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Mini-symposium: Asthma Phenotypes

PHENOTYPES OF REFRACTORY/SEVERE ASTHMA

Andrew Bush [a,*], Louise Fleming [b]

[a] Professor of Paediatric Respirology, Imperial School of Medicine at National Heart and Lung Institute; and Honorary Consultant Paediatric Chest Physician, Royal Brompton Hospital
[b] Clinical Fellow Paediatric Allergy, Imperial Healthcare NHS Trust

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SUMMARY

The acid test of phenotyping is that it leads either to a clinically useful or mechanistically important insight. Phenotypes may change over time, but the exact definition of a phenotype shift is unclear. Methods of phenotyping are either investigator driven, in which *a priori* prejudices are applied to the data, or (semi) objective, in which mathematical techniques or systems biology approaches are applied to the dataset. However, the *composition* of the dataset is driven by investigator prejudice. Phenotyping is likely most useful in severe asthma, because mild and moderate asthma responds to simple treatments, and no great subtlety is required. Our non-evidence based approach is to define the subpopulation of genuine severe, therapy-resistant asthmatics from the generality of problematic severe asthma. We then investigate them invasively with bronchoscopy and a steroid trial using intramuscular triamcinolone to determine the nature of any inflammatory process; whether inflammation and symptoms are concordant or discordant; whether the inflammatory process is steroid resistant or sensitive; and whether the child has persistent airflow limitation. Other possibly relevant phenotypes include the child with severe exacerbations; brittle asthma; and severe asthma with fungal sensitization. Severe, therapy resistant asthma is a disparate disease, and only international uniform approaches, carefully characterising the children as a prelude to focussed clinical trials will allow progress to be made, and vindicate (or otherwise) our suggested approach.

Phenotyping asthma is an occupation which, skilfully done, leads to a profusion of high impact factor publications, big grants and International lectures in exotic environments, but these are not of themselves sufficient justification for the activity. The purpose of this review is critically to define what we mean by a phenotype, to assess the real usefulness (if any) of phenotyping wheeze syndromes, and discuss the strengths and weaknesses of different approaches used in paediatric wheeze syndromes.

WHAT IS A PHENOTYPE?

Recourse to the dictionary or the internet will produce a multiplicity of definitions. We prefer a pragmatic and operational definition: ''a feature, or more usually, a cluster of features which leads to the separation of a specific group from the generality of wheezing children at a given time''. These features may be in a single domain (for example, sputum cellularity) or in combinations of domains (for example, symptom patterns, sputum cellularity and airway physiology). Crucially, some useful action must result from the division, be it an approach to treatment or a fresh insight into disease mechanisms. This last point is the acid test of the approach; there is less than no point in endlessly subsplitting for the sake of it. Note that this definition does not carry the implication that a given phenotype will be stable over time; this crucial mistake is heartily embraced by some critics of symptomatic phenotyping of pre-school wheeze[1,2] [Table 1]. Temporal stability is needed only insofar as it makes the phenotype useful in some way. There is no minimum agreed period – clearly a phenotype changing every day is unlikely to be a useful concept, but stability over several weeks may well be. Careful consideration also needs to be given to what actually constitutes a change in phenotype; a child with eosinophilic asthma may acquire a secondary bacterial bronchitis or even a viral lower respiratory tract infection leading to a switch from an eosinophilic to a mixed cellularity or even neutrophilic phenotype, but does this necessarily mean a change in underlying pathophysiology?

HOW SHOULD WE PHENOTYPE?

The initial approach was investigator driven; coming to a dataset with particular prejudices and insights, and teasing out

* Corresponding author. Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. Tel.: +207 351 8232; fax: +207 351 8763.
E-mail address: a.bush@rbh.nthames.nhs.uk (A. Bush).

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Table 1
Asthma phenotyping; conceptual issues to be considered

- **Definition:**
  What constitutes a phenotype?
  A feature, or more usually, a cluster of features which leads to the separation of a specific group from the generality of wheezing children at a given time
- **Utility:**
  - What useful action results from the division, be it an approach to treatment [clinical utility] or a fresh insight into disease mechanisms
- **Temporal stability:**
  - Temporal stability is needed only insofar as it makes the phenotype useful in some way
  - Careful consideration needs to be given to what actually constitutes a change in phenotype
- **Domains assessed**
  - **What domains are assessed? eg,** a single domain (for example, sputum cellularity) or in combinations of domains (for example, symptom patterns, sputum cellularity and airway physiology)
- **Assessment approaches**
  - **What assessment approaches are used?**
    - **Clinical insight**
    - **Measurement techniques: inflammometry, physiology**
    - **Mathematical analysis techniques, e.g. latent class analysis**

phenotypes. This approach is not to be despised; but it relies heavily on the investigator having brilliant insights. The utility is shown by the beautiful differentiation of diabetes insipidus and diabetes mellitus by Matthew Dobson, or Heberden's classic description of angina pectoris from other causes of chest pain long before the detailed pathophysiology of these conditions was understood.[3] More recently, mathematical techniques have been applied, such as latent class analysis and principal component analysis, which allows phenotypes to emerge from the data.[4,5,6] Another approach is to use an 'unbiased' systems biology approach to integrate high dimensional data. Such approaches are increasingly being used in other areas of medicine and are soon to be applied to a large cohort of patients with severe asthma.[7] All these approaches sound like very good ideas, but these approaches too suffer from lack of intellectual rigour. It is disingenuous to think that these mathematical gymnastics give rise to an objective set of phenotypes. An analytical tool can only analyse the data that has been entered, and so immediately an opportunity for investigator prejudice arises; because those prejudices will inevitably determine what data actually is analysed. So if in fact very distal inflammation is a key factor, and this is not measured, then no mathematical technique will identify it as important. Furthermore, as with genetic studies,[8] it is surely correct to investigate two cohorts, the first to generate hypotheses about phenotypes, and the second to validate them. How often if at all is that done in studies of asthma phenotypes?

MECHANISMS OF DISEASE VERSUS TREATMENT OUTCOMES

Another sometimes overlooked point is that although it is intellectually tidy to understand pathophysiology, and use these insights to develop phenotypes which will determine treatment, this orderly progression is not necessary for clinical utility. To take an absurd example, if the diameter of the great toe defined which child would respond to inhaled corticosteroids (ICS), we would all be asking the children to remove their socks and shoes, even though toe-measuring gave us no mechanistic insights.

In summary, the assessment of any phenotypic analysis begins with answering those two eternally important questions, 'so what?' and 'what for?' If a satisfactory answer is not forthcoming, then the approach should be discarded. In the remainder of this article we try to apply these principles to current phenotyping approaches in school age children, especially with severe asthma.

WHAT *IS* AN INFLAMMATORY PHENOTYPE?

Traditionally, inflammatory cellular phenotypes are divided on the basis of induced sputum cell counts into eosinophilic, neutrophilic, mixed cellularity and pauci-inflammatory.[9] There is a reasonable (but by no means perfect) correlation between induced sputum and BAL, but a very poor correlation between either of these investigations and endobronchial biopsy.[10] The relative importance of mucosal and luminal inflammation is unclear. The failure of anti-IL5 monoclonal antibody strategies in early studies[11] has been attributed to failure to eliminate mucosal eosinophilia.[12] On the other hand, a follow up study of young adults in apparent complete clinical remission of asthma showed mucosal eosinophilia indistinguishable from that of active asthma,[13] implying that mucosal eosinophilia may be necessary, but is certainly not sufficient to cause clinical asthma. This leads to an important insight – just because a particular cell is present, does not necessarily mean it is important in causing disease.

At least in adult studies, there is evidence that distal inflammation, assessed with transbronchial biopsy (TBB), may be key in nocturnal asthma.[14,15,16] There are no direct or indirect methods that can be used to assess this in children. TBB is unsafe as a research technique,[17] and although partitioning nitric oxide production between proximal and distal[18,19] can distinguish between groups of asthmatics,[20] the overlap between groups is such that the measurements are not useful in managing individuals.[21]

In summary, phenotyping children with asthma is primitive in the extreme. Sputum phenotypes, which may be useful in driving treatment (although more evidence is needed to prove this) cannot be said to relate to mucosal and distal inflammation.

PHENOTYPING SCHOOL AGE ASTHMA: USEFUL?

The evidence for benefit is not clear cut. Indeed, most children with asthma will respond to properly administered, low dose ICS, and subtle phenotyping is not needed for good management. The SARP group has used cluster analysis to phenotype a combined group of adult and paediatric severe asthmatics,[22] a good example of a unified approach, but one which so far has failed to move the field forward in terms of mechanisms or treatment regimes. The rest of the field comprises rather haphazardly determined and generally pragmatic phenotypes, in the main restricted to severe asthmatics.

PHENOTYPING ASTHMA: A PRACTICAL APPROACH

Our personal and non-evidence based practice has been described in detail elsewhere.[23,24] Far more important than the nuances of phenotyping is to get the basics right [Table 2]. Thus when referred a child with problematic severe asthma (an

Table 2
Step-wise Approach to Phenotyping Refractory Asthma in Children

- **Entry Point:**
  - **Problematic Severe Asthma**
- **Initial assessment**
  - **It is really asthma, or a wrong diagnosis?**
  - **Manage co-morbidities:**
    - **Rhinosinusitis**
    - **Obesity**
    - **Vocal cord dysfunction**
  - **Optimise asthma care:**
  - **Nurse led optimisation of asthma skills, corticosteroid therapy**
    - **Outcome: Severe, Therapy Resistant Asthma**
  - **Assessment**
    - **Airway Inflammation**
    - **Phenotype concordance**
    - **Corticosteroid responsiveness**
    - **Persistent airflow limitation**
  - **Individualised management**