Year in review 2013: paediatric and adult clinical studies

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This is the first of two reviews of *Thorax* in 2013 focusing on manuscripts dealing with the clinical aspects of paediatrics and adult respiratory medicine. Our prizes last year were a popular addition and so we have retained this in 2013. Decisions are purely those of the editors and deputy editors. Our only restriction has been to not consider manuscripts from Imperial, Leicester and Oxford, not because they were too numerous or too good (regrettably), but because we have conflicts of interest.

PAEDIATRICS

Cystic fibrosis (CF) is an area with major research activity, especially with the introduction of new therapies bolstered with good randomised controlled trials. Aerosolised antibiotics have been the mainstay of therapy for chronic *Pseudomonas aeruginosa* infection since Margaret Hodson's trials in the 1980s, replicated in the USA more than a decade later (if it did not happen in the USA, it did not happen!). Once daily nebulised amikacin had a good profile in a phase II trial¹—but should it be reserved for atypical *Mycobacterial* infection? Dry powder devices are increasingly being used instead of nebulisers to try to reduce treatment burden, so an important study showed that for colomycin the two methods of delivery were equivalent.² An accompanying editorial³ discussed how a favourite *Thorax* set of whipping boys, the National Institute of Health and Care Excellence, have made a dog's breakfast of their recommendations. Finally, non-CF bronchiectasis is an orphan disease, so good to see nebulised ciprofloxacin being shown to be effective in a phase II trial in this group.⁴ Another theme is the increasing realisation of the importance of pulmonary exacerbations (also known as lung attacks) in CF. High frequency chest wall oscillation is an expensive adjunct to airway clearance, which is much hyped at meetings. A randomised controlled trial,

the winner of our bronze award in this category, showed it was inferior to standard cheap positive pressure devices in terms of prevention of exacerbation, the primary endpoint,⁵ and an accompanying editorial pointed out that if spirometry had been used instead, no difference would have been shown.⁶ Byrnes *et al*⁷ showed that exacerbations were a marker for progressive lung disease even in pre-school children, extending previous observations in older children and adults.^{8–12} Diagnosis of exacerbation is often circular, as we pointed out—it is an exacerbation so I give antibiotics, and I define exacerbation by the fact antibiotics were given—so better objective diagnostic measures are needed. Nick *et al*¹³ showed that diagnosis of an exacerbation was improved measuring the upregulation of six genes in peripheral blood leucocytes and validated this in a second cohort. What constitutes an improvement with antibiotic treatment of an exacerbation? Horsley *et al*¹⁴ showed that multiple biomarkers improve, but as ever in medicine, the obvious proved to be wrong—sputum markers were not useful. Finally, intravenous anti-*Pseudomonas* antibiotics also reduce *Aspergillus fumigatus* in the sputum:¹⁵ difficult to understand, but emphasising the importance of interactions between species in the CF airways. The final CF manuscript looked longitudinally at quality of life,¹⁶ increasingly favoured by another favourite whipping boy, the FDA, as a patient reported outcome and showed that health-related quality of life declined slowly, with declining spirometry predicting a decline in quality of life.

We highlighted the sinister ongoing achievements of *Mycobacterium tuberculosis* with a themed issue to coincide with world TB day in November. Interferon-based tests have been a major diagnostic step forward in recent years, but importantly, in a high prevalence TB area (South Africa) they did not add anything to diagnostic algorithms for active TB in children,¹⁷ a really important finding in a resource poor area. This manuscript wins the paediatric gold medal for a really practical message, and confirming that the old dogs may not always have to learn new tricks (a relief to your editors). Screening strategies in a resource poor

area were formally evaluated,¹⁸ and for young children, blind treating of contacts was the best approach, also an important resource-saving finding.

Other topics of importance this year include prematurity and its long-term consequences, which continue to be highlighted to bring some much needed new focus to adult chest clinics.^{19–20} Basic mechanisms first: important abnormalities in surfactant protein D function were reported in preterm as compared with term infants.²¹ A meta-analysis showed that, although spirometry in some preterm survivors is improving with successive cohorts, even those pretermers with minimal respiratory issues at birth have long-term decrements, so better neonatal intensive care will not solve the problem.²² Impaired long-term lung function was confirmed in another cohort study²³—adult chest physicians take note! Snoring in children has been seen as a source of merriment (Fat Joe in *Pickwick Papers*, for example); but the increased morbidity in the 3 years before diagnosis, as well as after, and the sevenfold increased mortality in children with obstructive sleep apnoea shown in our silver medal winning paper makes snoring far from a laughing matter.²⁴ Finally, obesity again, this time maternal. This seems to predispose to transient infant wheeze, another risk factor for later COPD,²⁵ but not allergy.²⁶ Thin is beautiful (if not carried to extremes, something of which the editors in chief are not in danger!).

ADULT CLINICAL

We had several contenders for 2013 *Thorax* papers of the year in the fields of interstitial lung disease and lung cancer. The pick of these, and the winner of the gold award in this category, is the paper by Shulgina *et al*²⁷ describing a large multicentre placebo controlled trial of long-term treatment with cotrimoxazole in patients with idiopathic pulmonary fibrosis. Treatment did not improve the primary outcome but was associated with a fivefold reduction in mortality in participants who were able to take treatment. This finding provided a strong basis for investigating potential microbial factors. Garzoni *et al*²⁸ did not find any difference in bronchoalveolar lavage bacterial communities in a small pilot study. In contrast, assessment using a similar 16S-based method showed clearly disturbed microbial communities in patients with non-CF bronchiectasis.²⁹ There remains debate about the best outcome measures in interstitial lung disease. *Thorax* did its best to fan the flames of controversy in this area and provided two new outcome measures:

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the King's Sarcoidosis Questionnaire³⁰ and the King's Interstitial Lung Disease Questionnaire.³¹ In non-small cell lung cancer, we learnt that aldehyde dehydrogenase1A1 and CD133 expression are associated with worse outcome in patients with early disease. We would like to see papers adding 'unless' to 'worse outcome'. Powell *et al*³² provide a new risk stratification tool for patients undergoing resection of lung cancer. The use of incentive spirometry post-thoracotomy was assessed as a potential 'unless' and found to be wanting by Agostini *et al*³³ in what we felt was an excellent physiotherapy led study, the winner of our bronze award in this category.

Two treatments for obstructive sleep apnoea were evaluated in high quality randomised controlled trials published in *Thorax* in 2013. The SKUP³ trial compared uvulopalatoplasty and expectancy and showed a clinically and statistically significant 60% reduction in the apnoea index.³⁴ In contrast, the nasal expiratory resistance valve Provent was no more effective than placebo.³⁵ As with all other chronic medical problems, patients' perception of the importance of treatment can be discordant with the clinicians' leading to poor treatment adherence. Adherence to an oral appliance device was assessed using an ingenious imbedded microsensor thermometer and found to be around 80% in committed clinical trial participants.³⁶ We bet it would be much less in a more typical population. Perhaps adherence would be better if patients were aware of the increased risk of wake up stroke in those with prolonged apnoeas;³⁷ but then again, perhaps not—people do not adhere to treatment for known killers like leukaemia.

The last 20 years have been disappointing for the development of new treatments for airway disease although there have been a few green shoots lately: how far have we really moved from ventolin and becotide for asthma? The green (greenback?) shoots have occurred because researchers have focused more on modifying specific and well-defined aspects of disease and have moved away from arbitrary and unhelpful disease labels. Regrettably we have seen little of this in *Thorax* in 2013. Findings were either predictable³⁸ or unimpressive.^{39–41} One exception, and the winner of the silver medal, was the AZISAST study investigating long-term treatment with low dose azithromycin in patients with moderate to severe asthma.⁴² Treatment was strikingly effective in the subgroup of patients with non-eosinophilic asthma as defined by a blood eosinophil count at baseline of $<0.2 \times 10^9/L$. The blood

eosinophil count is the winner of our biomarker of 2013 as compelling evidence suggests that this biomarker might allow clinicians to make better clinical decisions: counts $>0.2 \times 10^9/L$ are associated with a poor outcome in patients with COPD lung attacks who are not treated with prednisolone;³⁹ counts $<0.2 \times 10^9/L$ with a better response to placebo than prednisolone;⁴³ and counts $<0.05 \times 10^9/L$ a poor outcome generally, probably because they signify significant sepsis.⁴⁴ Peak expiratory flow (PEF) monitoring was an OK marker of the occurrence of severe asthma lung attacks although there is clearly more to these episodes than airflow limitation as many reported episodes were not associated with a $>20\%$ fall in PEF.⁴⁵ In subjects with asthma, we learnt that clinical control and inflammation control are not closely linked;⁴⁶ that active eosinophilic airway inflammation may be associated with defective antirhinovirus immunity mediated by increased systemic tryptophan catabolism;⁴⁷ and that climbing to >6000 m results in increased symptoms and neutrophil airway inflammation, probably mediated by increased exposure to cold dry air.⁴⁸ (Back to the sofa and PlayStation!)

Pulmonary rehabilitation and peripheral muscle function in patients with COPD was a much more productive area for research and we had several high quality manuscripts in 2013. Much focus is on quadriceps function as this is important, is clearly abnormal in patients with COPD and is treatable. It can be assessed easily and reproducibly using the five-repetition sit-to-stand test⁴⁹ and potentially earlier by detecting muscle-specific messenger RNA in plasma.⁵⁰ Training results in significant improvements in quadriceps strength and size but the molecular mechanisms remain unclear and there is no evidence that the training effect can be augmented by dietary supplements.⁵¹ Delivering pulmonary rehabilitation in an appropriate and convenient setting remains a challenge. The PRINCE trial showed that a structured primary care-based rehabilitation programme is feasible and may be more accessible for frail elderly patients.⁵²

Thorax had a busy year in the pulmonary infection field as both pneumonia and TB were the subjects of themed issues. The use of inhaled steroids was shown to be associated with a marked increased risk of non-tuberculous mycobacterial disease⁵³ and a modest but dose-related increased risk of TB.⁵⁴ The risk of drug-induced reactivation of TB is an order of magnitude higher for TNF blockers but currently recommended methods for identifying those at risk may be inadequate as a

significant number of patients assessed as being low risk have immunological evidence of latent infection.⁵⁵ Diagnosis of active disease is also not always straightforward and it is often necessary to start treatment before confirmation of the diagnosis. This practice might become a thing of the past as the Xpert MTB/RIF test on bronchoalveolar lavage fluid results in a positive diagnosis more reliably and 30 days more quickly than sputum smear and culture.⁵⁶ Susceptibility to serious lung infection was the topic of several good papers in 2013. Mortality due to pneumococcal pneumonia seems to be more a function of host than bacterial factors.⁵⁷ Host factors that were not considered but which might be relevant include vitamin D deficiency, which was found to be common and associated with more severe disease in patients with bronchiectasis;⁵⁸ and hyperglycaemia, which promotes Staphylococcal aureus infection via a mechanism that is inhibited by metformin.⁵⁹

Finally, the 'you please, you sleaze' award to our sister journal, the *BMJ*, for their demonstration of how much the government really cares about public health. Read their expose about how the red carpet was rolled out for the drinks industry to meet everyone in town, evidence was suppressed and anyone who had the temerity to try to put an opposing view (Sarah Wollaston, Tory MP and GP) was ruthlessly blocked. Result—minimum price for alcohol down the drain. Treble trebles all round, and looking good for the tobacco industry, the past masters of these tactics, in 2014.

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