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Asthma – it hasn't gone away

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ABSTRACT – Asthma most definitely hasn't gone away. This article provides a review of the Royal College of Physician's conference in March 2012, which progressed attendees' understanding of both the basic science and clinical aspects of asthma care. The article highlights key clinical messages from the programme for general physicians – eg how best to approach the assessment of patients with severe asthma.

KEY WORDS: asthma, inflammation, adherence

'If you're not going forward you're going backward' JW von Goethe

Just in case you were in doubt, asthma remains the most common respiratory disease on the planet, affecting about 300 million individuals worldwide and costing European healthcare systems an estimated £15 billion annually.[1] Furthermore, mortality from asthma remains significant; indeed, it is sufficiently great in the UK to prompt the Royal College of Physicians to instigate a national review of all asthma deaths. It is with this backdrop that asthma most definitely 'hasn't gone away' and thus this conference was timely in taking us forward.

Going forward in understanding asthma

Ice cream in Ghana?

Professor David Strachan opened proceedings with a session, peppered with quotes from Goethe, that discussed the work performed in the three phases of the International Study of Asthma and Allergies in Childhood (ISAAC) (http://isaac.auckland.ac.nz/). Since its inception more than 20 years ago, this global endeavour has provided a detailed description of the prevalence and characteristics of childhood asthma. Indeed, having included nearly two million children from more than 250 centres across the world, Professor Strachan aptly described the study as 'reaching the parts that other studies couldn't reach'; but what can we learn from this?

Firstly, we learn that the prevalence of asthma symptoms varies considerably across the world, such that the prevalence of asthma symptoms in childhood is nearly 10-fold higher in the UK compared with in Indonesia and Albania. Time-trend analysis demonstrates a slight reduction in the prevalence of symptoms in older children in the UK; however, ISAAC clearly shows that although asthma 'hasn't gone away', it hasn't even arrived in some other countries.[2] This prompts the need for further studies specifically examining differences between centres with high and low prevalences.

A second point is that descriptive terminology is important. Indeed, in some countries, three terms are required to describe 'wheeze' adequately. Accordingly, phase 2 of ISAAC evaluated the relationship between 'wheezy' symptoms and bronchial responsiveness to hypertonic saline. At a centre level, the relation between these measures was poor, leaving investigators to ponder the gold standard. Having said this, participation in this component of ISSAC did have certain rewards – for example, it guaranteed an ice cream for volunteers in Ghana.

Asthma – all in the genes?

Professor Bill Cookson continued the theme of 'big studies' by discussing data from the GABRIEL consortium genomewide association study, in which more than 10,000 patients and controls were genotyped.[3] When data was dichotomised by age of asthma onset (with a cut-off age of 16 years), a difference in signal was seen. More specifically, later onset disease seemed to be influenced by major histocompatibility complex genes, whereas childhood disease was associated with a specific signal on chromosome 17 (*ORMDL3*).

Other key messages highlighted included the fact that circulating immunoglobulin E (as a surrogate for atopy) does not seem to be a driving factor underpinning asthma and that overall heterogeneity is marked, such that <4% of asthma heritability (the variance in trait due to genetics) is currently understood. The hunt is on for the 'missing heritability', with work evaluating multiple small associations, rare mutations and epigenetic effects. The last of these are highly susceptible to environmental influence, so the message for physicians is to stay focused on the environment.

The secret is in our childhood

Professor Andrew Bush outlined the importance of early life influences on respiratory health, indicating that we probably need to look backwards to move forwards. He discussed a number of longitudinal studies that illustrate consistent evidence of 'tracking' in lung function[4] – if you start low, you stay low. Indeed, he presented data indicating that lung development may be 'done and dusted' by the age of nine years. This may be of limited interest to adult physicians; however, Professor Bush emphasised that adequate lung development underpins future development of respiratory disease, so we should work hard to ensure that young adults achieve the optimum trajectory in lung

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Table 1. Approach to 'difficult' asthma for the physician.

Question	Consider
1 Is the diagnosis secure?	• Supporting physiological data – eg lung function and bronchial hyper-reactivity • Measures of inflammation • CT findings
2 Are additional abnormalities/ comorbidities contributing?	• Additional CT findings – eg evidence of bronchiectasis • Sinus disease • Gastroesophageal reflux • ENT review to provide assessment of vocal cord function
3 Is there evidence of good treatment adherence?	• Record of prescription filling/ frequency of inhaler use • Drug serum assays (eg prednisolone or aminophylline) • Medical concordance discussion/ intervention
4 Are symptoms out of proportion (ie to that expected)?	• Breathing control/physiotherapy review • Psychological factors/contributors

CT = computed tomography; ENT = ear, nose and throat.

growth and attenuate the rate of subsequent decline in lung function (by stopping them smoking).

It is not easy to look backwards, however, as Professor Bush illustrated with data from a study that assessed an adult's recall of their childhood infection history.[5] The findings indicated that it is probably as accurate to toss a coin. Some adults will therefore blame their mothers, perhaps not without good reason, as relevant factors in lung development include a maternal history of smoking and antibiotic use.

Going forward in managing asthma

Time to get SMART?

Many readers will be aware of a single combined inhaler approach as both an asthma 'preventer' and a 'reliever': the Single Maintenance and Reliever Therapy (SMART) approach. However, Professor Neil Barnes spent time outlining the place of this approach and the rationale for its position in the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guideline.[6] The use of a single budesonide/formoterol inhaler is potentially indicated for poorly controlled patients at step 3 of the guideline; Professor Barnes cautioned that data is currently insufficient to conclude that this approach completely satisfies the criteria dictating good clinical or airway inflammation control.[7] In addition, although it may seem a 'smart' approach to some physicians, Professor Barnes highlighted the importance of adequate patient education to ensure that patients really understand the dual purpose of the device – ie that they should not use SMART with an additional reliever inhaler (as he often encountered in practice).

What should the physician do with severe asthma?

About 5% of patients with asthma are said to have severe problematic or 'difficult-to-treat' disease. General physicians will recognise the impact of this population of patients in terms of their frequent use of healthcare resources and heightened morbidity and mortality. Appropriately, therefore, both Professor Andrew Bush and Dr Andrew Menzies-Gow spent time outlining a pragmatic approach to the assessment of patients with severe asthma.

A good starting point is the definition, and Dr Menzies-Gow highlighted that using the term 'difficult asthma' for patients who remain symptomatic despite being prescribed therapy at step 4 of the BTS/SIGN asthma guideline was both logical and practical. Moreover, he emphasised that physicians should avoid using the term 'brittle' asthma, which, although he conceded was iconoclastic of his institution,[8] was not clinically pragmatic. He then highlighted that physicians should consider four key questions when faced with difficult asthma (Table 1).

Both Professor Bush and Dr Menzies-Gow made it clear that a systematic approach to the assessment of patients with severe asthma is vital. The role of this assessment is to ensure that the correct patients receive the correct treatments especially given the increasing emergence of targeted (and expensive) therapies. One such treatment is bronchial thermoplasty; a novel therapy in which radiofrequency energy is delivered to the airway wall with the aim of attenuating the action of local smooth muscle. Professor Neil Thomson expatiated on the virtues of this technique for difficult asthma;[9] however, he cautioned that its precise place in the management of asthma and its long-term safety remain to be established.

Time to confront poor adherence?

Establishing good 'adherence' or 'concordance' with a prescribed treatment (based on an agreed 'shared' decision) is a key tenet in the management of any chronic disease. Professor Liam Heaney highlighted that asthma is certainly no different, with poor adherence relating to both morbidity and mortality.[10] Indeed, he cited early recognition of this fact by Dr John Elliston (1791–1868), who stated that: 'A medical man, when he orders a patient to inhale vapours, must give his personal attention to the manner in which it is performed if he wishes to have his intentions efficiently carried out…'

The problem really begins with trying to establish the presence of poor adherence and accounting for confounders such as the 'Hawthorne effect' – that is, the influence of external assessment on an individual's behaviour. Professor Heaney described how some units employ prednisolone/cortisol blood assays to assess adherence covertly, but, regardless of approach, evidence now

shows consistently poor adherence in more than half of the population of adults with asthma across the UK. Surprisingly, the best approach to poor adherence seems to be to 'confront' the patient in a 'medical concordance' interview. Professor Heaney outlined data indicating the clear benefits of such an approach and a subsequent intervention programme.[11]

'It's the eosinophil stupid'

Professor Ian Pavord opened an engaging session addressing airway inflammation by citing Lord Kelvin: 'If you can't measure something, you can't improve it'. The presentation that followed certainly aptly demonstrated that his group has invested considerable energy following this edict.

To this end, many physicians will be aware of the wealth of data indicating the benefits of assessing airway inflammation (or inflammometry) to tailor asthma treatment.[12] Professor Pavord expanded on this theme by outlining the role of airway eosinophilia (concentration of eosinophils in sputum >3%) in airways disease and the benefits of targeting this signal to attenuate exacerbations and steroid burden. He continued by discussing the virtues of exhaled nitric oxide and suggested that although some clinicians have been less sanguine regarding this approach, the deficiencies in data likely relate to aspects of trial design and choice of appropriate cut-off values.

Professor Pavord closed by commenting that novel targeted treatments (for example, interleukin 5 blockers such as mepolizumab) offer great promise in a subgroup of patients with refractory eosinophilic asthma.

Is it chronic obstructive pulmonary disease or asthma and should we care?

Professor Chris Brightling addressed the complexity of phenotyping of patients with airways disease and presented data from novel approaches in this area, such as evaluation of airway geometry and computational airway 'fluid' dynamics. However, he was keen to stress that phenotyping should not simply be a 'tool for academics', emphasising that clinical efficacy is a paramount endpoint.

To this end, Professor Brightling reinforced the comments made by Professor Pavord, highlighting that recent data targeting phenotypes of chronic obstructive pulmonary disease could have profound implications for the way exacerbations are managed.[13] This work parallels findings in asthma and thus signifies that it is perhaps not 'what it is' but 'how we should treat it' that is important.

Summary

At the end of the day's proceedings, it was clear that asthma most definitely hasn't gone away, and the sessions detailed above certainly were formative in moving us forward. Box 1 lists a number of key clinical take-home messages, and physicians are encouraged to visit the RCP's webpage for the National Review of Asthma Deaths (www.rcplondon.ac.uk/projects/national-review-asthma-deaths).

Box 1. Key clinical take-home messages for the physician

- Don't rely on an adult's recall for an accurate childhood infection history
- In patients with severe asthma, consider and address the key areas described in Table 1
- Systematic assessment of patients with severe asthma is important to ensure that the correct patient gets the correct therapy
- Don't overlook treatment adherence as a factor that confounds 'difficult' asthma
- Phenotypes are only as useful as their clinical efficacy – but consider recent evidence highlighting the benefits of a biomarker-targeted approach to treatment
- Bronchial thermoplasty may be a therapeutic option in some patients with severe disease following systematic assessment in a specialist centre

References

1 Braman SS. The global burden of asthma. *Chest* 2006;130:4S–12S.
2 Asher MI, Montefort S, Björkstén B *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–43.
3 Moffatt MF, Gut IG, Demenais F *et al.* A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363:1211–21.
4 Sears MR, Greene JM, Willan AR *et al.* A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414–22.
5 Johnston IDA, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 1998;338:581–7.
6 Douglas G, Higgins B, Barnes N *et al.* British guideline on the management of asthma: a national clinical guideline. *Thorax* 2008;63:iv1–121.
7 Chapman KR, Barnes NC, Greening AP, Jones PW, Pedersen S. Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal. *Thorax* 2010;65:747–52.
8 Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest* 1977;71:73.
9 Thomson NC, Bicknell S, Chaudhuri R. Bronchial thermoplasty for severe asthma. *Curr Opin Allergy Clin Immunol* 2012;12:241–8.
10 Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax* 2012;67:268–70.
11 Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med* 2011;105:1308–15.
12 Pavord ID, Shaw DE, Gibson PG, Taylor DR. Inflammometry to assess airway diseases. *Lancet* 2008;372:1017–19.
13 Bafadhel M, McKenna S, Terry S *et al.* Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48–55.

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