

Review of the British Thoracic Society Winter Meeting 2017, 6–8 December 2017, London, UK

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***Joint first**

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Introduction

The British Thoracic Society (BTS) Winter Meeting 2017 attracted 2300 delegates to London. The Meeting showcased the latest advances in respiratory science including clinical and translational research. This article summarises selected key sessions.

BTS/British Lung Foundation/British Association of Lung Research early career investigators symposium

This exciting session, featuring six emerging early-career academics, provided a glimpse at the future of UK academic respiratory medicine. Dr Wortley (London, UK) won the BTS award for his research which utilised *in vivo* and *ex vivo* experimental approaches to demonstrate that bacteria can activate sensory nerves, specifically via TLR-2¹. These effects could explain increased coughing episodes that occur during acute bacterial infection. Runner up for this award was Dr Walstead (London, UK and Copenhagen, Denmark) who presented data from six subjects with exercise-induced laryngeal obstruction showing that respiratory work and neural drive increases in close association with paradoxical laryngeal closure in this condition².

Dr Wood (Cambridge, UK) was awarded the British Association of Lung Research prize for work demonstrating that complement protein C5A can impair neutrophil phagocytosis of *Staphylococcus aureus* in a PI3-kinase dependent manner³, raising speculation that that these mechanisms could be manipulated to alter susceptibility to nosocomial infections. The runner up was Dr Bonvini (London, UK), for her work focussing on the role oestrogen plays in airway sensory nerve activation. β -oestradiol induced depolarisation of isolated guinea pig vagal nerves *ex vivo* but oestrogen receptor antagonist administration had no effect on transient receptor potential ion channel (TRPM)-3 mediated depolarisation, suggesting that the effect of oestrogen on sensory nerve activation may occur upstream of TRPM-3.

The British Lung Foundation award was won by Dr Dickens (Cambridge, UK) who presented her work on cell trafficking defects related to pathogenic surfactant protein C mutant 173T associated with familial pulmonary fibrosis⁴. These defects may cause type 2 pneumocyte dysfunction and therefore could be important in the development of both familial and sporadic forms of the disease. Finally, Dr Hippolyte (London, UK) received the highly commended BLF award for her work using the UK cystic fibrosis registry data to examine gender differences. Females have worse clinically relevant outcomes including earlier chronic *Pseudomonas aeruginosa* infection and greater associated lung function decline⁵.

Highlights from *Thorax*

Four notable studies published in *Thorax* were showcased at this year's symposium. Dr Jean-Michel Sallenave's group (Paris, France) highlighted that *Pseudomonas aeruginosa* elastase LasB is a secreted virulence factor that can downregulate CFTR and degrade anti-bacterial immune mediators IL-6 and Trappin-2, important epithelial derived antimicrobial factors⁶. Intranasal administration of LasB in mice also induced inflammation, weight loss and death, effects that were rescued by overexpression of *IL6* and *Trappin2*. These data suggest that targeting LasB could represent a novel therapeutic strategy for patients susceptible to *Pseudomonas* infections including those with cystic fibrosis and COPD.

Dr Lucile Sese (Bobigny, France) presented thought provoking data from a prospective cohort study showing that acute exacerbations of idiopathic pulmonary fibrosis (IPF) are significantly temporally associated with an increase in mean level of atmospheric ozone and that exposure to elevated levels of particulate matter PM₁₀ and PM_{2.5} are associated with increased mortality⁷.

Dr Andrey Zinchuk (New Haven, USA) presented a multi-centre observational study in which polysomnographic data was used to characterise novel phenotypes of obstructive sleep apnoea (OSA)⁸. Subgroups could be identified that captured risk of adverse cardiovascular outcomes otherwise missed by conventional OSA severity classification criteria. These classification methods could have future importance for risk stratification and treatment selection.

Dr Cecilia O'Kane (Belfast, Northern Ireland) used human *in vivo* and *ex vivo* models of lipopolysaccharide-induced inflammation to demonstrate that aspirin could reduce pulmonary neutrophilia and neutrophil-mediated inflammation⁹. These effects raise speculation that use of aspirin could be beneficial in neutrophil-driven pulmonary inflammatory diseases such as acute respiratory distress syndrome (ARDS).

Plenary Scientific

The plenary Scientific session showcases some of the brightest rising stars of UK respiratory academia.

Prof David Kiely (Sheffield, UK) emphasised the importance of a multimodality approach to diagnosis and prognostication in pulmonary hypertension. The potential use of *in silico* approaches, combined with computational modelling and machine learning, to classify patients could reduce future need for invasive tests.

Dr Charlotte Summers (Cambridge, UK) presented her work on neutrophil biology. Her data, which included some fascinating video images, indicated that neutrophil transit time across the pulmonary circulation is faster than previously thought and that primed neutrophils are retained in the vasculature and subsequently deprime and are re-released into the systemic circulation. Defects in these processes may underlie development of ARDS.

Dr. Robert Snelgrove (London, UK) discussed his work into a novel anti-inflammatory pathway in which leukotriene A4 hydrolase degrades an

extracellular matrix-derived neutrophil chemoattractant proline-glycine-proline (PGP). Using a mouse model of allergic airways disease, he demonstrated that PGP accumulation drove pathological epithelial remodelling, mucus production and airway hyper-responsiveness. Subsequently, he demonstrated that PGP is elevated in the sputum of patients with severe asthma, raising speculation that this could provide a viable future therapeutic target.

Finally, Dr John Hurst (London, UK) highlighted the importance of exacerbation risk in COPD, suggesting that an episode of hospitalised exacerbation should be a call to arms for healthcare professionals. He also discussed the importance of disease activity in COPD and raised speculation that small airway imaging could provide an early window to identify active disease that requires intervention.

The Morriston Davies Lecture

The Morriston Davies lecture was given by Professor John Ioannidis (Stanford, USA) and he proposed a controversial viewpoint that most published clinical research is not useful. The eight criteria of clinically useful research were outlined which include: problem base, context placement, information gain, pragmatism, patient-centredness, feasibility, transparency and value for money. Importantly, most journals do not consider all 8 when assessing submitted manuscripts. Professor Ioannidis additionally highlighted the importance of large scale collaboration and adoption of replication culture (increased focus on reproducible science).

The BTS Lecture

Professor Sir Michael Marmot (London, UK) gave a rousing lecture on health inequalities and social justice. Describing the links between poverty and exposure to pollution it becomes easy to understand the striking associations between social deprivation and lung disease across the UK. Professor Sir Marmot described how improving education, housing and household pay could all have lasting impacts on a child's long-term health. In doing so, he created a compelling case for social transfer (government provided social assistance), arguing that, without it, we are simply treating people and then sending them back to the conditions that made them unwell.

Pulmonary Vascular Disease

Dr Luke Howard (London, UK) presented the new BTS outpatient pulmonary embolism (PE) guidelines, due to be published this year. Several studies, including randomised controlled trials (RCTs) and meta analyses, have shown that outpatient management of low-risk patients with confirmed PE is as safe and effective as inpatient care^{10 11}. The 11-point PESI score is based on easily obtained clinical data and is the most widely validated risk score for PE (although it is not validated for use in pregnancy). The simplified version (s-PESI) is equally able to identify patients at low-risk of mortality¹². There is no value in adding BNP, troponin or right ventricular (RV) function assessments to the PESI/sPESI as it does not improve prediction of early mortality, which is key when deciding between outpatient or inpatient care^{13 14}. First line treatment for confirmed PE is

either a direct oral anticoagulant (DOAC) or initial low molecular weight heparin (LMWH) with a subsequent switch to a DOAC, such as dabigatran or edoxaban. There are no data yet for the use of DOACs in cases of suspected PE, but guidelines suggest a DOAC could be used instead of LMWH whilst awaiting outpatient imaging (ideally within 24 hours).

Dr Gregory Piazza (Boston, USA) discussed different treatment options for acute PE. He highlighted that ultrasound-assisted catheter-directed thrombolysis, which combines low-dose local fibrinolytics and mechanical clot disruption can rapidly improve RV function in intermediate/high¹⁵ and high-risk patients¹⁶ with pulmonary embolism. In contrast to the 2% risk of intracranial haemorrhage associated with systemic thrombolysis, there were no reports of this complication with catheter-directed therapy¹⁷. Furthermore, lower dose (8mg tPA) and shorter duration (2h) therapy was recently shown to be as effective as standard catheter-directed regimens (24mg tPA over 12-24 hours) for submassive PE. In some centres in the US, multidisciplinary PE teams have been founded to evaluate patients and make treatment decisions¹⁸. This is especially useful in the care of intermediate/high risk PE, where clinical trial data and guidelines are inadequate. These teams consist of specialists from respiratory medicine, cardiology, vascular surgery, radiology and haematology. It will be interesting to see if there will be a demand for this type of service in the NHS in the future.

The risk of PE recurrence is significant, even in patients with 'provoked' PE (25% over 10 years). The EINSTEIN CHOICE study compared 100mg aspirin to prophylactic and treatment doses of rivaroxaban for prevention of further VTE in patients with unprovoked and provoked PE. Rivaroxaban reduced the relative risk of VTE by 70% (20mg) and 60% (10mg) compared with aspirin at 1 year, which raises the question of whether we should be considering long-term anti-coagulation in all patients.¹⁹

Interstitial lung disease

Patients with sporadic IPF have shorter telomeres compared with age-matched controls and mutations in telomerase genes have been identified in patients with familial IPF, implicating telomere dysfunction in the pathogenesis of IPF^{20 21}. Professor Paul Wolters (San Francisco, USA) showed that deletion of the telomere shelterin protein TRF1 in alveolar epithelial cells (AECs) leads to the spontaneous development of lung fibrosis in mice, suggesting that telomere dysfunction in AECs contributes directly to the development of lung fibrosis²². He explained that the telomere link may extend beyond IPF and predispose to other fibrotic lung diseases. Mutations in telomere genes have been identified in 12% of patients with rheumatoid arthritis-associated ILD patients²³ and telomere length also correlates with survival in chronic hypersensitivity pneumonitis²⁴.

Dr Philip Molyneaux (London, UK) argued that infection could be the cause of IPF given that previous studies have shown that immunosuppressing patients with is harmful²⁵. Until recently, the lungs were thought to be sterile but thanks to new culture-independent techniques we now recognise that the lungs of healthy individuals harbour diverse bacterial populations. Patients with IPF have an

increased bacterial burden in bronchoalveolar lavage (BAL) samples compared to healthy controls and COPD patients. In patients with IPF bacterial load at the time of diagnosis correlates with survival^{26 27}. Interestingly, during acute exacerbations, there is a further increased in bacterial burden and significant change in the profile of the microbiome, which is not detected by routine culture²⁸. The results of two ongoing studies examining the effect of antibiotics on IPF outcome (TIPAC 2 and CleanUp IPF) are eagerly awaited.

Professor Martin Kolb (McMaster, Canada) presented the hypothesis that mechanical stretch associated with breathing contributes to disease progression in IPF²⁹. Stretching stiff fibrotic lung tissue leads to the release and activation of the pro-fibrotic cytokine, TGF- β , which is embedded in the matrix.³⁰ This occurs at much lower levels in normal compliant lung. Enhanced TGF- β activation contributes to deposition of further matrix proteins, leading to stiffer lungs and a detrimental feed-forward loop. This could explain why fibrosis has a propensity to develop in the subpleural regions where the pressure change and stretch is greatest.

Dr Billy Fahy (Stevenage, UK) explained that, in the future, biomarkers could be used to differentiate subsets of IPF patients and guide therapeutic decisions. However, there are no biomarkers currently in clinical use. He spoke about the challenges of biomarker identification and how machine learning is being used to identify biomarker signatures in large datasets. Using data from the longitudinal cohort PROFILE study, an epithelial biomarker signature was recently shown to predict disease progression and death in IPF³¹.

While IPF grabbed a lot of the headlines, we also heard from Dr Vijay Maharajan (Cambridge, UK) who described ways to automate the analysis of cystic lung disease. Splitting the lung into zones could allow accurate scoring of cyst distribution and differentiate between diseases. The automated counting and assessment could also play a role in long-term follow up and clinical trial design.

Asthma

Professor Maria Belvisi (London, UK) focussed on the non-allergic influences on asthma. Many non-allergic asthma triggers, such as pollution and tobacco, can cause cough and breathlessness, symptoms that are largely unresponsive to current treatments targeting inflammation. She hypothesised that irritants directly activate Transient Receptor Potential (TRP) ion channels to initiate these sensory reflex events. She highlighted that TRPV4 activation releases ATP, which in turn acts on P2X3 present on sensory nerves, resulting in the cough reflex³². The discovery of this axis opens up a completely new therapeutic opportunity for improving symptoms with use of either P2X3 or TRPV4 antagonists³³.

Professor Adnan Custovic (London, UK) showed that the effect of early-life exposures (e.g. to cat) on sensitization and asthma differs over time, rendering the generalization of effects from cross-sectional analyses misleading³⁴. Therefore, the findings of apparently contradictory cross-sectional studies may be due to markedly different trajectories of clinical outcomes between individuals exposed or not exposed in early life³⁴. He showed that mite allergen avoidance in children,

using allergen-proof bedding, reduces emergency hospital attendance with severe asthma exacerbations³⁵ and that temperature-controlled laminar airflow (TLA) devices in real-life studies reduces asthma exacerbation rates.³⁶ This raises the question of whether asthma guidelines should reassess the role of allergen avoidance as a treatment option. More controversially, he challenged the dogma that allergen desensitisation is ineffective in asthma control. Sub-lingual immunotherapy (SLIT) is certainly safe, and there is an increasing body of evidence that dust mite SLIT tablet may be clinically effective in adults with partially controlled allergic asthma³⁷. Grass SLIT tablet may also modify the natural history of airway symptoms in grass-allergic children³⁸

Professor Liam Heaney (Belfast, Northern Ireland) described the progress on the UK MRC RASP programme on severe asthma³⁹. The aim of this programme is to understand disease control using composite endpoints, and by assessing drug adherence using FeNO and the inhaler compliance assessment (INCA) device.. This could enable the down-titration of medication where feasible. He described the wide range of novel biologics competing for a narrow market although with potentially major health economic benefits through exacerbation reduction.

Dr Stephen Fowler (Manchester, UK) contrasted and compared the BTS/SIGN guidelines with new NICE asthma guidelines. There is some agreement, but the NICE guideline uses FeNO as part of an un-validated complex web-based diagnostic pathway and does not take into account the age and gender differences in the FeNO normal range. In addition, NICE guidance does not include important topics such as smoking, co-morbidities, devices or pregnancy. There was agreement that both guidelines were based on efficacy RCTs in unrepresentative populations. We therefore urgently need clinical effectiveness data in broader populations on which to base future guidelines.

COPD

Mechanistic aspects of COPD were focussed on at this year's meeting with intriguing data from Lodge *et al*⁴⁰ (Cambridge UK) showing that hypoxia increases neutrophil elastase in a PI3-kinase-dependent manner, effects that are further augmented during exacerbations. Evaluation of the neutrophil secretome in hypoxic conditions showed several upregulated proteins that may contribute to tissue damage. These proteins could represent future therapeutic targets. Ryan *et al* (Edinburgh, UK) highlighted mechanisms of impaired macrophage efferocytosis in COPD. Sulforaphane an agonist of the transcription factor Nrf2 (which regulates antioxidant-response-elements) was shown to partially rescue defective efferocytosis in monocyte derived- and alveolar macrophages from patients with COPD⁴¹.

Gillpin (Belfast, Northern Ireland) *et al* presented work looking at the effects of cigarette smoke and electronic cigarette vapour extracts on growth and biofilm formation of COPD relevant bacteria including *H. influenzae* and *P. aeruginosa* *in vitro*. They demonstrated that both cigarette smoke and electronic cigarette vapour extract enhanced inflammatory responses to bacteria and increased biofilm formation⁴². It remains to be seen whether these potentially adverse effects of electronic cigarette vapour observed *in vitro* also occur *in vivo*.

Infection

Dr Abubakar (London, UK) *et al* presented data from PREDICT, a large UK multi-centre study⁴³. In this study, subjects who were new migrants or contacts of active TB cases were screened for latent TB. There were 97 out of 9610 participants (1%) who developed active TB during the study. The authors identified that using either interferon-gamma release assay (IGRA) based tests or tuberculin skin test with a 15mm threshold were best suited to screening in low-risk populations.

Dr Szylar (London, UK) *et al* evaluated the effects of regulatory T cells (Tregs) on macrophage inflammatory responses to *S.pneumoniae*⁴⁴. Co-culture of monocyte derived macrophages (MDM) with Tregs reduced MDM production of TNF- α and IL-6. They also demonstrated, using a novel human *in vivo* model of pneumococcal challenge involving intradermal injection of UV-killed *S.pneumoniae*, that Tregs accumulate at the site of injection. These preliminary findings suggest Tregs could be important in modulating macrophage inflammatory responses to *S.pneumoniae*.

Dr Plowright (Nottingham, UK) evaluated outcomes following cardiovascular events in a large cohort of 101,597 patients with bronchiectasis⁴⁵. After adjusting for age and sex, there was no difference in *in-hospital* mortality following acute myocardial infarction, coronary artery bypass graft or percutaneous angioplasty in individuals with bronchiectasis compared with the general population. The presence of bronchiectasis was, however, associated with longer mean hospital stay.

Smoking

Dr Sanjay Agrawal (Leicester, UK) argued that there is no strong evidence to suggest that cigarette smokers who use e-cigarettes are less likely to quit smoking. Recent data suggests that vaping does increase the success of quit rates⁴⁶. E-cigarettes are generally thought to be a safer alternative to smoking traditional cigarettes, but little is known about the long-term effects of vaping on lung health.

There are >7000 different flavours of e-liquids available in the US, all with very different chemical compositions. There is no regulation or inhalational toxicity testing performed prior to their release onto the market, which is a cause for concern. Dr Robert Tarran (North Carolina, USA) showed data demonstrating the toxic effects of different flavour e-liquids on human airway epithelial cells *in vitro*⁴⁷. Examination of sputum from healthy smokers and vapers demonstrates raised levels of proteases and mucins compared with controls, which raises the possibility that vaping could also cause emphysema⁴⁸. He also showed bronchoscopic images indicating marked erythema in the airways of e-cigarette users. He suggested this may be due to direct heat damage from e-cigarettes, but further studies are required to investigate this.

Dr Rachel Murray (Nottingham, UK) described the challenges to successfully implementing smoking cessation in the NHS. In 2015/2016 475,000 hospital

admissions were directly smoking-related. Moreover, even greater numbers of current smokers are admitted to hospital every year (1.1 million smokers in 2010/11). This represents a huge number of opportunities to intervene and promote smoking cessation. Smoking cessation interventions are the most effective method available, but *Stop Smoking Services* have been badly hit by funding cuts⁴⁹. Dr Murray argued that, although NICE guidance and Department of Health policy outline key interventions for smoking cessation, without regulatory drivers there is no incentive for Trusts to deliver.

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