Phenotype-specific treatment of difficult asthma in children

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Implicit in the title of this paper are three issues:

1. What is ‘asthma’?
2. What does ‘asthma phenotype’ mean in this context?
3. Does a reductionist approach to phenotypes help to achieve a treatment plan while accepting it is an inevitable oversimplification? In other words, so what?

This paper considers only the older child; the problems of the pre-school years are discussed in another paper in this series.

DEFINITION OF ASTHMA

The initial paediatric consensus statement defined asthma as ‘cough and/or wheeze in a context where asthma seems likely and other, rarer, diagnoses have been excluded’. This definition has the superb merit of not confusing pathological findings with clinical presentations, the importance of which has long been appreciated. In older children, the addendum that ‘asthma is a condition which causes airflow obstruction which varies over time and with treatment’ is entirely appropriate, although it could be criticised as linking a physiological investigation with a clinical finding; in practice, few if any would be prepared to diagnose asthma if there was never any evidence of changing airflow obstruction. However, variable airflow obstruction, although highly specific but not very sensitive in a community context, may be less specific in tertiary practice where variable airflow obstruction may be caused by, for example, bronchiectasis of any cause. Thus the demonstration of reversibility should not mean the end of diagnostic efforts. For the purposes of considering phenotype-specific treatment, we use the clinical definition with the physiological supplement. This broad definition means that asthma is not a very specific term. Furthermore, since many guidelines pre-judge the issue of whether all asthma is inflammatory by including inflammation in the definition, even though it is rarely measured in clinical practice, the term ‘asthma’ may well have outgrown its usefulness. For both these reasons, we believe that ‘asthma’ is best replaced by the term ‘asthma syndrome’, as argued elsewhere.

Summary

Most children with asthma can be treated successfully with low-to-moderate doses of inhaled corticosteroid and long-acting β-2 agonist. Those that fail to respond are a heterogeneous group. We propose that the nature and type of any steroid-resistant inflammation, the extent of any persistent airflow limitation and the extent of bronchial hyper-reactivity should be determined separately to allow a rational treatment approach to these children, rather than the haphazard advice of many current guidelines. Reasons for persistent difficult asthma include persistent eosinophilic inflammation, non-eosinophilic inflammation, airway reactivity without residual inflammation and persistent airflow limitation. We propose a protocol that uses non-invasive and invasive (bronchoscopic) methods to document the response to systemic steroids (depot triamcinolone). The aim of the protocol is to determine an individualised treatment plan; for example, cyclosporin for persistent eosinophilic inflammation, azithromycin for persistent neutrophilic inflammation and continuous subcutaneous terbutaline if there is airway reactivity without residual inflammation. Multi-centre studies are required to test the utility of this approach.
WHAT DOES PHENOTYPE MEAN?

A phenotype may be considered as a cluster of either clinical or pathological features (not both, in our view) that tend to be associated and which are useful in some way, such as in managing the child or understanding the mechanisms of disease. There may be overlap between phenotypes and they may change over time. If the existence of phenotypes is proposed, the onus is on the proposer to justify the use of the term. The ‘so what?’ question is addressed at the end of this paper.

WHAT ARE THE COMPONENTS OF THE DIFFERENT ASTHMA PHENOTYPES?

The vast majority of children with asthma respond to low-dose inhaled corticosteroids with no side-effects. It is only in children with more problematic asthma that a discussion of phenotypes is profitable. The most important question is, what is it about this child and this child’s asthma that is different from the run-of-the-mill disease that is so easily treatable? In this context, we believe that it is helpful to consider components of the asthma syndromes to be:

- extent and nature of any airway inflammation;
- degree of bronchial hyper-reactivity (BHR); and
- extent of persistent, apparently irreversible, airflow obstruction/limitation (PAL).

Our hypothesis is that by attempting to dissect out these components, a rational treatment plan can be achieved in those children with therapy-unresponsive asthma. This will be justified in subsequent sections of this paper. Clearly, before embarking on a detailed assessment, it is essential to ensure that the diagnosis is correct, the medication is being taken and environmental and psychological issues have been addressed as far as possible (and see other articles in this series).

Airway inflammation

Traditionally, asthma, at least in older children, has been considered as a Th2-lymphocyte-mediated, eosinophil-driven disease of airway inflammation. Bronchoscopic studies have demonstrated that at least some children with asthma have eosinophilic airway inflammation. However, although undoubtedly well founded in many asthmatic children, the concept that the eosinophil is the sole important inflammatory cell has been challenged. In particular, studies utilising bronchoalveolar lavage (BAL), bronchial biopsy and induced sputum have characterised non-eosinophilic forms of asthma that may account for up to 50% of childhood asthma irrespective of age. Further doubts have been raised by the demonstration of the ability of anti-cytokine therapy to reduce airway and peripheral blood eosinophilia dramatically with little change in asthma severity. It is possible that this reflected a failure to clear eosinophils from the airway wall. Non-inflammatory asthma phenotypes have been described. There are many different potential airway inflammatory pathways (Table 1); assuming that wheeze equals eosinophilic airway inflammation, or even inflammation at all, may be a mistake.

Bronchial hyper-reactivity

This has traditionally been considered one of the hallmarks of asthma. The traditional model has been that inflammation causes BHR and that BHR causes symptoms of asthma. This paradigm has also been challenged. Firstly, although there is a good correlation between BHR and severity of asthma for groups, there is much overlap between individuals within the groups; thus for an individual, there is only the poorest correlation between BHR and asthma severity. Furthermore, BHR is not a single entity but can be determined in many different ways; abnormalities may result from many different mechanisms (Table 2). There are different dose–response curves to therapy with inhaled corticosteroids; the curve is relatively flat in exercise-induced BHR, compared with, for example, allergen challenge. There is very poor correlation between eosinophilic airway inflammation and BHR. It is true that a single study in adults showed a better correlation between change in BHR and change in eosinophilic airway inflammation and used BHR as a surrogate for inflammation; however, overall, our hypothesis is that in a clinical model, BHR and inflammation should be considered as, at best, overlapping phenomena.

| Table 1 | Different aspects of airway inflammation. |
| Cellular mechanisms | Resident cells – epithelial, fibroblast, myofibroblast, smooth muscle cell |
| | Invading cells – eosinophil, neutrophil, others |
| Chemical mechanisms | Cell–cell signals – cytokines, chemokines |
| | Lipid mediators – leukotrienes and other products of arachidonic acid metabolism, platelet activating factor |
| | Reactive oxygen species – 8-isoprostane, other reactive oxygen species |
| Neurogenic mechanisms | Non-adrenergic, non-cholinergic nervous system – neurotransmitter release, including nitric oxide |
Persistent airflow limitation

This is an important practical consideration; there is no point in escalating treatment if there is no further capacity to dilate the airway. PAL may be due to anatomical reduction in airway calibre, either antenatal or postnatal and alteration in airway wall compliance, either as a primary effect on wall structure or due to loss of the alveolar guy-rope effect (Table 3). Antenatal factors that can reduce airway calibre include maternal smoking, maternal atopy and (in a single study) maternal hypertension of pregnancy. Postnatally, obliterator bronchiolitis may be due to adenoviral (or other virus) infection or gastro-oesophageal reflux and aspiration. Airway remodelling is seen in association with airway inflammation in some of the asthma syndromes. However, the limited evidence does not support an association between remodelling changes and PAL in severe asthma. Alterations in compliance of the airway wall have been suggested to be of importance, whether this is due to alterations in wall structure or reduced alveolar tethering, as seen, for example, in guinea pig pups exposed to tobacco smoke in utero, is difficult to determine without pathological studies.

ASTHMA PHENOTYPES IN THE OLDER CHILD WITH SEVERE ASTHMA

Introduction

The treatment of severe asthma (Stages 4 and 5 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines) is haphazard. Treatment options such as oral steroids and steroid-sparing agents are advocated, with no real attempt to answer the fundamental question as to what has made this particular child’s asthma so difficult to treat. We have developed a protocol (Table 4) to try to determine a rational approach to severe asthma, predicated on the belief that there are many different reasons why asthma may be therapy resistant. There are a number of different definitions as to what constitutes severe asthma; ours is a child still symptomatic while taking ≥1 mg fluticasone dipropionate (or equivalent) and failed trials of leukotriene receptor antagonists and long-acting β-2 agonists. The protocol is a compromise between what is scientifically ideal and what is ethically acceptable; for example, it might be preferable to bronchoscope the child both before and after treatment with systemic steroids. However, we know of only a single paediatric study in which two bronchoscopies were performed, a study of eradication of Pseudomonas aeruginosa in cystic fibrosis. Instead, we felt it correct to rely on induced sputum to determine airway cellularity before the course of steroids, accepting that some will have too severe airflow obstruction for this to be attempted and that in 20% of children over 12 years old, it will not be possible to obtain a sample (more in younger children). At the first visit (when the patient is enrolled and after a full assessment has been performed), a diary card is supplied to confirm continuing symptoms. Home peak flow monitoring is generally so poorly performed that we have stopped using it as a clinical tool in this context. At the second visit, non-invasive measurements of airway inflammation are performed and the child is given a single intramuscular injection of a depot preparation of triamcinolone (in preference to a course of oral prednisolone). At the third visit, 2 weeks later, the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Components of bronchial hyper-reactivity. It is likely that if the baseline airway calibre is reduced, the response to any stimulus will be increased.</th>
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</thead>
<tbody>
<tr>
<td>MECHANISM</td>
<td>CHALLENGE</td>
</tr>
<tr>
<td>Direct on smooth muscle</td>
<td>Histamine, methacholine</td>
</tr>
<tr>
<td>Via release of inflammatory mediators</td>
<td>Exercise, adenosine</td>
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<tr>
<td>Via NANC neuronal pathways</td>
<td>Exercise, adenosine</td>
</tr>
<tr>
<td>NANC, non-adrenergic, non-cholinergic. For more details of the different direct and indirect challenges and their mechanisms, see Joos GF et al. Eur Respir J 2003; 21: 1050–1068.</td>
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<tr>
<th>Table 3</th>
<th>Components of persistent airflow limitation.</th>
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<tr>
<td>Fixed narrowing due to developmental effects</td>
<td>Prenatal – passive smoking, maternal atopy, hypertension of pregnancy</td>
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<tr>
<td>Postnatally acquired mechanisms of fixed narrowing</td>
<td>Obliterator bronchiolitis – adenoviral or other infection, reflux and aspiration</td>
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<tr>
<td>Remodelling – secondary to, or in parallel with, airway inflammation</td>
<td></td>
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<tr>
<td>Abnormal lung mechanics</td>
<td>Altered airway wall compliance, loss of alveolar tethering (may be difficult to distinguish without lung morphometric studies)</td>
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Table 4  The difficult asthma protocol.

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<tr>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physiological measurements</td>
<td>Spirometry</td>
<td>Spirometry, including response to β-2 agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assess symptoms, new peak flow diary</td>
</tr>
<tr>
<td></td>
<td>Give peak flow diary</td>
<td></td>
</tr>
<tr>
<td>2. Non-invasive inflammatory and other markers</td>
<td>Exhaled nitric oxide</td>
<td>Exhaled nitric oxide</td>
</tr>
<tr>
<td></td>
<td>Sputum induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radioallergosorbent or skin prick tests as appropriate</td>
<td></td>
</tr>
<tr>
<td>3. Invasive studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchoscopy, bronchoalveolar lavage and bronchial biopsy</td>
<td></td>
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non-invasive measurements are repeated and a fibre-optic bronchoscopy is performed with BAL and airway biopsy. We do not perform transbronchial biopsy. The safety of this approach has been evaluated and found to be acceptable.32 The different phenotypes that we have recognised so far are summarised in Table 5 and discussed in detail below.

One aim of this protocol is to determine how good the child’s lung function can become. We assume that a depot injection of triamcinolone, followed by inhaled high-dose β-2 agonist, is sufficient to correct any reversible element. This has, however, not yet been confirmed.

Steroid-sensitive asthma

The most common single phenotype is the child who, on high-dose systemic steroids, becomes completely asymptomatic with normal lung function and no airway inflammation on airway biopsy and BAL. We then plan to reduce the oral steroids to the minimum dose that controls symptoms and (ideally) non-invasively measured inflammation. If prednisolone cannot be reduced to a level where side-effects are minimal or tolerable, we would use a steroid-sparing agent, usually cyclosporin. However, our experience has been that these agents seem to work less well in this group than in the steroid-resistant asthmatics (below). Children requiring high-dose steroids to control asthma are also assessed as far as is possible for causes of secondary steroid resistance.

Steroid-resistant, eosinophilic asthma

This phenotype comprises biopsy and/or BAL evidence of eosinophilic inflammation in children in whom adherence to steroid therapy has been assured by giving depot triamcinolone and who remain symptomatic.10 In some of these steroid-resistant children, we have found abnormalities of steroid-receptor binding and translocation of the steroid-receptor complex from cytoplasm to nucleus.33 It must be said that these measurements are not easy to interpret and remain in the domains of research.

The causes of steroid resistance are a subject of controversy. It must be stressed that the most common cause is failure to adhere to steroid treatment! Congenital steroid deficiency, characterised by a very low number of steroid receptors of normal binding affinity, is very rare.34 Secondary steroid resistance is much more common and is usually characterised by a normal or increased number of steroid receptors with reduced affinity for glucocorticoid. One putative mechanism is via allergen drive in a sensitised subject; this causes increased IL-2 and IL-4 release from white cells, which in turn modulates steroid resistance.35 This underscores the need for attention to the environment and allergic sensitisation in these children. Another (not necessarily mutually exclusive) cause of steroid resistance is a switch in the phenotype of a subunit of the steroid receptor to a phenotype with reduced affinity.36 Animal experiments suggest that latent viral infection is a mechanism to be considered. Our own studies (submitted for publication) suggest that the mechanism of persistent eosinophilia is not persistence of the characteristic TH2 drive, based on the absence of typical TH2 signature cytokines such as IL-4 and IL-5 in bronchial biopsies. However, the true mechanism remains to be elucidated.

We elect to treat these children with alternative anti-inflammatory therapies, usually cyclosporin. The protocol has been published elsewhere;37 briefly, meticulous attention to detail of monitoring drug levels and renal function is essential. We would attempt a minimum of a 3-month trial of treatment if tolerated and, if the response is good, try to wean the dose of steroids (initially oral, then inhaled) to the minimum dose tolerated. There is no evidence to prefer cyclosporin to methotrexate or azathioprine; it comes down to patient preference and the experience of the physician.

Persistent eosinophilic inflammation with no symptoms

We have seen this phenotype in the context of our severe asthma protocol. The phenotype has been described best in a group of young adults who, to all clinical intents and
purposes, have outgrown their asthma. They are off all therapy and have a normal lifestyle and would be discharged from the clinic. However, detailed investigation in this group has shown persistent airway eosinophilia on biopsy. The interpretation of this finding is difficult and management recommendations are purely conjectural. It is possible that in these circumstances, some extra factor is absent; when this factor is present, it combines with eosinophils to produce asthma symptoms. It is equally possible that the eosinophils are producing subclinical ongoing airway inflammation and airway wall damage and that these young people will have PAL in later life. In practice, it seems unlikely that these people will take inhaled medication if they perceive themselves to be well. Furthermore, the best evidence is that airway remodelling is an early phenomenon and that progressive changes are unlikely by this age. Were we to observe this phenotype in severe asthma, we would treat the child as for steroid-sensitive asthma (above). In the context of the adolescent who appears to have outgrown the disease, it is difficult to believe, given the current evidence, that re-instituting treatment is likely to be acceptable. More work is needed to provide an evidence base.

Finally, in the context of eosinophilic bronchitis in adults, eosinophils in the airway mucosa were not associated with BHR. The only pathological difference between asthmatic patients with airway eosinophilia and those with eosinophilic bronchitis but no asthma was not in eosinophil

<table>
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<tr>
<th>Clinical scenario</th>
<th>Presumptive diagnosis</th>
<th>Suggested action</th>
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| 1. Continued airflow obstruction, no inflammation, no reversibility to β-2 agonists | Presumed obliterative bronchiolitis, or remodelling secondary to chronic inflammation etc. | • Inspiratory and expiratory computed tomography scan  
• Use minimum treatment that maintains lung function |
| 2. Continued airflow obstruction, no inflammation but with reversibility to β-2 agonists | Presumed steroid resistance, non-inflammatory bronchial reactivity | • Look for causes of secondary steroid resistance (environment etc.)  
• Continuous subcutaneous terbutaline infusion  
• Look for causes of secondary steroid resistance  
• Treat with either prolonged high-dose steroids or steroid-sparing agent  
• Consider using computerised drug delivery device to confirm adherence |
| 3. Persistent eosinophilic inflammation, with either or both of airflow obstruction and symptoms | Presumed partial or complete steroid resistance | • Look for causes of secondary steroid resistance  
• Continuous subcutaneous terbutaline infusion  
• Consider using computerised drug delivery device to confirm adherence |
| 4. Persistent eosinophilic inflammation, with no airflow obstruction or symptoms | Lagging of clearance of inflammation | • Look for causes of secondary steroid resistance  
• Continuous subcutaneous terbutaline infusion  
• Consider using computerised drug delivery device to confirm adherence |
| 5. Presumed inflammation completely resolved with steroids (normal lung function, no symptoms) | Steroid-sensitive asthma but requiring high-dose treatment | • Look for causes of secondary steroid resistance  
• Taper steroids to level at which symptoms are controlled without side-effects or use steroid-sparing agent  
• Check environment |
| 6. Persistent non-eosinophilic inflammation | Presumed other inflammatory mechanisms (other cells, e.g. neutrophilic inflammation; neurogenic mechanisms) | • Reduce steroid treatment to minimum level needed to control eosinophilic inflammation  
• Consider macrolide therapy, 5-lipoxygenase inhibitor or theophylline if neutrophilic inflammation |
| 7. No detectable prednisolone in blood, normal cortisol levels | Poor adherence to treatment | • Consider repeating study after depot steroid injection  
• Psychological assessment |
| 8. Apparently normal lung function, no inflammation but ongoing symptoms | Poor symptom perception  
Psychological problems  
Not asthma at all | • Exercise test with Borg scale  
• Review by psychologist |
numbers or distribution (which were identical) but that the asthmatics had increased numbers of mast cells in the muscle layer. Eosinophils by themselves are neither necessary nor sufficient to cause asthma. The most important message, applicable to neutrophils and other cells as well as the eosinophil, is that the mere presence of a cell is not proof that it is causative of a problem.

**Steroid-resistant, non-eosinophilic inflammatory phenotype asthma**

There have been a number of induced sputum and bronchial biopsy studies in which a neutrophil-dominated or exclusive phenotype has been reported. This phenotype may account for around half the burden of asthma at all ages. These patients are symptomatic and poorly responsive to steroids. What is unclear is the role of the neutrophil in this phenotype. Possibilities include that it is the effector cell for this type of asthma, that the presence of neutrophils merely reflects the effects of corticosteroids prolonging neutrophil survival by delaying apoptosis or that the neutrophils are a beneficial response to an unknown stimulus (for example, an occult infection with Chlamydia or Mycoplasma pneumonia) and it is the unknown stimulus that is driving the asthmatic symptoms. What are lacking are studies which demonstrate that reducing airway neutrophil count leads to an improvement in symptoms.

Possible agents to reduce airway neutrophilia, assuming this to be desirable, are largely used on an empirical basis, in the absence of knowledge as to which neutrophil chemoattractants are important in driving airway neutrophilia. These would include reducing the synthesis of leukotriene B₄ or blocking its receptor when suitable agents become available, blocking IL-8 production with a macrolide antibiotic or accelerating neutrophil apoptosis with oral theophyllines. Anecdotally, we have treated patients with neutrophil-dominated asthma with a 6-month trial of azithromycin, using the same protocol as for our cystic fibrosis work; some have shown apparently dramatic responses, although it is not clear whether this was a placebo effect. This is an under-researched phenotype and more data are needed before firm recommendations can be made.

**Non-inflammatory, persistent BHR**

Children with this phenotype have no evidence of residual airway inflammation on bronchoscopy, BAL and biopsy at the second visit. However, they remain symptomatic and have marked bronchodilator reversibility. The molecular basis of this phenotype is unclear. It would seem illogical to treat such children with ever more potent anti-inflammatory therapies. This group have usually already tried high-dose inhaled and often oral long-acting β₂ agonists without success. We have used a continuous subcutaneous infusion of terbutaline with some success in this group. This is a demanding therapy but deemed worthwhile by the children who respond. The child carries a syringe pump in a waist bag; the needle is placed under the skin of the abdomen and changed every 1–2 days, rotating the site of insertion. We start with a low dose (generally 2.5 mg over 24 h) and increase as high as 10 mg/24 h depending on symptoms and any side-effects. Education and support from a very experienced respiratory nurse is essential. When symptom control has been obtained, we reduce the dose of oral and then inhaled corticosteroid as tolerated, monitoring airway inflammation with non-invasive techniques. It is unlikely that this is a pure non-inflammatory phenotype and we would not anticipate being able to stop inhaled corticosteroids altogether; more plausible is that underlying airway inflammation is more easily treated than BHR.

**Persistent airflow limitation**

This can be part of many of the asthma syndromes described above. In pure form, such as an undiagnosed obliterative bronchiolitis, there is no evidence of airway inflammation or BHR at either visit and no change in lung function during the steroid trial. Treatment is reduced until evidence of BHR or inflammation appears. Therapy can usually be discontinued completely.

There are numerous causes of this syndrome of airway obstruction, characterised by PAL, absence of BHR and absence of inflammation. Typically, obliterative bronchiolitis is the result of adenovirus bronchiolitis or severe reflux and aspiration; it is also the result of lung transplant rejection, drug reactions and collagen vascular disease but these are rare in paediatric practice. The presence of PAL has often not been appreciated and treatment has been escalated. Measurements of peak flow over time, bronchodilator reversibility and an exercise challenge should guide the clinician away from this diagnostic mistake. It should also be noted that the diagnosis of PAL should be made with caution. We have studied children who have had 2 weeks of high-dose, oral prednisolone in whom adherence was assured as far as possible by measuring prednisolone and cortisol levels. We measured their spirometry after inhaled β₂ agonist and then followed them up for 1 year; Around 10% achieved better spirometry, most normalising lung function; this subgroup could not be predicted from baseline characteristics.

**Poor compliance with therapy**

The two most common causes of steroid-resistant asthma are wrong diagnosis (‘not asthma at all’) and not taking the treatment. Doctors are notoriously poor in predicting which patients are compliant. Failure to take prednisolone treatment is suggested by undetectable serum prednisolone at the third visit, with failure to suppress cortisol. If theophylline has been prescribed and is undetectable, poor adherence is a likely contributory factor. Intramuscular-
injection of 80 mg depot triamcinolone frequently leads to the disappearance of ‘steroid-resistant asthma’. This is an issue that requires very sensitive handling, trying to explore the reasons for reluctance to take treatment in a ‘no blame’ manner. The help of a psychologist is often essential.

**Poor perception of symptoms**

There is a great deal of literature on both over-reporting and underperception of symptoms in asthma; this will only be summarised here. Over-reporting may lead to overtreatment. Older children may complain that they get exercise-induced asthma, whereas in reality they are simply unfit; a formal exercise test may clarify this point. A methacholine challenge with a visual analogue score of perceived breathlessness may reveal either a perception of marked breathlessness with little change in spirometry or, more worryingly, no perception of breathlessness in the face of progressive airflow obstruction.47 There is some evidence that treatment with inhaled steroids may blunt the perception of symptoms48 and also that at least some of those prone to acute severe deteriorations have a blunted symptom perception.49 This group, in particular, may benefit from regular monitoring of peak flow at home.

**PHENOTYPIC APPROACH TO THE OLDER CHILD WITH SEVERE ASTHMA – IS IT WORTHWHILE?**

We have proposed a largely pathological classification of severe asthma in childhood as a means for rationalising treatment. There is still much work to be done to try to work out the relationship between airway pathology and some clinical phenotypes, for example Types 1 and 2 brittle asthma. We have tested the utility of this approach in over 100 patients but larger studies are needed to confirm whether the invasive and expensive tests are worthwhile. Ultimately, we need to go from an analytical approach to a synthetic one, producing an understanding of the whole of asthma. An analogy may help; perhaps we are in the position of Neanderthal man contemplating a car that sometimes does not work; a reductionist, phenotypic position of Neanderthal man contemplating a car that sometimes does not work; a reductionist, phenotypic approach may help Neanderthal man mend a puncture but at the moment there is no sign of the quantum leap.

**A PHENOTYPIC APPROACH TO ASTHMA – CONCLUSIONS**

There has been an explosion of research into the basic mechanisms of asthma and we believe that this has clearly shown that there are different phenotypes which require a different approach to treatment. However, we have been slow to apply this knowledge in the clinic. There is a real need for studies to test the validity of the approaches discussed here. It is likely that a multi-centre and probably multi-national approach is needed if this is to be done. This seems to be the only way forward if the question, ‘is a phenotypic approach to the treatment of asthma really worthwhile?’, is to be given a satisfactory answer.

**PRACTICE POINTS**

- If a child with asthma is not responding to simple treatment, it is important to ask what it is about this child and their asthma that makes it therapy resistant.
- There are several different subgroups of difficult asthma with different underlying causes.
- Consider separately the possible contributions of bronchial hyper-reactivity, airway inflammation and persistent airflow limitation to symptom persistence in severe asthma.
- Poor adherence to therapy and overperception of symptoms are important causes of apparent therapy-resistant asthma symptoms.
- Consider a fibre-optic bronchoscopy in therapy-resistant asthma to determine underlying mechanisms and hence a logical treatment plan.

**RESEARCH DIRECTIONS**

- What are the mechanisms of steroid-resistant, persistent airway inflammation in some cases of severe asthma?
- What are the mechanisms of persistent airway hyper-reactivity without residual inflammation?
- What is the relationship between airway inflammation and structural airway changes (remodelling)?
- Multi-centre studies are required to determine whether a phenotypic approach to severe asthma is worthwhile.

**REFERENCES**

PHENOTYPE-SPECIFIC TREATMENT OF DIFFICULT ASTHMA


