLEMENT ACTIVATION FOLLOWING LUNG TRANSPLANTATION?

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We have previously demonstrated that complement activation, as judged by lung allograft deposition of C3d/C4d, is common early post-lung transplant and may be triggered by primary graft dysfunction and/or airway infection. Given that Mannose-Binding Lectin (MBL) is a key driver of complement activation, we hypothesised that MBL levels may increase early after transplantation.

Methods Serum blood MBL levels (ELISA, pg/ml) and function, as measured using a previously characterised C4b deposition assay, was assessed pre-transplant, and 3, 6, and 12 months post-transplant in 41 lung transplant recipients. MBL function was correlated with a number of clinical outcomes including primary graft dysfunction, acute rejection episodes, microbial infection and chronic graft dysfunction.

Results MBL genotype (AA, n = 22; AO, n = 13; OO, n = 6) predicted pre-transplant serum levels of MBL. Levels of MBL were elevated at all times post-transplantation compared to pre-transplant levels (1.6 µg/ml pre-transplant vs. 2.8 µg/ml, p < 0.005; 3.1 µg/ml, p = 0.01; and 2.3 µg/ml, p = 0.02 at 3, 6 and 12 months post-transplant respectively). C4 deposition was elevated at 6 months post-transplant compared to pre-transplant levels (0.42 U/100 ml vs. 0.54 U/100 ml, p < 0.05).

Conclusion MBL levels increase significantly following lung transplantation, and may potentially result in the activation of complement that is known to be associated with poor graft function. As such, our results provide mechanistic support to previous studies that have demonstrated that complement inhibition early post-transplant reduces primary graft dysfunction.

Supported by Alfred Hospital Short Project Grant.
PRECEEDING RESPIRATORY VIRAL INFECTION IS A STRONG RISK FACTOR FOR FUNGAL INFECTION IN LUNG TRANSPLANT RECIPIENTS

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Introduction: Respiratory viral infections (RVI) are associated with significant denudation of the bronchial epithelium and requirement for pulse steroid therapy for management of acute allograft dysfunction. Consequences of this may include fungal colonisation and subsequent invasive disease.

Aim: To evaluate the risk of fungal acquisition within 8 weeks of diagnosis of RVI in lung transplant patients.

Methods: Retrospective analysis of 151 patients from a single institution between January 2003 and July 2008. Those with symptoms of respiratory viral infection underwent nasopharyngeal aspirates (NPA) and patients with positive samples (human Metapneumovirus, RSV, parainfluenza 1–3, influenza or adenovirus) and graft dysfunction received a treatment protocol incorporating intravenous ribavirin, pulse steroids and/or broad spectrum antibiotics.

Invasive fungal infection was defined according to Mycosis Study Group definitions.

Results: Seventy-four patients had 459 visits for NPA studies with 129 samples (28.1%) PCR positive for RVI. On 44 occasions (34.1%) in 34 RVI positive patients, a filamentous fungal pathogen was isolated on lower respiratory tract sampling within 8 weeks of diagnosis with Aspergillus species the most common isolate (67%). Invasive infection was confirmed in 62% of patients with a fungal isolate with no predilection for a particular RVI.

Conclusions: Aggressive antifungal prophylaxis is warranted in all lung transplant recipients presenting with respiratory viral infection to diminish the risk of subsequent invasive disease.

ELEVATED EXPRESSION AND ACTIVITY OF MATRIX METALLOPROTEINASE (MMP) 2 & 9 IN AIRWAYS OF LUNG ELEVATED MMP 2 & 9 IN AIRWAYS OF LUNG TRANSPLANT RECIPIENTS

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BOS is fibroproliferative disease of lung allografts. Epithelial to mesenchymal transition (EMT) has been implicated in its development. MMPs are upregulated in EMT, degrade basement membrane and increase cell motility. We hypothesized that MMPs are upregulated in bronchial epithelium in BOS.

Aim: To assess MMP 2 & 9 expression and activity in bronchial epithelium in BOS vs. non-BOS lung transplant recipients and determine their role in EMT.

Methods: Epithelial was obtained from large (LAEC) and small (SAEC) airway of BOS and non-BOS patients (n = 4 & 15) and healthy paediatric controls (n = 5). MMP 2 & 9 and TIMP 1 & 2 gene expression was assessed by qPCR and immuno-histochemistry (IHC). MMP activity was assessed using zymography in broncho-alveolar lavage (BAL) supernatant of a primary cell culture model of EMT.

Results: MMP 2 & 9 gene and protein (IHC) expression was significantly increased in BOS LAEC (2.5, p < 0.01 & 6.6 fold, p = 0.02 respectively). Expression was non-significantly elevated in BOS SAEC (2.2 & 1.3 fold respectively). MMP 2 & 9 activity was significantly increased in BAL of BOS patients compared to non-BOS (3.72, & 2.97 fold respectively, p < 0.01) and also in SAEC and LAEC undergoing EMT in vitro.

Discussion: Elevated MMP activity is a central feature of EMT and may play a key role in BOS pathogenesis. MMP inhibitors (eg doxycycline) may have clinical utility in BOS.

RESPONSE TO UNCONJUGATED PNEUMOCOCCAL VACCINE IN CHILDREN WITH BRONCHIECTASIS OF UNKNOWN AETIOLOGY

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Background: Diagnosis of an underlying primary immune deficiency may influence treatment, prognosis, and has wider family implications as many are genetic disorders. Bronchiectasis (BX) is found between 1.5 and 17.8 per 100 000 children per year in New Zealand depending on ethnicity. Studies in adults with apparently idiopathic BX found an underlying defect of specific antibody production to polysaccharide antigens in approximately 10%. There are no series assessing this in children.

Aim: To assess response to unconjugated pneumococcal vaccine in children with BX of unknown aetiology to reveal a possible immunoglobulin subtype deficiency.

Methods: Children aged 2–16 years attending BX clinic had an immune workshop review. If pneumococcal responses had not been tested, baseline serology was obtained, Pneumovax® given with consent, and a further serology sample obtained 3 weeks post vaccination. Paired sera were sent to the Royal Children’s Hospital, Melbourne for serotype specific assay.

Results: 178 children attended the BX clinic in 2008, 122 fulfilled inclusion criteria, 18 were lost to follow-up, leaving 104 children approached with 90 (87%) vaccinated. Nine were abnormal – 3 definitively abnormal, 6 inconclusive, all had delayed post vaccine blood taken up to 4 months later. One child is being considered for regular immunoglobulin therapy, 4 have been put on regular prophylactic antibiotics with good clinical response, 5 are awaiting further immune workshop with other vaccine responses.

Conclusion: We detected abnormalities in pneumococcal vaccine subtype responses in 10% of these children with idiopathic BX. This testing should be standard practice as part of the immune work up for BX.

Conflict of Interest: None.
NEBULISED ANTIBIOTICS REDUCE SYMPTOMS, BACTERIAL DENSITY AND ORAL ANTIBIOTIC USAGE IN CHILDREN WITH NON CYSTIC FIBROSIS BRONCHIECTASIS

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Introduction Nebulised antibiotics have proven benefit for cystic fibrosis (CF) but have not been trialled in children with non CF bronchiectasis (BX). BX has twice the incidence of CF in our community and is associated with significant morbidity and mortality.

Methods We conducted a randomized, double-blind, placebo-controlled crossover (2 × 3 month treatment periods) trial of 80 mg gentamicin nebulised twice daily (PARI LC plus nebuliser). Entry criteria included age 5–15 years, HRCT scan proven BX, negative sweat test, reliability with spirometry and chronic Haemophilus influenzae infection. Outcomes recorded included monthly spirometry, symptom scores, hospitalisation & antibiotic history and sputum samples for microbiology.

Results 15 participants were enrolled; 53% female, 93% from Pacific Indigenous communities and 80% had idiopathic or post-infectious BX. Disease was extensive – all had bilateral involvement (mean of 4 lobes) with mean FEV1, 63% predicted. Improvements were seen in sputum bacterial density (mean fall of 2.66 vs rise of 1.5 log10 cfu/ml, p < 0.001), symptom score (mean fall of 1.5 points vs rise of 1.1, p = 0.01) and oral antibiotic usage (mean 1 vs 10 days, p = 0.04) while on gentamicin therapy compared with placebo. No significant differences were found in lung function or hospitalisation rate. Recorded adherence was poor.

Conclusion This pilot study found nebulised gentamicin was well tolerated, reduced bacterial infection, reduced symptoms and reduced oral antibiotic usage but did not improve lung function or hospitalisation rates. While this may prove a useful adjunctive therapy, the low adherence in our community is a concern.

Sponsor Child Health Research Foundation, New Zealand.

Conflict of interest None.

VIDEO-COLLABORATIONS: ENHANCED RESPIRATORY RESEARCH COMMUNICATIONS VIA EXCLUSIVE AARNET INTERNET NETWORK

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Internet-based communications have revolutionised research communication and collaborations across the world. Recent rapid increases in computing power, network bandwidth and speed have added data-rich graphic and video/movies to traditional text and file interactions. The wide deployment of optical fibre along the Australian academic network backbone (AARNet) and internationally now permits collaborative environments supporting instant file sharing, multiple real-time video streams, whiteboards, remote sensing, virtual and collaborative interactions. All at once. Because AARNet links all Australian academic institutions separate from the commercial Internet the reliability, speed, and capabilities far exceed public Internet capabilities. Our academic networks already support data-rich experimental and collaborative interactions.

This presentation will outline two free research-specific video-collaboration tools (EVO, AccessGrid) and review the extraordinary levels of optic-fibre based collaboration and ‘telepresence’ becoming available (OptiPuter). With continually developing infrastructure, and end-user support via NCRIS sponsorship, respiratory researchers should not ask of Internet collaborations ‘what can I do’, but ‘what do I want to do’? Supported by the NH&MRC.
RESPIRATORY SYMPTOMS IN THE FIRST 3 YEARS OF LIFE IN EX-PREMATURE INFANTS AND CHILDREN

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Changes in neonatal care over recent decades have dramatically affected the outcome for premature infants. In particular the epidemiology and nature of lung disease in this group has changed. There is a paucity of contemporary information regarding the respiratory health of young children born preterm with and without lung disease.

Aims To determine the frequency of respiratory symptoms in young children with a history of preterm birth and examine the effects of postnatal lung disease (bronchopulmonary dysplasia – BPD) on respiratory symptoms.

Methods Parents of children born at less than 32 weeks gestation between July 1993 and December 2003 completed a postal respiratory symptom questionnaire at 1, 2 and 3 years of age.

Results Of 2634 surviving children, information about duration of supplemental oxygen requirement was available for 2414 (31% with BPD). There were no significant differences between the BPD and nonBPD groups with 31% and 27% respectively having wheeze in the previous 12 months. Similarly there were no significant differences in the prevalence of cough without colds in the previous 12 months or parentally reported or doctor diagnosed asthma ever.

Conclusion Children aged 4 to 8 years and born preterm have worse lung function when compared to healthy controls. In these preterm children with and without BPD we found similar symptom prevalence. Respiratory symptoms are common over the first 3 years of life in ex-premature children. Children with a history of BPD have more symptoms, and more respiratory illnesses than those without. This effect persists at 3 years of age.
PULMONARY FUNCTION ABNORMALITIES ON LONG-TERM FOLLOW-UP OF CHILDREN WITH TRACHEOBRONCHOMALACIA

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Primary tracheobronchomalacia (TBM) is a disease of the large airways. No long-term follow-up studies of TBM patients have been reported. This study was undertaken to further elicit this natural history of this condition and the presence of concomitant reactive airways disease through clinical profiling and pulmonary function testing.

Methods Twenty-one children diagnosed with TBM by bronchoscopy between 1998 and 2001 in Queensland were recruited in 2006. Parents completed a questionnaire detailing their child's respiratory symptoms over the previous 12 months. Children then undertook pulmonary function testing to define spirometry parameters, flow-volume loop classification, and mannitol bronchial provocation testing (MBPT).

Results Data from 19 children (12 males) were analysed. The median age was 9.4 (range 7.6, 14.3) years. 15 parents indicated their child's symptoms were unresolved. The mean FEV1pp was 81% with 7 < 80% predicted. This was significantly lower than the percent predicted population mean (p = 0.0005). Mean FEV1/FVC, FEF25–75 and peak expiratory flow (PEF) were also lower than the percent predicted population mean (p < 0.0001). 4 participants had a classical TBM flow-volume loop on analysis. MBPT was negative in all participants. There was no correlation between Spirometry parameters, MBPT and symptom severity.

Conclusions Clinical symptom profiles and pulmonary function indicate persistent functional mechanical abnormalities of the large and small airways in TBM patients, and the absence of reactive airways disease as defined by MBPT. Supported by the UQ School of Medicine & RCH Working Wonders Foundation.

Conflict of Interest No.

SPIRO-GP: BASELINE FINDINGS FROM A TRIAL OF PEDIATRIC SPIROMETRY IN GENERAL PRACTICE

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Background Guidelines recommend spirometry for diagnosis and monitoring of asthma control. SPIRO-GP is a trial of spirometry to improve management of asthma in General Practice (GP). Here we report baseline findings in children and adolescents.

Methods A randomised controlled trial involving 31 GPs randomised to 3 groups: Group A 3 monthly spirometry and regular follow-up; Group B spirometry before and after the trial; Group C usual care. All participants had 'Doctor diagnosed Asthma'. All completed the Paediatric Asthma Impact Survey (PAIS) at Baseline, 3, 6, 9 and 12 Months. The modified Children and Adolescent Asthma Management (ICAM) survey was completed at Baseline. Spirometry was performed before and after bronchodilator (BD) following ATS/ERS guidelines.

Results 75 patients (median age 13, 8–18 years), 41 (55%) males. 37 (49%) had episodic asthma and 38 (51%) persistent asthma.32 (43%) participants had PAIS scores >55 indicating substantial impact on daily function, 20 (63%) of these had persistent asthma. Mean FEV1 (%predicted) was 86.7%, (range 57% to 116.5%). 16 (29%) had FEV1 below 80%, 9 (16%) of these had persistent asthma. There was no correlation between prior asthma and Spirometry (Spearmann's rho = 0.019, p = 0.89).

Conclusions The quality of life of children and adolescents with asthma managed by GPs is substantially impaired. However spirometry was not closely related to the pattern of asthma or quality of life. Supported by NHMRC.

LOWER RESPIRATORY TRACT INFECTION (LRTI) LENGTH OF STAY (LOS) AS A QUALITY OF CARE INDICATOR

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Background Quality of hospital care is difficult to define and even harder to measure. Over 90% of bed days at Alice Springs Hospital Department of Paediatrics are for Aboriginal children, with a high burden of infectious diseases. Of the ~2000 admissions/year, the greatest diagnostic groups are LRTI and Acute Gastroenteritis (AGE). We developed indicators based on LRTI and AGE ICD-10 codes, and examine LOS monthly.

Methods Business Objects was used to interrogate the medical records database on a month-by-month basis from January 2001- Jun 2008. All relevant ICD-10 codes for LRTI and AGE were identified. All hospital discharges with these codes were counted, and their lengths of stay in hospital added each month. The accumulated and average LOS were examined by month. Time series analysis was used to analyse change.

Results An analysis of LOS and episodes shows a decline in LOS over time, and since 2006 the number of episodes has fallen more steeply and those episodes are discharged sooner.

Conclusion The LRTI LOS tool offers a good snapshot of activity (accumulated score) and efficiency (average LOS) of care of hospitalized paediatric respiratory cases. No funding nor conflict of interest.

COMPARISONS OF QUALITY OF LIFE AND COUGH COUNTS IN CHILDREN WITH CHRONIC COUGH FOR DIFFERENT RESPIRATORY DIAGNOSES

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Cough is consistently the most common symptom presenting to general practitioners and respiratory doctors. Chronic cough causes a significant burden at the personal level (through impaired quality of life). We compared the QOL of children with different diagnoses to evaluate if QOL was worse in some respiratory diagnoses.

Methods At recruitment parents of 88 children with chronic cough (>3 weeks) completed a parent specific cough QOL (PC-QOL) (min 0, max 7).

A subgroup (N = 30) had their cough recorded using a digital voice recorder. Total cough counts were compared between diagnoses. The diagnosis was made by the treating physician based on TSANZ cough position statement. The physicians were unaware of the QOL results.

Results The median age of the children with Protracted Bacterial Bronchitis (PBB) (N = 59) was 1.8 years (IQR 3.02), that of other diagnosis (N = 29) was 3.3 years (IQR 2.71). The median QOL for children with PBB was 4.78 (IQR 1.70), QOL of other diagnosis was 4.88 (IQR 1.61) (p = 0.96). Within the group with PBB (N = 59), those with only PBB (N = 24) had a similar QOL to those with PBB and a secondary diagnosis (respective QOL was 4.85 (IQR 1.85), 4.78 (IQR 1.70), (p = 0.81). The median total cough count was highest in the children with bronchiectasis (178, IQR 381) and lowest in those with asthma (50, IQR 412) (p = 0.22) but there was no significant difference.

Conclusion The cough specific QOL of parents with a child with chronic cough is poor and is independent of diagnosis. Objective cough counts did not significantly differ between groups. Supported by Royal Children's Hospital Foundation.
WHAT DO TSANZ MEMBERS KNOW ABOUT CHILDREN’S ENVIRONMENTAL HEALTH?

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A number of childhood diseases are linked to unsafe and degraded environments. However, many health care providers (HCP) are unable to recognize, assess and manage environmentally-related diseases in children. To obtain a better understanding of potential environmental threats to children’s health, a survey was conducted amongst members of the TSANZ. All members were invited to participate through a web based questionnaire enquiring into the extent of their awareness of issues in children’s environmental health (CEH). Responses were received from 5 paediatricians, 21 adult physicians, 7 allied health personnel and 10 scientists, with 26.3% of respondents indicating their knowledge of CEH was minimal or non existent, 66.7% graded their knowledge as average and only 7% considered their knowledge in CEH as extensive. Responses however were indicative of low awareness of hazardous environments to children. Disparities were found in the type of hazards perceived to negatively affect children’s health and the different impacts of environmental threats on the health outcomes of girls and boys. The lack of awareness and knowledge on CEH within TSANZ members highlights the need for advocating for the inclusion of CEH in the educational preparation of HCP dealing with children to prevent, recognize, manage, and treat environmental-exposure-related disease. Such educational efforts should be included in undergraduate, postgraduate and continuing paediatric, medical and nursing education.

AIRWAY CELLULARITY IN CHILDREN WITH NON-CYSTIC FIBROSIS BRONCHIECTASIS: IMPLICATIONS FOR CLINICAL MANAGEMENT

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Bronchiectasis is an important disease in Northern Territory children. Although airway cellular profiles are a recognised tool in managing respiratory disease there is little data available on the airway cellularity associated with paediatric non cystic fibrosis (CF) bronchiectasis (BE). This preliminary study aims to characterise the airway cellularity associated with non CF BE and determine if findings would influence clinical management.

Methods Total and differential cell counts were performed on bronchoalveolar fluid (BAL) collected from children undergoing flexible bronchoscopy at Royal Darwin Hospital. BE was confirmed by HRCT.

Results BAL was processed from 27 children (26 Indigenous) with a median age of 2.3 years (range 0.7–9.8 years). The median cell count per ml BAL retrieved was 0.48x10^6 (0.15–11.3). The median percent of macrophages was 68.7% (range 0.3–90.7%). That for neutrophils was 10.0% (0–69.7%), lymphocytes was 5.3% (0–61.7%) and eosinophils was 2.3% (0–59.7%). Airway eosinophilia (>2%) was present in 15 of the 27 children (55.6%).

Conclusion A substantial number of children with bronchiectasis in the NT have clinically important airway eosinophilia. As the presence of airway eosinophilia alters clinical management we conclude that in addition to providing microbiological data, BAL provides information that would alter the clinical management of children with non-CF bronchiectasis in our region. The reasons for the high airway eosinophilia found remains undetermined.

EXPLAINING DIFFICULT DIAGNOSES – HOW DO SPECIALISTS EXPLAIN SARCOIDOSIS TO THEIR PATIENTS AND WHAT DO PATIENTS LOOK FOR?

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Introduction Explaining complex medical disorders such as sarcoidosis, so patients understand, requires both an awareness of the patient’s general understanding of the body, as well as the need for important facts to be conveyed.

Method Two questionnaires were created – one to ask specialists how they explained sarcoidosis to their patients and whether they used resource materials, and the other to ask patients how well they thought they understood sarcoidosis, if they read or accessed other materials, and how this helped them. Internet materials were evaluated using the DISCERN quality assessment tool.

Results 12 specialists and 10 patients were surveyed. The results indicated a uniformity of information necessary to be conveyed by the specialists, and a variety of resources accessed by the patients because of their curiosity and belief that they may not have time to go over it again, and thus seek out their own information base. Internet based information, evaluated in terms of the DISCERN criteria, is discussed.

Conclusion Because patients access the Internet for information, specialists should support their own explanations by directing their patients to valid, reputable sites.
Conclusions
Most GPs self-reported practice of prescribing inhaled corticosteroids recommendations. They were aware of the national guidelines, less than 30% were familiar with guidance. An asthma action plan was suboptimal and familiarity with national asthma guideline recommendations was low despite a high level of awareness. These findings suggest the importance of determining baseline practice and beliefs and indicate the potential for an educational intervention to improve paediatric asthma management practice. Supported by the Australian Government Department of Health and Ageing.

Results
Post-bronchodilator (post-bd) spirometry was available for 445 subjects (mean age 65 years, 51% female).

Diagnosis
Definition Prevalence
COPD Post-bd FEV1/FVC (ratio) < 0.70 257 (58%)
GOLD 2 As above & FEV1 < 80% predicted 216 (45%)
GOLD 3 or 4 As above & FEV1 < 50% predicted 103 (23%)
Possible asthma Pre-bd T in FEV1 > 12% & ≥200 ml 63 (14%)
Normal Pre-bd ratio <0.70 & FEV1 > 80% pred. 88 (20%)

Conclusions
A substantial proportion of patients identified as having COPD in general practice do not have the condition according to spirometric criteria. This may result in inappropriate management for these patients. Reasons for the high level of inconsistency and barriers to using spirometry in general practice need to be examined and addressed.

Supported by NHMRC.
Conflict of Interest
Nil.

THE STATUS OF PAEDIATRIC ASTHMA MANAGEMENT IN NSW GENERAL PRACTICE

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As paediatric asthma is largely managed in primary care, understanding general practitioner (GP) beliefs about asthma management in children is important. We set out to measure the baseline beliefs and reported current paediatric asthma management practice among GPs participating in a randomised controlled trial of the Australian PACE program.

Methods
A total of 114 GPs (50% of study GPs) completed a baseline questionnaire about beliefs, confidence and current paediatric asthma management practice.

Results
Of the 114 GPs, 82% reported appropriately prescribing inhaled corticosteroids (ICS) for patients with interval symptoms, and over 50% were confident in their ability to discuss and monitor side effects of ICS. 90% of GPs reported providing spacers and 86% of GPs agreed that patients should have an asthma action plan. However, only 66% reported regularly providing spacers and 86% of GPs agreed that patients should have asthma action plans was suboptimal and familiarity with national asthma guideline recommendations was low despite a high level of awareness. These findings suggest the importance of determining baseline practice and beliefs and indicate the potential for an educational intervention to improve paediatric asthma management practice. Supported by the Australian Government Department of Health and Ageing.
Pathogenes have influenced the evolution of humans, with signatures of natural selection detected in pathogen-specific resistance genes as well as several immune genes. An important role of the immune system is in protection against many different tropical parasites and this is mediated by Th2 immune responses. Based on these observations plus previous preliminary data on limited numbers of subjects and genotypes, we hypothesized that human populations living closer to the equator would retain Th2-biased immune responses compared with humans living in temperate or colder environments.

Methods To investigate this in a broader range of populations and genotypes, we tested for correlations of genetic bias towards Th2 responses with ancestral latitude and climate. Study populations (Inuit, Finns, European and Aboriginal Australians, Italians, Xhosans and Warao Amerindians) were genotyped for 24 Th1-2 polymorphisms. Genotype data from a subset of the Hapmap populations were chosen to supplement the analyses.

Results The majority of pro-Th2 allele frequencies correlated with latitude (17 vs. 7; P = 0.064) and climate (18 vs. 6; P = 0.024). Using principle component analysis, 32% of the variation in the pro-Th2 dataset was correlated with both latitude (r = 0.894; P = 0.003) and climate (r = 0.838; P = 0.009).

Conclusion These results suggest that a genetic bias away from Th2 responses evolved in non-tropical vs. tropical populations. These findings may have important implications for population susceptibility to Th1-2 diseases.

Funding NH&MRC and ARC.
Nomination None.
Conflict of Interest None.

PARADOXICAL REACTION OCCURRING FIVE YEARS AFTER COMPLETION OF ANTI-TUBERCULOUS TREATMENT

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Paradoxical enlargement of tuberculous lesions is a known phenomenon that may occur during the course of anti-tuberculous chemotherapy. Less well described is the enlargement or development of sterile granulomatous lesions after completion of adequate therapy. We report a single case of smear- and culture-negative granulomatous lesions occurring 5 years after initial presentation.

A 30-year-old Korean man presented to our institution in 2004 with right-sided cervical adenopathy and fever. He had previously been diagnosed with tuberculous lymphadenitis of the neck in 2001 and undergone 18 months of non-observed therapy with rifampicin, isoniazid and ethambutol for a fully sensitive organism. We performed fine needle aspiration that was smear-positive for acid-fast bacilli. Mycobacterial culture was negative. Directly observed therapy was commenced with rifampicin, isoniazid, ethambutol and pyrazinamide. After initial improvement the mass enlarged five months into treatment and prednisone was commenced for presumed paradoxical tuberculous reaction. The lymph nodes recrudesced and anti-tuberculous medication continued for a total of nine months. In 2006 the patient represented with a recurrent right-sided neck lesion and oedematous draining sinus which was excised surgically. Histology showed caseating, granulomatous inflammation with no organisms seen on Ziehl-Nielsen and methenamine stains. Culture was negative for M. tuberculosis. Quantiferon gold assay and tissue PCR were both positive. No further anti-tuberculous or steroid therapy was given and the patient remained disease-free after 2 years observation.

This case demonstrates that smear- and culture-negative lesions with characteristic histology and positive PCR may occur some time after cessation of treatment and that they can be managed without recourse to further anti-tuberculous chemotherapy.

MYCOBACTERIUM ASIATICUM DISEASE IN QUEENSLAND, AUSTRALIA

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Mycobacterium asiaticum was first reported as a cause of human disease in 1982. The paucity of cases in the literature makes it hard to identify the full spectrum of disease, the clinical significance of isolates and appropriate management.

Aim To describe the epidemiology, clinical features, radiology, and treatment of disease due to M. asiaticum in Queensland.

Methods A retrospective review (1989–2008) of patients with M. asiaticum isolates was conducted. Data was collected through the Queensland TB Control Centre database. Disease was defined in accordance with the American Thoracic Society criteria.

Results There were 23 patients (13 female) who had a positive culture of M. asiaticum, with many residing around the Tropic of Capricorn. M. asiaticum was considered responsible for pulmonary disease (n = 1), childhood lymphadenitis (n = 1), and olecranon bursitis (n = 1). There were 6 cases of possible pulmonary disease and 2 possible wound infections. Risk factors for pulmonary infection included bronchiectasis, chronic obstructive pulmonary disease, cystic fibrosis and lung cancer, and wounds/lacerations for extrapulmonary disease. Clinical features were similar to those observed for other nontuberculous mycobacterial (NTM) species. Extrapulmonary disease responded well to local measures. In the patient with significant pulmonary disease, spumon conversion was eventually achieved with a combination of amikacin, azithromycin and minocycline.

Conclusion Despite the distribution of cases, even in a relatively small cohort, this study adds to the growing body of literature regarding M. asiaticum disease. Further evaluation of disease characteristics and treatment approaches is warranted.
Socioeconomic Deprivation in Bronchiectasis

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Introduction The prevalence of bronchiectasis is higher in Maori and Pacific Islanders (PI) than Europeans. It is not known whether this is the result of different host defence mechanisms or socioeconomic deprivation. The aim of this study was to evaluate the socioeconomic status of a cohort of patients with bronchiectasis.

Methods Socioeconomic status was evaluated using the NZ deprivation 2006 index (NZDep06) which provides a deprivation score for a geographical unit based on residential address (1 = least deprived, 10 most deprived). Scores for 331 bronchiectasis patients (63% female, mean age 62 yrs, FEV1% predicted 63) were determined. Demographic and clinical variables were recorded. Ethnicity was compared to NZ Department Statistics 2006 census data for central Auckland.

Results PI (21%) and Maori (12%) are over-represented in this cohort and European (47%) and Asian (15%) under-represented. The median NZDep06 score was higher for PI (9) and Maori patients (8) than Asian (5) and European (5). When compared to local demographics the percentage of patients in deciles 8–10 is higher for all ethnicities except Asian. The FEV1 %predicted was significantly lower in Maori and PI compared to European and Asian patients (p < 0.0001) and remained so when corrected for smoking status and NZDep06 score (p = 0.0003).

Conclusion Bronchiectasis is more common in PI and Maori and associated with a high prevalence of socioeconomic deprivation. Using FEV1 %predicted as a marker of severity, disease is more severe in Maori and PI independent of socioeconomic deprivation and smoking. Further study is required to investigate if this is related to cultural or host defence differences. No conflict of interest.

Innate Immune Response of Bronchial Epithelial Cells to Human and Avian Influenza Virus

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Human bronchial epithelial cells (BECs) are the primary site of infection by influenza viruses, and their antiviral response to infection is likely to influence the outcome of infection. Our aim was to characterize and compare the anti-viral responses in BECs during human and avian influenza viruses infections. Our aim was to characterize and compare the anti-viral responses in BECs during human and avian influenza viruses infections.

Methods Calu-3 and A549 was used as a model for proximal and distal BECs, respectively. Primary bronchial epithelial cells (pBECs) were obtained by endobronchial brushing from healthy non-smoking volunteers. Human influenza A/H3N2 and a low pathogenic avian influenza A/H1N1 were used to infect BECs at an MOI of 5. RIG-I, MDA-5, TLR3 and IFN-β mRNA induction was measured by RT-qPCR. Supernatants and whole cell lysates were harvested for protein detection by western blotting and viral replication by plaque assay on MDCK cells.

Results Human influenza replicated to a higher titre than the avian influenza in Calu-3 (p < 0.05). Replication was significantly lower in pBECs. RIG-I, MDA-5, and IFN-β mRNA were highly induced, TLR3 and PKR mRNA were slightly induced by both viruses. H1N19 induced higher RIG-I, MDA-5 and IFN-β protein expression in Calu-3 and pBECs compared to H3N2 infection. Conclusion Low pathogenic avian influenza virus replicated less well in human airway epithelial cells and was associated with a greater innate antiviral response to infection. This appeared to be due to better post translational inhibition of early innate responses by the human adapted H3N2 strain.

Conflict of Interest None.

Use of the ‘CURB 65’ Score in Clinical Practice

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Background The ‘CURB-65’ score is a well validated, easy to use tool for the assessment of severity in community acquired pneumonia (CAP). Use of the score is recommended best practice in many hospitals but whether this happens is unknown. The aim of this study was to determine the frequency of use of the score in routine clinical practice and correlate this with clinical decision making and patient outcome.

Methods Retrospective cohort study of all patients with CAP (n = 186) presenting in 3 months. Demographic and clinical outcome data was recorded and comparisons were made between those patients who had score applied on admission with those that did not. A CURB-65 score was assigned to all patients using data from the patient record, and admission decisions were compared.

Results Only 9 (4.8%) CAP patients had the ‘CURB-65’ score applied at admission and 12 (6.4%) patients were managed as outpatient. The overall mortality rate was 4.3% with confusion associated with significantly higher mortality (35%, p < 0.0001). On applying a score to all cases retrospectively, mortality rate and length of hospital stay for patients with moderate or severe pneumonia was in accordance with published results. 24 (13%) patients under age 65 with mild CAP and no co-morbidities were admitted.

Conclusions These data demonstrate that clinical decision making in respect of moderate or severe CAP is the same whether or not a pneumonia severity score is applied. However failure to use the score leads to patients with mild CAP, who could have potentially been treated at home, being admitted. This study indicates that use of the CURB-65 score in routine hospital practice might reduce unnecessary admission. Conflict of Interest Nil.

Eradication of Pseudomonas Aeruginosa in Patients with Non-CF Bronchiectasis with Intravenous Antibiotics and Nebulised Colomycin

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Background Patients with bronchiectasis who are colonised with Pseudomonas aeruginosa (PA) have reduced quality of life and more frequent exacerbations. Eradication can be difficult and optimal therapy is not well defined. The aim of this study of patients with bronchiectasis with PA isolated from sputum who were admitted for intravenous treatment was to determine the frequency of prolonged eradication and predictors of success.

Methods A review of consecutive patients admitted following a first isolate of PA between 2003 and 2007 was performed. Clinical characteristics, lung function, treatment and clinical outcome data were reviewed.

Results Thirty-three patients were identified; 8 (24%) male, mean age was 47.5 years (16.8 SD). Twenty-eight (85%) patients had failed initial treatment with oral ciprofloxacin. The mean duration of anti-pseudomonal intravenous antibiotic treatment was 10 days (1SD) and 32 (97%) patients were treated with nebulised colomycin for 1 month after discharge. At 12 months 13 (39%) patients remained culture negative for PA and 10 (30%) patients had sustained eradication for the duration of follow-up which included regular surveillance. The mean length of follow-up was 2.6 years (1.2SD). The mean FEV1 in the cohort with sustained eradication was 75.6% compared to 69.2% (p = 0.47).

Conclusion Invasive treatment followed by nebulised colomycin resulted in a sustained period of PA eradication in 30% of non-CF bronchiectasis patients. The mean FEV1 was higher in the cohort with sustained eradication. Successful PA eradication was associated with a reduction in hospital admissions. Conflict of Interest None.
ADHERENCE TO NATIONAL COMMUNITY ACQUIRED PNEUMONIA GUIDELINES IS SUBOPTIMAL

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**Introduction** Following the CAPTION national audit in 2005, targeted interventions were performed to increase adherence to Therapeutic Guidelines (TGs). This audit aimed to assess local management of community acquired pneumonia (CAP) and determine the effectiveness of these interventions.

**Methods** A retrospective casenote audit of CAP over winter 2007. Data included investigations, pneumonia severity index (PSI) use, initial antibiotic choice, length of stay, inpatient mortality and concordance with TGs.

**Results** 108 cases were analysed. Comparisons to CAPTION are summarised in the table below. Cultures: sputum sent in 41%, blood in 68%, both in 10%. 23% claimed rarely or never to prescribe according to the guidelines. 23% claimed rarely or never to prescribe according to the guidelines.

| CAPTION 2007 | Current Audit 2007 |
|--------------|-------------------|
| PSI documented, % | 5 (13) |
| Concordant with guidelines, % | 18 (19) |
| Adequate empiric therapy, % | 37 (70) |

**Conclusions** There has been no improvement in assessment and treatment of CAP since CAPTION 2005. Further education is required to improve concordance and this must also target senior staff.

A RANDOMISED CONTROLLED TRIAL OF HIGH FLOW VERSUS TITRATED OXYGEN THERAPY IN THE MANAGEMENT OF PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA

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It is well recognised that a sub group of patients with COPD will develop an increase in PaCO2 when high concentration oxygen therapy is delivered. It is uncertain whether a similar effect may occur with the administration of high concentration oxygen therapy in other respiratory disorders. We investigated the effects of high flow versus titrated oxygen on PaCO2 in patients with pneumonia.

**Methods** 120 patients with suspected community acquired pneumonia (cough, respiratory rate > 18 breaths per minute and at least one of sweating, rigors and/or fever > 37.8°C) were randomised to high flow (8 litres via a Hudson mask) or titrated oxygen (delivered to keep oxygen saturation between 93 to 95%) for 60 minutes. Transcutaneous CO2 measurements (tCO2) were made at 0 and 60 minutes.

**Results** With three withdrawals in the high flow group, data from 57 patients in the high flow group and 60 patients in the titrated group were analysed.

| High Flow O2 | Titrated O2 | Relative Risk | P value |
|--------------|-------------|---------------|---------|
| Rise in ICO2 >4 mmHg | 31/57 (54.4%) | 8/60 (13.3%) | 4.1 (CI 2.1 to 8.1) | <0.001 |
| Rise in ICO2 ≥8 mmHg | 9/57 (15.8%) | 2/60 (3.3%) | 4.7 (CI 1.1 to 21.1) | <0.001 |

Mean rise in ICO2 (SD 3.2) | 3.9 mmHg (SD 1.5 mmHg) | 2.4 mmHg (SD 2.5 mmHg) | (95% CI 1.4 to 3.5) | <0.001 |

**Conclusion** High concentration oxygen therapy results in an increase in ICO2 when delivered to patients with community-acquired pneumonia.

**Conflict of Interest** No.
IS THERE AN EASY ROAD TO ESTABLISHING A PULMONARY ARTERIAL HYPERTENSION PRESCRIBING CENTRE?

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Introduction With the increasing number of prescribing centres in Australia and the evolving complexities of treatment for pulmonary arterial hypertension (PAH), a coordinated and specialised multi-disciplinary collaborative approach is required.

Aim To discuss an outpatient model of care involving the coordination of multiple disciplines that has resulted in improved patient outcomes.

Method Of 800 patients referred to a single PAH tertiary centre since 2003, 185 patients on specific PAH therapies (45 idiopathic PAH, 60 PAH associated with collagen vascular disease, 20 chronic thrombo-embolic pulmonary hypertension, 45 PAH associated with congenital heart disease and 15 others). Furthermore, 110 patients are participating in the Australian Scleroderma Screening Program. Collaboration with departments and services such as rheumatology, cardiology, cardio thoracic surgery, sleep physicians, interventional radiology and allied health is essential. In 2007, 800 echocardiograms, 60 right heart catheters and 2000 6MWT’s were performed.

Conclusion For the last 5 years The Prince Charles Hospital has developed an outpatient model of care with successful coordination of multiple disciplines that has reduced inpatient length of stay despite the complexities of drug therapies and limited resources.

ASTHMA ADMISSIONS TO A PUBLIC TEACHING HOSPITAL: HOW DO WE MEASURE UP?

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Introduction Hospital admission rates for acute asthma in Australia have fallen over the last decade by 45% (adults) and 42% (children). However, significant numbers of Australians are still admitted to hospital each year with acute asthma.1 The Australian Council on Healthcare Standards (ACHS) accreditation process involves collection of data across Australia concerning the management of these patients.

Aim To determine whether management of asthma at Austin Health conforms to benchmarked ACHS clinical indicators of best practice.

Methods We performed a medical record audit of separations for Diagnostic Related Groups J45.9 and J46 (asthma unspecified, status asthmaticus) between July 2006 and June 2008. Records were examined for the presence of ACHS required clinical indicators (CI). These were: Emergency Department (ED) measurement of at least one of peak expiratory flow (PEF), spirometry or arterial blood gases (ABGs); inpatient (IP) measurement of at least one of PEF, spirometry or ABGs; discharge (D) provision of a written asthma management plan, provision of inhaled corticosteroids and medical review within four weeks.2

Results Proportion of patients achieving clinical indicators

| Age        | ED | IP | D       | Achieved all CI’s (%) |
|------------|----|----|---------|-----------------------|
| n (M ± SD) |    |    | N (%)   | N (%)                 |
| Adult      | 280| 48.1, 20.7 | 112 (40) | 86 (31) | 118 (42) | 73 (26) |
| Paediatric ≤15 yrs | 73 | 4.2, 3.6 | 6 (8) | 0 (0) | 68 (90) | 0 (0) |

Conclusions Many eligible patients admitted to hospital with asthma are not undergoing recommended assessments during their ED/inpatient stay and discharge. We hypothesise this may contribute to ongoing morbidity, increased length of stay and recurrent admission after discharge. The clinical indicators for ED and inpatient stay in the younger paediatric population (<7 years) may warrant review given the difficulty obtaining PEF or spirometry in this age group.

References
1 Australian Centre for Asthma Monitoring 2008.
2 ACHS Clinical Indicator Trend Report 2001–2007.
AUSTRALIAN NURSES KNOWLEDGE, ATTITUDES AND PRACTICE IN SMOKING CESSATION

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Introduction Nurses are the largest group in the health workforce and are ideally placed to provide smoking cessation interventions for patients. Despite the release of clinical guidelines and recommendations increasing focus on smoking cessation strategies, there remains a deficit in the provision of such interventions in routine clinical patient care.

Aim (1) To ascertain the prevalence of smoking among nurses. (2) To examine nurses’ knowledge and attitudes to smoking cessation that has implications for their own practice.

Method A descriptive, exploratory study was conducted using a self-administered questionnaire to over 3,200 nurses. Questionnaires were attached to the payslips in one major metropolitan network in Victoria, Australia in August month 2007.

Results The questionnaire was completed by 1,029 nurses, a response rate of 32%. Eleven percent of nurses (n: 113) in this sample reported smoking at least one cigarette per day. Non-smoking nurses were more likely to perceive themselves as having a role in the routine provision of smoking cessation advice to patients compared with nurses who smoke (P < 0.01). Seventy-percent of nurses reported a lack of formal training in smoking cessation approaches to use with patients. Nurses generally perceived smoking cessation interventions as an important part of their role, 57% indicated ‘definitely yes’, and 37% stated ‘maybe yes’. However, less than half of the nurses (37%) believed that brief advice provided by a health professional can help patients to stop smoking.

Conclusion Smoking amongst nurses appeared to lessen the perceived importance of routine provision of smoking cessation interventions for patients. The nurses in this study were unprepared and lacked confidence towards providing routine smoking cessation interventions for patients. Given their significant contact with patients and their important role in public health, nurses are a unique group who deserve special attention in regards to their own personal quit attempts. Competency in the provision of brief smoking cessation interventions needs to become a minimum standard for nursing education.

PERI-PHARYNGEAL TISSUE MOVEMENT WITH TRACHEAL TRACTION

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Caudal tracheal traction (TT) increases upper airway (UA) patency but the mechanisms remain uncertain. We used an animal model to examine the effect of graded TT on peri-pharyngeal tissue position and UA pharyngeal luminal size and shape.

Methods Computed tomography was used to image a surgically isolated UA in 3 supine, anaesthetised, tracheostomised, NZ white rabbits during TT (0 to 10 mm). We quantified at 3 UA levels (L): 1) tissue movement (% radial deviation from the TT = 0 mm luminal centroid position [i.e. fixed centroid] in anterior [A], posterior [P] and lateral [Lat] directions); 2) luminal AP/Lat diameter ratio and; 3) change in luminal cross-sectional area ($\Delta$CSA %). Data were analysed using linear regression.

Results Table: Linear regression slopes (mean ± SD). All P < 0.05. NS = not significant.

| (per mm TT) | L1 (base of tongue) | L2 (hyoid bone) | L3 (soft palate/epiglottis) |
|------------|----------------------|----------------|----------------------------|
| $\Delta$A % | 2.8 ± 0.2            | 3.0 ± 0.8      | −6.6 ± 1.2                 |
| $\Delta$P % | NS                   | 1.5 ± 0.3      | 3.28 ± 0.7                 |
| $\Delta$Lat Left % | 1.1 ± 0.2          | 2.0 ± 0.5      | NS                         |
| $\Delta$Lat Right % | 0.9 ± 0.2           | 1.5 ± 0.1      | −3.5 ± 1.2                 |
| AP/Lat     | NS                   | NS             | NS                         |
| $\Delta$CSA % | 2.9 ± 0.2           | 4.3 ± 0.5      | −1.6 ± 0.7                 |

Conclusion TT associated tissue movement results in increased luminal patency in regions of the pharynx at and cranial to the hyoid. TT related stability of the caudal pharyngeal region may be related to other effects (e.g. increased wall stiffening). Supported by the NHMRC of Australia and Faculty of Medicine, University of Sydney.

Conflict of Interest No.

SNORING-LIKE VIBRATION OF THE CAROTID ARTERY REDUCES TISSUE CYCLIC GUANOSINE MONOPHOSPHATE (cGMP)

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Introduction Heavy snoring may be a risk factor for early carotid atherosclerosis. We hypothesised that snoring-like vibratory energy (E) contributes to carotid atherogenesis by reducing endothelial nitric oxide (eNO) bioavailability.

Methods In 4 supine, anaesthetised, tracheostomised, ventilated, male, NZ White rabbits, right carotid arteries (RC) were exposed to direct mechanical vibration (60 Hz for 6 hours). E was calculated from power spectral analysis of pressures measured in tissues adjacent to the RC, left carotid (LC) and femoral artery (F) walls (pressure transducer tipped catheters, Millar). Two rabbits underwent the same protocol without vibration. RC, LC, aortic (A) and F segments were then excised and cGMP levels measured with or without exposure to 1 mM acetylcholine (ACh; increases cGMP via an eNO-dependent mechanism).

Results For vibrated RC (E = 160 ± 14 × 10⁻⁶ cmH₂O² per 6 hrs, mean ± SEM), baseline cGMP levels were less than for pooled non-vibrated control (control; E = 35 ± 2 × 10⁻⁶ cmH₂O² per 6 hrs, p < 0.01, unpaired t test) arteries (13.8 ± 2.8 [n = 3] vs 24.1 ± 1.6 pmol/mg protein [n = 8] respectively, p < 0.01). After 1 mM ACh, vibrated RC cGMP levels remained less than for control arteries (43.7 ± 1.8 [n = 4] vs 75.4 ± 3.5 pmol/mg protein [n = 8], p < 0.01). cGMP in ACh-treated vessels was inversely related to E (R² = 0.75 in cGMP per 50 × 10⁻⁶ cmH₂O² increase in E, p = 0.49, p < 0.01).

Conclusion Snoring-like vibratory energy acutely reduces both baseline and ACh-induced carotid artery cGMP, suggesting decreased eNO bioavailability (i.e. endothelial dysfunction), a known precursor to atherogenesis. Supported by the NHMRC and University of Sydney Postgraduate Award.
The prevalence of Obstructive Sleep Apnoea (OSA) is increasing in developed societies and individuals with OSA are likely to suffer more frequent and serious adverse post-operative outcomes than those without the condition. Simple, rapid methods for identifying OSA prior to surgical procedures are needed. The Berlin Questionnaire (BQ) is an effective screening tool for OSA which has not been previously validated using full polysomnography (PSG) in an operational setting.

Methods 41 consecutive adult subjects (from a database of 257 hepatobiliary surgical subjects who had completed a pre-operative BQ), underwent overnight diagnostic PSG. 22 subjects were high-risk for OSA as per BQ, and 19 were low-risk. Subjects were classified as having no OSA (apnoea-hypopnoea index (AHI) < 15), mild OSA (AHI 15–30), and moderate-severe OSA (AHI > 30) following PSG.

Results 99 of 257 subjects (39%) were high-risk (HR) of OSA based on the BQ. 41 subjects underwent PSG (22 HR, 19 LR). Of the HR subjects, 55% were male, mean age was 50 yrs (SEM 3.6) and mean BMI was 35.2 (SEM 1.8). Of 19 LR subjects, 74% were male, mean age was 58 years (SEM 3.9), and mean BMI was 26.1 (SEM 1.9). Interim analysis of the first 20 subjects’ results showed an 81% sensitivity and 92% specificity of the BQ in identifying OSA with a PPV of 77%, while 6 out of 7 LR subjects had no significant OSA.

Conclusions The BQ is a simple, accurate method of screening for OSA pre-operatively in a general surgical population, with a higher sensitivity for identifying OSA than previous estimates in a general population. It provides useful additional information and could become a routine part of pre-operative surgical and anaesthetic risk assessment protocols.
THE EFFECT OF SHORT ACTING BRONchodilATORS ON THE COMPLIANCE OF AIRWAY DIAMETER AND LENGTH

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Background In patients with long-standing asthma, chronic inflammation results in airway remodelling and irreversible airflow obstruction presumably due to a loss of airway compliance within the bronchial tree. Short-acting bronchodilators (BD) have limited effect in reversing loss of lung compliance. Currently it is unknown whether the primary site of improved compliance is the large or small airways, and whether it is predominantly length or diameter dependent.

Aim To investigate the effect of BD on the compliance of airway lumen inner diameter (DI), airway outer diameter (DO) and length (L), in large and small airways, in asthmatic patients.

Methods 8 asthma patients underwent partial HRCT scans at FRC, TLC and a mid-volume (MID). Individual airways were identified in consecutive scans, from which DI, DO and airway wall thickness (WT) were measured. Mean differences in L were calculated from differences in WT, assuming conservation of airway wall volume. The relationship between both DI and DO compliance and airway size was quantified, before and after BD, using a novel methodology that enables 3-dimensional representation of airway compliance specific to airway size.

Results Small airways (DI < 3 mm) DI and DO are more compliant than large airways (DI > 8 mm), before and after BD. Following BD: 1) Mean WT at FRC decreased by 2%, corresponding to a 2% increase in mean L. 2) In the small airways, the increase in DI and DO (from FRC to TLC) was 27% and 10%, respectively; in the large airways, the increase in DI and DO (FRC to TLC) was 9% and 16% greater, respectively.

Conclusion Our study showed that airway compliance attributable to DI, DO and L are non-uniform between FRC and TLC. Our findings demonstrate that the small airways and DI are important for improved lung compliance in asthma.

Supported by the CRC for Asthma and Airways and Asthma NSW.

Conflict of Interest No.

MULTIPLE BREATH NITROGEN WASHOUT IN HEALTHY ADULTS: PARAMETERS AFFECTING SCOND AND SACIN NORMAL VALUES

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Background Multiple Breath Nitrogen Washout (MBNW) allows the global measurement of ventilation heterogeneity, with the ability to distinguish acinar (Sacin) from conductive airways (Scond) components. Anthropometric parameters that affect Scond and Sacin values in healthy subjects are still unknown.

Aim To determine which anthropometric parameters affect Scond and Sacin values in healthy subjects and to determine relationships between MBNW and spirometry.

Methods 18 male and 18 female healthy adult volunteers with less than 5 pack-years smoking history and with no lung or cardiac disease were recruited. Subjects underwent measurements of spirometry, lung volume by plethysmography, and Sacin and Scond by MBNW.

Results The mean (range) age was 41 (19–89) years, BMI was 25.2 ± 3.8 kg/m2 and FEV1 was 95 ± 16% of predicted. Scond correlated significantly with age (R² = 0.29, p < 0.001), weight (R² = 0.14, p = 0.03) and BMI (R² = 0.27, p = 0.001), but not with FRC/TLC. In multivariate analysis, age and BMI were independent predictors of Scond. Sacin correlated solely with age (R² = 0.16, p = 0.004). Sex had no significant influence on MBNW values. Scond and Sacin were not correlated with spirometry measurements, either as absolute or as percent predicted.

Conclusions Acinar and conductive heterogeneity increase with age. Obesity worsens ventilation distribution only in conducting airway zone, which was not due to decrease in lung volume, but possibly to basal airway narrowing and closure.

Supported by CRC for Asthma and Airways, University of Sydney Bridging Grant U1089, Foundation SICPA, Fondation Andreas P Naef pour la chirurgie thoracique, Fondation pour la recherche et le traitement des maladies respiratoires, and Société Académique Vaudoise.

Conflict of Interest No.

UTILITY OF THE STOP AND STOP-BANG QUESTIONNAIRES IN A PRE-SCREENED POPULATION PRESENTING FOR OVERNIGHT POLYSOMNOGRAPHY

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Obstructive Sleep Apnoea (OSA) is a common condition, the diagnosis of which is often delayed by prolonged waiting lists at the point of referral or in the sleep laboratory. Clinical prediction tools may become useful in triaging assessment and management of this condition. Recent publications have proposed and validated two new pre-operative screening tools for Obstructive Sleep Apnoea (OSA) in surgical patients (STOP and STOP-BANG). These screening tools have not been examined in a general sleep population.

Methods All patients attending for in-laboratory polysomnography at Box Hill Hospital during the study period were asked to complete the STOP questionnaire, and sleep scientists recorded the biometric data required for the BANG component. Polysomnography proceeded with sleep staging and event scoring performed according to the Chicago Criteria. Risk stratification by the STOP and STOP-BANG tools was combined with total Respiratory Disturbance Index from polysomnogram reports.

Results 25 patients have been reviewed, although data continues to be collected. There is a high prevalence of moderate or severe OSA within this population (22/25, 88%). The STOP-BANG tool maintains higher sensitivity, negative predictive value and odds ratios than the STOP tool at each degree of OSA severity examined.

Conclusions With ongoing data collection we hope to confirm trends seen in predictive values with these tools. Removal of less discriminatory criteria may improve their statistical usefulness, perhaps allowing development into risk stratification tools that will assist in triaging investigation and management of patients with suspected OSA.
Dynamic collapse of the large airways during tidal breathing is observed commonly during bronchoscopy. It may be so severe as to totally close the trachea on expiration. This phenomenon, dynamic airways compression (DAC), may be a cause of chronic cough and perhaps dyspnoea (1). Previous attempts to correlate DAC with standard respiratory function tests have been unsuccessful. We hypothesised that impulse oscillometry (IOS) would be able to detect DAC as IOS may distinguish large from small airway obstruction in tidal breathing.

Methods Patients found to have DAC at bronchoscopy proceeded to have IOS and pulmonary function tests (PFTs) performed. The cross sectional area at the criocoid was referenced as the maximal cross sectional area of the trachea. A tracheal area ratio between inspiration and expiration of less than 0.5 was taken as indicative of significant DAC (cases), whereas a ratio greater than or equal to 0.75 as having no DAC (controls). Patients with COPD on standard PFTs were excluded.

Results 6 cases and 6 controls were recruited. The indication for bronchoscopy in 5 of the 6 cases was chronic cough. All 6 cases had 100% DAC either at the trachea or main bronchi. The mean resonant frequency (RF) of those with DAC was significantly higher than those without DAC (26.167 ± 17.018–35.595) vs. 9.214 (7.85–10.945), p < 0.003. Only one patient with DAC had a RF < 20. The mean difference in inspiratory RF and inspiratory RF was significantly larger in those with DAC compared to those without (10.812 [6.004–16.735] vs. 0.416 [−1.948 to 4.528], p < 0.003). There was also a greater fall in reactance (X) at 5Hz in participants with DAC compared to those without DAC (−0.446 [−0.148 to −0.889] vs. −0.060 [−0.01 to −0.093], p < 0.003).

Conclusions IOS is potentially a non-invasive investigation for DAC. Further investigation is required with a larger sample size and to include patients with COPD who have DAC and those who do not.

MORGAN S, COLLIER HG. Tracheobronchomalacia and Excessive Dynamic Airway Collapse. Respirology 2006; 11: 386–406.

IMPAULS: Interactions with Obstructive Sleep Apnoea (OSA) RITA PERRI1, KRISTINA KAIRAITIS2, JOHN R WHEATLEY1, TERENCE C AMIS1
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Larger mandible size in males (mandibular sexual dimorphism) is typical across mammalian species (both modern and ancestral) and may represent evolutionary pressure for increased bite force. We explored relationships between gender, cranial dimensions, and mandible size and also calculated mandibular (MV) and retro-mandibular (RMV) enclosure volumes, in subjects with and without OSA.

Methods We studied 61 awake, seated, healthy Caucasian volunteers (29 males, age 36 ± 14 yrs (mean ± SD), height 175 ± 10 cm, BMI 25 ± 3 kg/m²; and 32 females, age 38 ± 12 yrs, height 166 ± 7 cm, BMI 26 ± 6 kg/m²; all without OSA as per Multivariable Apnoea Prediction Questionnaire score < 1), in addition to 54 OSA subjects (apnoea hypopnoea index > 10 events/hr; 39 males, age 56 ± 17 yrs, height 173 ± 6 cm, BMI 32 ± 5 kg/m²; and 15 females, age 57 ± 12 yrs, height 158 ± 9 cm, BMI 37 ± 10 kg/m²). Using skin surface cephalometry, we measured 11 cranial and 18 mandible/maxilla dimensions. We imaged the trachea in participants with DAC compared to those without (10.812 [6.004–16.735] vs. 0.416 [−1.948 to 4.528], p < 0.003).

Conclusions There are no significant differences in HPhEmMRI image analysis between Mch and Mnt challenges in stable asthmatic subjects. This is a novel quantitative method of analysing topographical changes in ventilation following airway challenge, and further work is required to correlate this with physiological measures of VH.

ANALYSIS OF VENTILATION HETEROGENEITY (VH) WITH HYPERPOLARIZED HELIUM MAGNETIC RESONANCE IMAGING (HPhEmMRI) FOLLOWING INHALED METHACHOLINE (MCH) AND MANNITOL (MNT) CHALLENGES IN ASTHMATIC SUBJECTS

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VH is a feature of asthmatic bronchoconstriction and contributes to airway hyperresponsiveness (AHR) and disease expression. Response to direct (Mch) and indirect (Mnt) inhalational challenges help to distinguish between remodelling and inflammatory components of AHR. HPhEmMRI provides topographical information about VH in asthma but has not been quantitatively analysed.

Aim To characterise VH as measured by HPhEmMRI following Mch and Mnt challenges in asthmatic subjects.

Methods Asthmatic subjects were recruited and had HPhEmMRI at baseline and following crossover Mch and Mnt challenges on separate days. Images were analysed and indices of VH performed using voxel analysis to construct a frequency histogram of ventilation. Qualitative analyses of image heterogeneity between Mch and Mnt challenges were also performed.

Results 8 asthmatic subjects (7F, 1M) were studied with baseline lung function comparable between Mch (FEV1 95 ± 13% pred) and Mnt (FEV1 94 ± 12% pred) challenge days. The maximal falls from baseline in FEV1 were 24% (Mch) and 13% (Mnt) respectively (p = 0.008) with opioid use and 12.8 times (3.2–50.4, p < 0.005) with diabetes while shift workers were 8.4 times (1.6–43.2, p = 0.004) more likely to have insomnia. Pharmacists reported the screening protocol and instrument as user friendly and feasible to implement.

Conclusions The development and pilot testing of the tool was successful. The prevalence of sleep disorders in the population sampled is high, but generally consistent with previous studies on the general or primary care population. Further large scale work will be required to validate the screening tool. These results have a way to enhance awareness of sleep disorders.

Supported by the Pharmacy Guild of Australia, Investigator Initiated Grants. Conflict of Interest None.
MEASUREMENTS OF ACINAR VENTILATION AFTER LUNG TRANSPLANTATION

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Long-term survival of lung transplant patients is limited, principally because of Bronchiolitis Obliterans Syndrome (BOS). Currently BOS status is diagnosed on the basis of spirometry however other more sensitive techniques based on small airway function have been proposed. This study assessed the ability of the Multiple Breath Nitrogen Washout test (MBW) to discriminate changes in ventilatory inhomogeneity of the acinar region of the lung in transplant patients. Also to detect changes in acinar heterogeneity within 6 months post transplant. 75 double lung transplant patients with varying degrees of BOS were recruited. MBW was performed alongside spirometry during outpatient visits. Correlation analysis was used to test the relationship between the MBW parameters, Scond and Sacin and BOS status. A strong correlation was found between Sacin (r = 0.706, p < 0.01) and BOS status, while the correlation between BOS status and Scond was relatively weak (r = 0.165, p < 0.05). Patients with BOS status 0, in the first 6 months of transplantation had a significantly higher Sacin 3 months post surgery (r 2 = 0.140 L^-1, p < 0.006). In conclusion we have demonstrated significant heterogeneity of acinar ventilation in patients following lung transplantation. Importantly the changes in Sacin were related to BOS staging.

Funding Source AllRmed.
Conflict of Interest No.

RETENTION OF INGESTED PHOSPHOLIPIDS ON THE ORAL MUCOSA

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Bananas contain surface active phospholipids (PL) and may potentially be a cheap and palatable means of administering exogenous PL to the pharyngeal mucosa for the treatment of obstructive sleep apnoea.

Method Eight healthy women (20.1 ± 1.4 years of age) were studied to determine how long banana PL are retained on oral epithelial surfaces. Epithelial cells were gently scraped from the inside of the subjects’ cheeks immediately before, and 1, 2, 4 and 6 hours after, subjects slowly drank 200 ml of an aqueous suspension containing 130 grams of ripe Cavendish banana. Fifty epithelial cells per cheek scraping sample were examined with epi-fluorescent microscopy after staining with the lipophilic fluorescent dye Nile red.

Results Cells collected before banana ingestion (BI) showed no evidence of epi-fluorescence, but the large majority of cells after BI displayed red epi-fluorescence indicative of PL. The diagram (mean data from 8 subjects) shows that the intensity of epi-fluorescence, was largely retained 6 hours after BI.

Time post banana

Conclusion Retention of ingested PL on epithelial surfaces may enable PL to exert a pharyngeal patency promoting action throughout an entire night which may prove to be of value in the treatment of obstructive sleep apnoea.

Supported by None.
Nomination Nil.
Conflict of Interest No.

REGIONAL AIRWAY COMPLIANCE IN ASTHMA MEASURED USING ANATOMICAL OPTICAL COHERENCE TOMOGRAPHY

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Background Asthma is associated with airway remodelling and can lead to stiffened airways. To date, measurement of the regional nature of this remodelling has been limited to biopsy studies in explanted airways. Anatomical optical coherence tomography (aOCT) is an emerging real-time endoscopic imaging technique able to measure airway cross-sectional area (CSA) at multiple sites during bronchoscopic procedures.

Methods During general anaesthesia, 5 asthmatics and 5 healthy controls underwent simultaneous bronchoscopy and aOCT assessment. While supine and breathing spontaneously, end-expiratory airway CSA was measured at the trachea, right middle lobe and the antero-basal right lobe while end-expiratory pressure was increased in 5 cmH2O increments from −10 to +20 cmH2O. The relationship between CSA and transpulmonary pressure was used to determine airway compliance at each site.

Results Compliance was obtained in 28 of the 30 airways assessed. Across the groups, airway compliance tended to be greatest in the trachea and least in the antero-basal right lower lobe. At each site, mean compliance in the asthmatic airways was lower than in the control group. This difference was statistically significant in the right middle lobe (0.85 vs 1.69 mm²/cmH2O p = 0.014).

Conclusions Regional airway compliance characteristics can be determined using aOCT during spontaneous breathing. Asthmatic airways tend to exhibit reduced airway compliance compared to controls during anaesthesia. Supported by the NHMRC. No conflict of interest.