Problematic, severe asthma in children: a new concept and how to manage it

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Most children with asthma respond to low doses of inhaled corticosteroids, but a few remain symptomatic despite being prescribed the routine usual asthma medications. The first steps are to ensure that the diagnosis is correct and that the inhaled medications are being given regularly with an appropriately used device. If the children continue to be symptomatic, with any or all of chronic symptoms, acute exacerbations, the need for regular oral corticosteroids, or persistent airflow limitation, then they are considered to have problematic, severe asthma. The next step is to perform a detailed evaluation, including a nurse-lead home visit, to determine whether the child has difficult to treat asthma which improves if the basics are got right, or severe, therapy-resistant asthma; the latter group would be candidates for cytokine-specific therapies. If severe, therapy-resistant asthma is the likely issue, then a detailed invasive investigation is performed, including bronchoscopy, bronchoalveolar lavage and endobronchial biopsy, and trial of adherence with a single intramuscular injection of depot triamcinolone. After detailed phenotyping, an individualised treatment plan is determined. Future work will determine the roles of proximal and distal inflammation, as well as the relative importance of intramural (mucosal) and intraluminal infection. The stability of paediatric asthma phenotypes over time is more variable than those of adults, and the implications of a change of phenotype are yet to be determined.

Key words: steroid resistance, allergen exposure, passive smoking, omalizumab, prednisolone, steroid-sparing agent, phenotype, nitric oxide, induced sputum, endobronchial biopsy

INTRODUCTION

As is well known, most children with asthma respond very well to low doses of inhaled corticosteroids (ICS); they do not require high-dose therapy, and indeed high dose ICS are actively harmful (1, 2). So, contemplating a child with treatment non-responsive to therapy, the key question is: what is it about this child and his/her asthma which makes it difficult to treat?

The first important point is that these children are rare; failure to respond to simple treatment is usually either due to wrong diagnosis or failure to get the basics right. Three recent studies illustrate this well. The first was an attempt to discover whether azithromycin or montelukast were a better add-on therapy in children who had persistent asthma despite moderately high-dose ICS and long-acting β-2 agonists (3). 292 children were assessed for entry, but only 55 were randomised, and the study, which was negative, was futile for want of power. The key reasons for exclusion were mainly non-adherence to treatment or that the child could not be shown to have asthma. The other two studies were related to the use of exhaled nitric oxide (FeNO) to improve asthma control (4, 5). In a study of inner city asthma, by the time the basics had been got right (proper, guideline-based therapy, with every effort being made to get the children to take it), asthma control was so much better that there was really little scope for further improvements by measuring FeNO (4). In the third paper, FeNO telemonitoring to guide asthma therapy was compared to a standard regime (5). There was intensive input and monitoring in both limbs of the study, and both groups improved equally. So the lessons of these three studies are: (1) severe asthma may not be severe, or asthma; (2) if you do the simple things well (6), then much of the problem will disappear. ‘KISS’ – Keep It Simple, Stupid – is not a bad rule in paediatrics!
Is it asthma at all? The differential diagnosis encompasses virtually the whole of paediatric respirology. Again, the KISS approach is recommended; a detailed history and physical examination comes first, rather than a multiplicity of tests. Points in the history and physical signs to be sought are summarised in Tables 1 and 2, respectively, and the differential diagnosis and possible investigations in Tables 3 and 4. None of these is exhaustive, and the key is to use clinical skills and experience.

Is the drug delivery device correct? This is often an issue that needs tackling (7, 8). A review of medication delivery devices should be part of every asthma consultation;

Table 1. Points to seek in the history suggesting an underlying serious diagnosis. A detailed history, targeted towards other respiratory conditions, is an essential first step in evaluating the child with problematic, severe asthma

- Are the child / family really describing wheeze or some other noise?
- Upper airway symptoms – snoring, rhinitis, sinusitis
- Symptoms from the first day of life
- Very sudden onset of symptoms
- Chronic moist cough / sputum production
- Worse wheeze or irritable after feed, worse lying down, vomiting
- Choking on feeds
- Any feature of a systemic immunodeficiency
- Continuous, unremitting or worsening symptoms

Table 2. Points to seek on examination suggesting an underlying serious diagnosis in a child with problematic asthma. Most children will have no physical signs; however, none will be found unless they are actively sought

- Digital clubbing, signs of weight loss, failure to thrive
- Nasal polyps
- Really severe chronic secretory otitis media, otorrhea
- Moist sounding cough
- Enlarged tonsils and adenoids, prominent rhinitis
- Unusually severe chest deformity (Harrison's sulcus, barrel chest)
- Fixed monophasic wheeze
- Stridor (monophasic or biphasic)
- Asymmetric wheeze or other auscultatory signs
- Crackles, particularly if coarse and present when the child is clinically well
- Palpable rales
- Signs of cardiac or systemic disease

Table 3. Differential diagnosis of problematic asthma, diseases which present as recurrent cough and wheeze

These conditions need to be considered and excluded prior to escalating therapy

- Upper airway disease – adenotonsillar hypertrophy, rhinosinusitis, postnasal drip
- Congenital structural bronchial disease – complete cartilage rings, cysts, webs
- Bronchial / tracheal compression – vascular rings, pulmonary and sling, enlarged cardiac chamber or great vessel, lymph nodes enlarged by tuberculosis or lymphoma
- Endobronchial disease – foreign body, tumour
- Oesophageal / swallowing problems – reflux, incoordinate swallow, laryngeal cleft or tracheo-oesophageal fistula
- Causes of pulmonary suppuration – cystic fibrosis, primary ciliary dyskinesia, persistent bacterial bronchitis, any systemic immunodeficiency including agammaglobulinaemia, severe combined immunodeficiency

Misc. – bronchopulmonary dysplasia, congenital or acquired tracheomalacia, pulmonary oedema secondary to left-to-right shunting or cardiomyopathy

Table 4. Investigations to be considered in the child with problematic asthma, if an alternative diagnosis is suspected

A selective approach is necessary, depending on what clues have been elicited from history, examination and simple investigations

- Suspected upper airway disease – polysomnography, RAST or skin prick tests (radiograph of postnasal space is rarely useful), MRI or CT of sinuses
- Known or suspected neuromuscular disease with dysfunctional swallow – speech and language therapy assessment, which may be combined with videofluoroscopy
- Suspected aspiration with normal neurology and no reflux – rigid bronchoscopy to exclude laryngeal cleft and H-type fistula
- Suspected oesophageal disease – pH probe, barium swallow, tube oesophagram, oesophagoscopy
- Suspected cystic fibrosis – sweat test, nasal potentials, genotype, stool elastase, three day faecal fat collection
- Suspected primary ciliary dyskinesia – saccharine test, nasal ciliary motility, electron microscopy including orientation studies, nasal and exhaled nitric oxide, culture of ciliary brush biopsy, genetic studies becoming available
- Suspected systemic immunodeficiency – immunoglobulins and subclasses; vaccine antibodies; lymphocyte subsets; lymphocyte and neutrophil function tests; HIV test; referral to paediatric immunologist
- Suspected structural airway disease – fibreoptic bronchoscopy
- Suspected tuberculosis – Heaf test, fibreoptic bronchoscopy and / or gastric lavage, combined with culture and PCR; ELISPOT, QUANTIFERON
- Suspected cardiovascular disease – echocardiogram, barium swallow to exclude a vascular ring or pulmonary artery sling, angiography (usually CT or MRI)
- Suspected bronchiectasis – high-resolution CT scan, investigations for local or systemic immunodeficiency
PROBLEMATIC, SEVERE ASTHMA

This has been proposed as an umbrella term to describe the children referred with suspected asthma not responding to treatment (9). Entry criteria are defined as one or more of (10, 11):

1. Persistent (most days, for at least 3 months) chronic symptoms (the necessity because of symptoms for short-acting β-2 agonists at least three times / week) of airways obstruction despite high dose medication (800 mcg/day budesonide equivalent, plus administration or failed trials of long-acting β-2 agonist, leukotriene receptor antagonist, and low-dose theophylline). This group would include Type 1 brittle asthma (12), although this patient group would need to be clearly and separately defined in any data analysis.

2. Recurrent severe asthma exacerbations despite any appropriate allergen avoidance, and attempts with medication (which, depending on the clinical context, would include trials of low-dose daily inhaled corticosteroids (13, 14), intermittent leukotriene receptor antagonists (15, 16) or intermittent high-dose inhaled corticosteroids (16, 17)) to abort exacerbations, that have required:

   either at least one admission to an intensive care unit, or at least two hospital admissions requiring intravenous medication/s, or ≥2 courses of oral steroids during the last year, despite the above therapy.

   This group would include Type 2 brittle asthma (12), although this patient group would need to be clearly and separately defined in any data analysis.

3. Persistent airflow obstruction: post-oral steroid, post-bronchodilator Z score < −1.96 with normative data from appropriate reference populations (18) despite the above therapy.

4. The necessity of prescription of alternate day or daily oral steroids to achieve control of asthma.

Another important concept is that of risk. Risk factors include: risk of failure of normal lung growth (children) or accelerated decline in lung function (adults); risk of future loss of asthma control; risk of future exacerbations; risk of phenotype change from episodic, viral to multi-trigger (mainly pre-school children) (19); risk of harm from medications. This category, although important, is one that is likely more important to professionals than it is to patients.

Inherent also is that the concepts of acute exacerbations and baseline control, although overlapping, are not the same thing (20). Loss of baseline control is, for example, characterized by a wide diurnal peak expiratory flow variation, while acute exacerbation is shown by a steep decline in peak flow, with no increased variability (20). Acute exacerbations are almost invariably virally mediated (13), although, at least in older children, the likelihood of admission to hospital with an exacerbation is greatest if there is also allergen sensitization combined with high levels of exposure to that allergen (13).

Children meeting these criteria are referred to as problematic, severe asthma. This is an umbrella term, comprising children with difficult to treat asthma, and severe, therapy-resistant asthma. In order to be in this category, all reasonable efforts to eliminate other, non-asthma, diagnoses must have been made. Appropriate tests will vary with the age of the child and the clinical context.

Difficult to treat asthma is the category in which poor response is due to issues such as poor adherence to medication; adverse environmental circumstances such as passive smoke or allergen exposure; psychosocial issues, including dysfunctional breathing; and co-morbidities such as rhinosinusitis and gastro-oesophageal reflux. Although the identification of these issues may not make the asthma easy to treat, these children would not be candidates for expensive, inconvenient and potentially toxic cytokine-specific therapies.

Severe, therapy-resistant asthma comprises those children who still remain in one of the above four categories, despite attention to co-morbidities and the other factors described above. This is not a homogeneous group, and it should be sub-phenotyped. The best way to do this is unclear, but the selection of a high sputum eosinophil group of asthmatics for recent trials of anti-IL5 (21, 22) underscores the need to split rather than lump together these children.

In our practice, children with problematic, severe asthma are severely disabled. We studied 71 children (35 male), 21 of whom were using regular oral steroids (23). The mean dose of fluticasone equivalent was 1 mg/day, range 0.5 to 3 mg/day. They had a median of 2 admissions to hospital, range 0–21, and 12 were ventilated on at least one occasion. Mean first second forced expired volume in one second (FEV1) was 76% (range 33–125), and, despite prescribed medication, median bronchodilator reversibility was 14% (range 12–106); 34% had persistent airflow limitation, defined here as FEV1 <75%, predicted despite prednisolone and high-dose β-2 agonists; 97% had current symptoms with an asthma control test (15) less than 20. Median FeNO was 52 ppb (range 5–171, normal <25). Atopy was common, with more than 50% being skin prick test (SPT) positive to house dust mite (HDM), grasses, cat and dog. Food sensitivity, at least as judged by SPT, was common (peanut 25%, egg and milk 5–10%); this has been reported before as an association of severe asthma (24, 25). These children are now investigated using a staged protocol.

Problematic, severe asthma: the first stage of the protocol. The first step is always a review of diagnoses and medication delivery devices (above). Thereafter, if it is clear that the problem continues, a detailed nurse-lead review is undertaken, including visits to the home and school. The home visit has proven particularly valuable. An overall assessment is performed, and four issues are re-addressed in detail: psychosocial, adherence, allergens, and smoking (active and passive).

Psychosocial morbidity. This is common in our series; nearly 50% have a formal psychological assessment. It is not useful to try to determine whether the psychosocial issues caused the asthma, or the asthma, by interfering with lifestyle, for example, caused the psychosocial issues. If both are present, then both should be addressed on their merits.
Parental or child, or both, may have anxiety or depression, and dysfunctional breathing is not uncommon. These issues have of course been discussed previously, but parents seem more ready to discuss these sensitive issues at home, and 75% of the referrals come only after the home visit (26, 27).

Adherence to medication. This is, of course, one of the hardest issues to determine. One method is to access the prescriptions collected from the general practice (28). Mere collection of a prescription does not equate to the medication being taken, but no prescription collected certainly means that none has been inhaled. In our series, less than 50% had collected enough prescriptions for them to have taken more than 80% of their medications, 30% of patients had collected less than 50% of their prescriptions, and nearly 25% could not readily produce a complete set of in-date medications at the home visits. Despite repeated tuition, nearly 40% did not have a good technique with their inhaled medications. Finally, the issue of parental supervision of medication was addressed.

In an American study, 25% of 7 year olds and 50% of 11 year olds are expected to assume responsibility for their medications (29); I doubt that this is appropriate. In our group, it emerged often that although mothers reminded children, frequently, in the business of family life, they did not actually stand over them to witness the inhalers being used.

Allergen exposure. The allergens which we focus on in particular are house dust mite and pets. HDM avoidance precautions were only rigorous in 16% of households. In terms of pets, 30 households had pets, 17 children were sensitized to the pet, but in only two there was any attempt at allergen avoidance being made.

Allergen avoidance is controversial. A Cochrane review concluded that there was no value in HDM avoidance (30). However, the review was flawed in many ways; studies in which HDM allergen levels were not reduced were included, and very short-term which HDM allergen levels were not reduced were included, further studies were all uncritically lumped together; in my view, it is possible to draw conclusions from this review. Furthermore, HDM avoidance, if done properly, is expensive and inconvenient, and is unlikely to be done efficiently unless the family perceives there is a major problem making the disruption of home life, and the expense of the intervention, likely to be worthwhile. The evidence in favour of allergen exposure is discussed below.

Tobacco smoke exposure. Salivary cotinine levels were high in around a third of children whose parents said they did not smoke, and in virtually all the children of smokers, irrespective of whether the parents claimed to smoke outside. At least two children acknowledged they were active smokers. Active smoking, and presumably also passive smoke exposure, is known to be a cause of steroid resistance (31–34).

School visit. The attendance record is checked. We also find out the school’s perception of the level of symptoms, which may sometimes differ significantly from what is reported in clinic. The school asthma policy may need to be discussed, and issues about ensuring that asthma does not prevent access to education are highlighted.

Does it work? As a result of this process, around half the children referred are placed in the ‘difficult’ rather than the ‘severe, therapy-resistant’ category and do not proceed to more detailed interventions. The changes made as a result of the visit include psychosocial referrals, environmental change, attention to adherence, and smoking cessation. These children are followed up regularly and may still subsequently progress to further testing depending on how the asthma progresses. Supportive of this approach was a large, multifaceted randomized control intervention trial to address many of these points in inner-city children with asthma (35). The intervention lasted a year, and the effect was still detectable at the end of a further year of follow-up.

Stages two and three: invasive investigations. If the child’s problems persist, then a detailed program of tests is put in place (Table 5) (36). In summary, the child has a detailed assessment of lung function, and airway inflammation non-invasively, as well as a fibreoptic bronchoscopy, bron-

### Table 5. The difficult asthma protocol

<table>
<thead>
<tr>
<th>1. Clinical assessments</th>
<th>Visit 1</th>
<th>Visit 2 (if no improvement)</th>
<th>Visit 3 (4 weeks later)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Asthma control test</td>
<td></td>
<td>• Asthma control test</td>
<td>• Asthma control test</td>
</tr>
<tr>
<td>• Nurse lead home visit</td>
<td></td>
<td>• Assess symptoms, new peak flow diary</td>
<td>• Assess symptoms, new peak flow diary</td>
</tr>
<tr>
<td>• School visit</td>
<td></td>
<td></td>
<td>• Allocate as steroid responder, non-responder</td>
</tr>
<tr>
<td>• Access GP records</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Psychological assessment as appropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Physiological measurements</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Spirometry including response to β-2 agonist</td>
<td>Visit 2 (if no improvement)</td>
<td>Visit 3 (4 weeks later)</td>
</tr>
<tr>
<td>Spirometry, including response to β-2 agonist</td>
<td>Spirometry, including response to β-2 agonist</td>
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<tr>
<th>3. Non-invasive inflammatory and other markers</th>
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<tbody>
<tr>
<td>• Induced sputum FeNO (variable flow)</td>
<td>Visit 2 (if no improvement)</td>
<td>Visit 3 (4 weeks later)</td>
</tr>
<tr>
<td>• RAST or skin prick tests as appropriate</td>
<td>• Induced sputum FeNO (variable flow)</td>
<td>• Induced sputum FeNO (variable flow)</td>
</tr>
<tr>
<td>Measure prednisolone and theophylline levels if appropriate</td>
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<tr>
<th>4. Invasive studies</th>
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<tbody>
<tr>
<td>• Bronchoscopy, bronchoalveolar lavage, and bronchial biopsy</td>
<td></td>
<td></td>
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<tr>
<td>• Intramuscular triamcinolone</td>
<td></td>
<td></td>
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<tr>
<td>• pH study</td>
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</table>
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Table 6. Components of steroid responsiveness (114–6)

<table>
<thead>
<tr>
<th>Symptom response</th>
<th>Spirometry response</th>
<th>FeNO response</th>
<th>Sputum response</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ACT rises ≥20/25</td>
<td>- FEV$_1$, normalises ≥80%</td>
<td>- Falls to normal (≤25 ppb)</td>
<td>- Eosinophil count falls to normal (&lt;2.5%)</td>
</tr>
<tr>
<td>- ACT rises by 50% or 5 points, whichever is greater</td>
<td>- FEV$_1$, rises by ≥15%</td>
<td></td>
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</table>

chaoalveolar lavage and endobronchial biopsy. A pH study is performed, and, during the anaesthetic, a single injection of depot triamcinolone 40–80 mg depending on the size of the child is administered. This ensures that the child has a real trial of steroids, and I will not diagnose steroid-resistant asthma unless such a trial has been performed. The symp-
toms, spirometry and non-invasive assessments of airway inflammation are repeated 3–4 weeks later, and the child is assigned to a particular phenotype, and treatments proposed accordingly (discussed in more detail below and summarized in Table 6). This work has taught us very clearly that severe, therapy-resistant asthma is not one disease but many, and a single approach is not sufficient.

Our previous manuscript (23) described the characteristics of problematic, severe asthma; they did not go through the nurse-led assessment prior to bronchoscopy. We have recently described the characteristics of children who had severe, therapy-resistant asthma (37). Those with difficult asthma had been identified at the first step of the protocol; these children went on to Steps 2 and 3, aiming to define their level of steroid responsiveness. One problem is that, unlike in adults, there is no generally accepted definition of steroid responsiveness in children. We have therefore broken this down into four compo-
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Severe, therapy-resistant asthma phenotypes

The process described above is based on the supposition that airway inflammation of various types, bronchial responsive-

Table 7. Responses to the triamcinolone trial (37)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Post-triamcinolone</th>
<th>P value</th>
<th>Number (% of individual responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (ACT score/25, median, range)</td>
<td>12 (6–24)</td>
<td>18 (5–25)</td>
<td>&lt;0.0001</td>
<td>23/47 (49%)</td>
</tr>
<tr>
<td>Spirometry (FEV$_1$%, mean, SD)</td>
<td>71 (21)</td>
<td>77 (18)</td>
<td>0.006</td>
<td>29/52 (56%)</td>
</tr>
<tr>
<td>Bronchodilator responsiveness (%)</td>
<td>16 (0–135)</td>
<td>11 (0–93)</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td>FeNO$_{50}$ (ppb, median, range)</td>
<td>48 (4–169)</td>
<td>28 (3–150)</td>
<td>0.0002</td>
<td>22/52 (42%)</td>
</tr>
<tr>
<td>Sputum eosinophils (median, range)</td>
<td>7.5 (0–92)</td>
<td>2 (0–43)</td>
<td>0.017</td>
<td>22/42 (52%)</td>
</tr>
</tbody>
</table>
The phenotypes we have described, and the approach we take to them, are summarised in Table 8. These are clearly still very broad categories, which require further detailed mechanistic exploration. Some of the limitations of the current approach (lack of measurement of distal inflammation, single time point, use of single phenotyping of luminal and mucosal inflammation) are discussed below.

A few explanatory comments are needed before treatment is considered. Some phenotypes are self-explanatory. We see some children who have apparently no airway inflammation, but whose peak flows continue to fluctuate wildly. It seems entirely illogical to treat such children with ever more powerful anti-inflammatory medications, if apparently there is no inflammation to treat. The use of subcutaneous terbutaline is discussed below. Another group is the child who becomes asymptomatic but who has persistent airway eosinophilia. It is worth recalling studies in adolescents and young adults who have ‘outgrown’ asthma – they were asymptomatic on no medications, but bronchial biopsy showed eosinophilic inflammation identical to that seen in age-matched patients with ongoing symptomatic asthma (43). The lesson is that the mere presence of a cell does not necessarily implicate it as the causative agent for severe symptoms.

Treatment of severe, therapy-resistant asthma in the older child

There is clearly no point in going through these detailed tests if no action results. The aim is to produce an individualised treatment plan for each child. It is important to distinguish two aspects of treatment, which are not the same (44):

- how can baseline asthma control be improved
- (much more difficult) how can acute exacerbations be prevented.

Much harm has arisen from confusing these two; it is arguable whether a child with good baseline control, judged on symptoms, lung function and non-invasive assessment of airway inflammation, but with acute, viral-induced severe exacerbations, will benefit from increases in baseline treatment.

The treatment themes that are important to consider are:

- addressing the causes of secondary steroid resistance
- the use of non-steroid based anti-inflammatory therapy
- the treatment of refractory airway hyper-reactivity
- the avoidance of over-treatment of PAL
- management of acute exacerbations.

These will be considered in turn.

Secondary steroid resistance. By definition, children with ongoing poor baseline asthma control are steroid-resistant. There is still much work to be done on the molecular mechanisms and their treatment. This section focuses on causes of secondary steroid resistance that are preventable in the context in which I work, namely passive cigarette smoke exposure and indoor allergens; in other settings there may be other important factors such as air pollution and indoor biomass fuel exposure.

Cigarette smoke exposure. The first step is to document that this is happening, with measurements of urine or sali-
vary cotinine. There is no doubt that active smoking causes a state of steroid resistance. A series of careful papers in adults has shown inferior treatment benefits for inhaled and oral corticosteroids in adults who smoke and are carefully phenotyped to ensure they truly have asthma, not COPD (31–34). The mechanism may be by the induction of proinflammatory cytokine release by activation of NF-kappaB and posttranslational modifications of histone deacetylase in macrophages (this was a cell line study) (45). Data in children are much sparser, but it seems likely that the effects of passive smoke exposure will be to induce steroid resistance. It is, of course, one thing to determine the cause, but another to persuade parents and older siblings to give up smoking.

Indoor allergen exposure. This is a highly controversial area. House dust mite is one of the commonest allergens, and a recent Cochrane review (30) and a Lancet editorial (46) concluded that house dust mite avoidance was of no value whatever. The role of pet allergen avoidance was not discussed, but I believe that, contrary to these learned views, the case that allergens are a potential cause of steroid resistance and that allergen avoidance should be strenuously pursued in children with severe, therapy-resistant asthma, is overwhelming. The evidence on which allergen avoidance is denigrated is flawed, and the interpretation of it is a classic example of the abuse of evidence-based medicine – evidence is the servant to be interpreted by the experienced clinician in the light of the clinical situation, not the master which dictates every possible action. The flaws include the following: inclusion of very short-term studies; inclusion of studies in which allergen avoidance was actually not achieved; including children and adults; and most critically, no adequately powered studies in children with severe, therapy-resistant asthma. This is critical, because to do allergen avoidance properly is expensive and time-consuming, and most unlikely to be achieved if the problems of the child are fairly trivial. Several strands of evidence argue in favor of allergen avoidance:

- Biological plausibility: resistance to the actions of steroids on proliferating mononuclear cells can be achieved by co-incubation with an allergen to which they are sensitized, via an interleukin (IL)-2 and -4 dependent mechanism (47, 48). The detailed mechanisms are unclear, a change in isoforms of the glucocorticoid receptor has been implicated by some (49) but by no means all (50) workers.

- Experimental studies: repeated low-dose inhalant allergen challenge, in a dose too low to lead to a change in FEV₁, leads to worsening of bronchial responsiveness and airway inflammation (as judged by induced sputum) (51).

- Observational studies: children who are cat-sensitive and are in a school class in which more than 18% of their classmates are cat owners develop a pattern akin to occupational asthma, progressively worsening during the week, improving at the weekend and in school holidays (52).

- Interactions with viral infections: in a study of children hospitalized for an acute attack of asthma, much the most significant odds ratios for admission were for the combination of sensitization to an aeroallergen and high levels of exposure in the home to that allergen. Of these, reduction in allergen exposure is the only thing amenable to intervention (13).

Non-IgE-mediated effects of allergens also need to be considered. Many allergens are also proteases (53) and so could cause airway damage independent of any IgE effects. In a study of adult asthmatics, non-sensitized patients who were exposed to high levels of either HDM or dog allergen had worse airway inflammation, as judged by FeNO, and worse bronchial responsiveness (54). An epidemiological study in Europe showed a dose effect for cat allergen exposure, leading to worse bronchial responsiveness in atopic, non-cat-sensitized people (55). Very recent evidence has cast some light on the mechanisms of non-IgE-mediated house dust mite actions, interacting with the innate immune system via TLR-4 (56, 57). This is particularly interesting given the discovery of the importance of the epithelial expressed gene Filaggrin in the pathophysiology of atopic disease, further implicating the importance of epithelial permeability (58, 59).

Thus, pending further intervention studies in severe, therapy-resistant asthma, it is and remains to advise stringent avoidance measures for all allergens to which the child is sensitised. Thus, any furry pets must be removed, and conventional house dust mite measures, such as the use of mite-impermeable bedding covers, hot-washing the sheets, removal of bedroom carpets, and the avoidance of synthetic conventional house dust mite avoidance measures, and the obese child may complain of non-asthma breathlessness. However, obesity is a systemic pro-inflammatory state, but paradoxically, obese asthmatics may have asthma with disproportionately low airway inflammation (60). Obesity is certainly a cause of steroid resistance (61). Whether obesity or asthma came first, in the individual child, it is important to tackle body weight issues in the obese. This is, of course, easy to say and harder to do.

Non-steroid-based anti-inflammatory therapy. This would be indicated for ongoing inflammation despite triamcinolone, or steroid-sensitive asthma which is requiring unacceptably high levels of steroids for adequate control. However, my experience is that a steroid-sparing strategy works much less well than steroids in those with steroid-sensitive asthma. The best non-steroid-based anti-inflammatory documented therapy is the anti-IgE monoclonal antibody omalizumab (Xolair\textsuperscript{\textregistered}). This expensive and inconvenient monoclonal antibody has been advocated as treatment for severe atopic asthma. In the UK, it is licensed for use in children over age 12 years (62) who have a total IgE of less than 700 IU/ml, but there is substantial clinical experience in the 6–12 age groups (63), so this is not an absolute contra-indication. If the child
has a very high IgE, above present recommendations, which is not uncommon in severe, therapy-resistant asthma, then he / she may still benefit from the top recommended dose (64). To qualify for this expensive and inconvenient treatment, the child must have been admitted to hospital twice in a year, or have three exacerbations, one requiring admission, over the same time period, together with the need for high-dose medication chronically. This definition is open to criticism, because it would exclude a child on high-dose oral steroids, whose disease is controlled, but at the cost of potentially horrible side-effects. It would not seem reasonable to reduce treatment so that the child becomes ill in order to qualify for a trial of this medication. Our own criteria include having gone through the above detailed work-up, and have taken every reasonable precaution to exclude allergens from the environment. As yet, we do not have enough data to assess the likelihood of response, but we have seen so far more responders than non-responders.

Other agents are much less evidence-based. Macrolide antibiotics such as azithromycin have numerous anti-inflammatory and anti-remodelling effects (65–67) and have been shown to be of proven benefit in cystic fibrosis (68–71). Hypothetically, they may be useful in neutrophilic asthma (72), but convincing evidence of long-term benefit is lacking. They also have activity in suppressing eosinophilic chemokine attractants and thus might have a wider application (73). Long-term, randomised controlled trials in both eosinophilic and neutrophilic asthma are awaited.

The evidence base for the treatment of neutrophilic asthma is minimal. My practice is first to eliminate possible non-asthmatic causes of neutrophilic airway inflammation, such as GER and aspiration, passive tobacco smoke exposure, and obstructive sleep apnoea (74). If BAL culture is positive for bacteria, I would investigate for causes of chronic supplicative lung disease such as CF and PCD (above), and, if none is found, treat presumed persistent bacterial bronchitis (75, 76) with a prolonged course of antibiotics. If these approaches prove unrewarding and the child appears to have true neutrophilic asthma, then azithromycin for a 3–6 month trial is my first strategy. Others to be considered include low-dose theophylline (anti-inflammatory level), which accelerates neutrophil apoptosis (77), as well as potentially restoring steroid sensitivity by an effect on nuclear histone deacetylase activity (78). A future option might be reduction of leukotriene B4 activity with 5-lipoxygenase inhibition. Multi-centre trials for these proposed strategies are required.

The evidence for other steroid-sparing agents in paediatric severe, therapy-resistant asthma is minimal (79). Choices include monthly intravenous immunoglobulin infusions (at least a six-month trial), oral low-dose methotrexate or azathioprine, and cyclosporin (80–82) (usually a three-month trial). Each has particular disadvantages, and the last three require regular and detailed monitoring from blood work, most intensively for cyclosporin. Possibly in the future, inhaled cyclosporin (83) or oral, more specific T-cell base strategies such as tacrolimus may be beneficial. There is no paediatric experience with cytokine-specific therapies such as anti-IL5 (21, 22) or etanercept (40). The recent serious adverse events due to a cytokine storm with human monoclonals is a warning of the dangers of these approaches (84). After a detailed evaluation, and after an open discussion of the experimental nature of the above therapies, the potential for side-effects, and the lack of guarantees of success, the experienced paediatrician may embark on one or more therapeutic trials.

The treatment of refractory airway hyper-reactivity, Children who turn out to have marked peak flow lability, but no evidence of continued inflammation, may respond to a continuous infusion of subcutaneous terbutaline, given by a portable Graseby or other pump, infused via a soft needle into the anterior abdominal wall (85). It is unclear why this may work when inhaled long-acting β-2 agonists are not successful. This is a very demanding treatment, albeit occasionally dramatically successful. It is preceded by a detailed evaluation (above) and an in-patient, double blind trial (Table 9) to eliminate the large potential placebo effect of such treatment. The pharmacist prepares the syringes, and the child and family know that neither they nor the paediatricians or nurses will know which is the active treatment. The interpretation of the trial is complicated; the child may improve in hospital independent of the subcutaneous infusion because asthma therapy is directly observed! This is the likely explanation if the child improves in hospital independently of which treatment is infused. If, on the other hand, there is a consistent treatment effect with the active infusion, which is lost during the placebo infusion, then a genuine treatment effect is likely. During the trial, symptoms and bronchodilator use are scored daily, spirometry and acute bronchodilator reversibility are also performed daily, and the peak flow measured four hourly and the coefficient of variation recorded over each time period. The child, family, nurse and paediatrician all score out of ten their subjective impression of the success of each therapy. At the outpatient review, before the code is broken, the decision is taken as to whether a genuine treatment effect can be identified. In the event that subcutaneous terbutaline is thought to be beneficial, then the respiratory nurse trains the

<table>
<thead>
<tr>
<th>Day of admission</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>1–3</td>
<td>Baseline, no therapy</td>
</tr>
<tr>
<td>4–6</td>
<td>Treatment A infused</td>
</tr>
<tr>
<td>7, 8</td>
<td>Washout period</td>
</tr>
<tr>
<td>9–11</td>
<td>Treatment B infused</td>
</tr>
<tr>
<td>12, 13</td>
<td>Washout period</td>
</tr>
<tr>
<td>14–16</td>
<td>Treatment A infused</td>
</tr>
<tr>
<td>17, 18</td>
<td>Washout period</td>
</tr>
<tr>
<td>19–21</td>
<td>Treatment B infused</td>
</tr>
</tbody>
</table>

Table 9. Timetable for the double-blind, placebo-controlled trial of subcutaneous terbutaline. The two treatments are subcutaneous terbutaline and normal saline. The interpretation of the trial is complicated; the child may improve in hospital independent of the subcutaneous infusion because asthma therapy is directly observed! This is the likely explanation if the child improves in hospital independently of which treatment is infused. If, on the other hand, there is a consistent treatment effect with the active infusion, which is lost during the placebo infusion, then a genuine treatment effect is likely. During the trial, symptoms and bronchodilator use are scored daily, spirometry and acute bronchodilator reversibility are also performed daily, and the peak flow measured four hourly and the coefficient of variation recorded over each time period. The child, family, nurse and paediatrician all score out of ten their subjective impression of the success of each therapy. At the outpatient review, before the code is broken, the decision is taken as to whether a genuine treatment effect can be identified. In the event that subcutaneous terbutaline is thought to be beneficial, then the respiratory nurse trains the
child and family in how to set it up. In selected patients, this demanding therapy may be well worthwhile.

The avoidance of over-treatment of PAL. There is clearly no point in escalating therapy to try to reverse irretrievably fixed PAL. The usual cause is post-viral obliterative bronchiolitis, but GER and aspiration may also cause a similar picture. The usual picture is PAL despite triamcinolone and acute inhalation of β-2 agonists, with no elevation of FeNO or evidence of inflammation on induced sputum. Medications should be weaned down with monitoring of acute bronchodilator reversibility and airway inflammation; although asthma and obliterative bronchiolitis may co-exist, usually the element of reversibility in obliterative bronchiolitis is minimal, and therapy can largely be withdrawn.

Management of acute exacerbations. This is about the most difficult field of all. Some attempts at prevention may be possible. Reduction of allergen exposure chronically in the home should be attempted (above), and avoidance of acute high-level exposure to allergen triggers is obviously sensible. Viral infections cannot be avoided, but influenza immunisation may be helpful and is certainly recommended. Titrating the regular anti-inflammatory therapy to suppress even asymptomatic airway inflammation may reduce exacerbations. The use of a single combination inhaler (Symbicort turbohaler”, the SMART strategy (86, 87)) may also prevent exacerbations. However, many will be unpreventable. Acute deteriorations are managed according to standard guidelines (6). An anecdotal strategy that may be useful for the really acute catastrophic deteriorations is the use of injectable adrenaline (Epipen™) while inhaled or nebulised β-2 agonist therapy is being prepared. Of course, all such patients should also have a course of oral steroids ready to hand. Much research is still needed into the prevention and management of exacerbations in the context of severe, therapy-resistant asthma.

Monitoring treatment of severe, therapy-resistant asthma

There are many studies looking at the role of ‘inflammometry’ in the management of asthma, usually in the context of mild-moderate disease. ‘Inflammometry’ may be used to titrate treatment, predict exacerbations, or indicate the likely success of treatment withdrawal. The characteristics of the ideal ‘inflammometer’ are shown in Table 10; sadly, none such exists. Trials using FeNO (88–90), sputum eosinophils (91, 92) and BHR (93, 94) have all shown benefit, but it is fair to say that even in moderate asthma, the exact place of each method is unclear. A recent cluster analysis in adults (60) suggests it is those patients in which there is discordance between symptoms and inflammation (either severe but asymptomatic inflammation, or multiple symptoms without evidence of inflammation) that are most likely to benefit from ‘inflammometry’. The data on severe asthma are very sketchy. Preliminary work from our laboratory suggests that treating severe, therapy-resistant asthma by normalising sputum eosinophils, even if the child is asymptomatic, may reduce exacerbations (95). This is another area for future research.

Table 10. Characteristics of the perfect ‘inflammometer’

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<thead>
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<th>Feature</th>
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<tbody>
<tr>
<td>Cheap</td>
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<tr>
<td>Easy to maintain and calibrate</td>
</tr>
<tr>
<td>Completely non-invasive</td>
</tr>
<tr>
<td>Easy to use, no co-operation needed</td>
</tr>
<tr>
<td>Direct measurement of all relevant aspects of inflammation</td>
</tr>
<tr>
<td>Rapid availability of answers</td>
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<tr>
<td>Evidence of beneficial clinical outcomes</td>
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However, it is also very complex; in this severity-group, in our hands phenotypes may be inconstant (96) (below), and the relationship between FeNO and sputum eosinophil counts may vary between individuals, and within the same individual over time, illustrating the complexity of the problem (97).

Phenotyping asthma in the older child: what is the future?

The phenotyping process described above depends on a single time point, with measurements of proximal events. Furthermore, the differences between mucosal and luminal phenotypes have not been addressed.

Is mucosal or luminal inflammation important? We have shown that there is only the poorest correlation between bronchial mucosal eosinophilia and eosinophil counts in either sputum or BAL. It is unclear which determines clinical phenotype. The literature is conflicting on the importance of mucosal eosinophilia. In one study (43), endobronchial biopsy was compared in three groups of young adults – active asthmatics, asthma in remission, and normals. The asthmatics in remission had no symptoms and were taking no treatment, but they had the same extent of airway wall eosinophilia as the active asthmatics. Clearly, mucosal eosinophilia on its own is insufficient to cause asthma. The distribution of inflammatory cells, rather than actual numbers, may be important; the clinical phenotypes of asthmatics and adult patients with eosinophilic bronchitis are determined by the distribution of mast cells, with smooth muscle mast cells being the determinant of classical asthma (98, 99).

By contrast, data from anti-IL5 studies suggest that mucosal eosinophilia may be important. Intravenous infusions of anti-IL5 lead to complete abrogation of sputum and blood eosinophilia, but had no effect on bronchial responsiveness in a group of mild adult asthmatics (100). However, when in another study endobronchial biopsies were examined, it was found that anti-IL5 had only halved the mucosal eosinophil count and had had no effect on major basic protein staining. It was suggested that the poor response was due to the failure to improve the mucosal pathology (101).

In summary, it is as yet unknown whether mucosal or luminal eosinophils are most important in driving the clinical asthma phenotype, and how to manage any discordance between the two. A real handicap is the lack of biomarkers relating to airway wall disease, comparable to the use of sputum for luminal changes.

The time domain: are phenotypes stable? Underpinning the strategy of normalising sputum eosinophil counts and
Proximal versus distal inflammation: what matters?

Adult studies have utilised transbronchial biopsy (TBB) to determine alveolar inflammation in asthmatics (102–104). Distal inflammation with CD4-positive lymphocytes correlated with nocturnal asthma. TBB has a significant risk of bleeding and pneumothorax in children (105), and it is difficult to see how it could be used as a research technique. It would need to be shown that diagnosing distal inflammation gives extra benefit to the individual child in planning treatment, which has yet to be done.

If TBB cannot be used, what other techniques might help?

In the context of CF, fractionating BAL showed that the first aliquot had different cellularity from pooled subsequent aliquots, and it was suggested that the latter represented an alveolar sample as against the first aliquot which represented the larger bronchi (106). This approach could be followed in asthma, but as yet it has not been studied. An approach used in adults has been the use of fine sampling probes which can be advanced into the very distal airways.

Another alternative is to partition NO production into airway (JNO) and alveolar (CALV), by measuring NO production at different expiratory flow rates (107). We have shown that in children JNO and FeNO50 correlate closely. As has been described before, both JNO and FeNO50 are elevated in atopic asthmatics but also in atopic non-asthmatics. However, CALV was only elevated in atopic asthmatics. Both JNO and CALV were elevated in poorly controlled asthmatics. In one adult study, CALV was used to monitor the response to treatment with ciclesonide, on the assumption that it would be more effective in treating inflammation distally (108). The group did show a fall in CALV with ciclesonide treatment, but the overlap between groups was so great that CALV did not seem likely to be useful in monitoring individuals.

Another approach might be to study distal airway function, albeit acknowledging that the function, at least in the proximal airways, does not necessarily correlate well with inflammation. The distal-most airways have historically been a ‘silent area’, because more than 90% can be obstructed before a signal shows up with spirometry. Recent developments include the analysis of lung wash-in and wash-out inert gas curves, calculating lung clearance index, and sophisticated partitioning of abnormalities to the conducting airways (SCond) and the acini (SACIN) (109–111). More data are needed before we can determine whether these measurements will enable us to detect peripheral inflammation.

CT indices of air trapping might be another approach, but the problems would include standardising the scans, in particular the lung volumes at which they are taken; the structural changes may represent remodelling, not inflammation; and the radiation dose.

Distal airways disease may be dissociated from proximal airway changes by the effects of treatment. Medication deposition in the most distal airways is problematic, but with the advent of fine-particle aerosols, such as HFA-beclomethasone (112) and ciclesonide (11), this problem may be addressed. An alternative might be low-dose oral steroids (say, 0.05 mg/kg) to ensure distal steroid delivery. What is now needed is to know whether (a) distal inflammation is truly significant in severe, therapy-resistant asthma, and (b) how we can monitor the effects of treatment.

Mathematical analysis. Conventionally, phenotypes are described by data inspection, but increasingly mathematical techniques such as principal component analysis are used to tease out objective phenotypes. These analyses require a large data set and preferably need to be validated on another cohort. A word of caution is necessary; although more objective than data inspection, these techniques are also vulnerable. Critical is the nature and quality of the information inputted, which in turn relies on the presuppositions and assumptions of the investigator. If crucial data are omitted, the analyses will fail to reveal important associations.

SUMMARY

We have a long way to go before we understand the phenotyping of severe asthma. At this stage, we do not even know whether true non-eosinophilic asthma exists; it may be that we are not looking for eosinophils in the right compartment. Indeed, a very small sputum study, which showed that the response to steroids was independent of sputum cellularity, might suggest this was the case. There is a real need for non-invasive biomarkers of distal airway and also mucosal disease.

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