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Severe Therapy Resistant Asthma in Children

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Abstract 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 the diagnosis is correct, and that the inhaled medications are being given with an appropriate device. If the child continues 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 if the child has *difficult to treat asthma*, which improves if the basics are got right, or *severe, therapy resistant asthma*, which latter group would be candidates for cytokine specific therapies. If *severe, therapy resistant asthma* is the likely issue, then detailed invasive investigation is performed, including a 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 Allergen exposure; Endobronchial biopsy; Induced sputum; Nitric oxide; Omalizumab; Steroid resistance

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 asthma non-responsive to therapy, the key question is, what is it about this child and his/her asthma which makes it difficult to treat. This paper, delivered in honour of the memory of a great paediatrician, summarises my thinking on this subject.

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The first important point is that these children are a lot rarer than we think. Three recent studies illustrate this well. The first was an attempt to discover whether azithromycin or montelukast was better add-on therapy in children who had persistent asthma despite moderately high dose ICS and long acting β-2 agonists.[3] Two hundred and ninety-two 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 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 second trial, 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 (2) if you do the simple things well,[6] then much of the problem will disappear. '**KISS**' – **K**eep **I**t **S**imple, **S**tupid – 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, a truth equally applicable today as in Dr Field's time.

Is the Drug Delivery Device Correct?

This is still an issue that needs tackling.[7,8] A review of medication delivery devices should be part of every asthma consultation. One problem is children being given spacers with a mask long after the mask can be dispensed with (usually at age 3 years). Another issue is the adolescent who discard the inhaler altogether, and use the metered dose inhaler directly into the mouth with predictably poor drug delivery, supposing that spacers are babyish.

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]

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 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 monophonic wheeze
• Stridor (monophasic or biphasic)
• Asymmetric wheeze or other auscultatory signs
• Crackles, particularly if coarse
• Palpable rattles
• 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 (CF), primary ciliary dyskinesia (PCD), persistent bacterial bronchitis, any systemic immunodeficiency including agammaglobulinaemia, severe combined immunodeficiency
- Misc. – bronchopulmonary dysplasia, congenital or acquired tracheomalacia, pulmonary oedema 2ry 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
- Suspected cardiovascular disease – echocardiogram, barium swallow to exclude a vascular ring or pulmonary artery sling, angiography
- Suspected bronchiectasis – high resolution CT scan, investigations for local or systemic immunodeficiency

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.

Inherent in this view is that the concepts of acute exacerbations and baseline control, although overlapping, are not the same thing.[19] Loss of baseline control is, for example, characterised by wide diurnal peak expiratory flow variation, while acute exacerbation is shown by a steep decline in peak flow, with no increased variability.[19] 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 sensitisation 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 geographical location.

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 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[20,21] 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.[22] 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 (FEV_1) was 76% (range 33-125), and despite prescribed medication, median bronchodilator reversibility was 14% (range 12-106). Thirty-four percent had persistent airflow limitation, defined here as FEV_1 <75% predicted despite prednisolone and high dose β-2 agonists. Ninety-seven percent 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.[23,24] 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. I doubt that it is useful 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.[25,26]

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.[27] 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;[28] 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 sensitised to the pet, but in only two was any attempt at allergen avoidance being made.

Allergen avoidance is controversial. A Cochrane review concluded that there was no value in HDM avoidance.[29] However, the review was flawed in many ways; studies in which HDM allergen levels were not reduced were included, children and adults were lumped as one, and very short term studies all contributed. 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. 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.[30-33]

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 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 then 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.

Stage Two and Three: Invasive Investigations

If the child's problems persist, then a detailed program of tests is put in place (Table 5).[34] In summary, the child has a detailed assessment of lung function, and airway inflammation non-invasively, as well as a fibreoptic bronchoscopy, bronchoalveolar 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 symptoms, 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 summarised 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.

Severe, Therapy Resistant Asthma Phenotypes

The process described above is based on the supposition that airway inflammation of various types, bronchial responsiveness and fixed airflow obstruction may contribute independently to the clinical picture of severe, therapy resistant asthma. I have no hesitation in rejecting the model that inflammation causes bronchial responsiveness, which subsequently leads to PAL due to airway remodelling. Firstly, there is only the very poorest relationship between inflammation and bronchial responsiveness;[35] secondly, inflammation may be reduced by treatment (monoclonal anti-IgE omalizumab, Xolair™) with no change in bronchial responsiveness,[36] and bronchial responsiveness may be reduced by treatment (the anti-TNFα strategy etanercept) with no change in inflammatory parameters;[37] and finally, structural airway wall changes may be independent of either, for example as a result of intra-uterine or early life influences, including viral obliterative bronchiolitis.[38] Hence, we empirically phenotype the children on the basis of inflammation, baseline airway calibre, and reactivity.

'Phenotyping' has become a trendy concept throughout medicine. A phenotype may be considered as a cluster of either clinical or pathological features which tend to be associated, and which are useful in some way, such as in managing the child or understanding the mechanisms of disease.[39] Thus, the concept of a phenotype is without value

Table 5 The difficult asthma protocol

	Visit 1	Visit 2 (if no improvement)	Visit 3 (4 weeks later)
1. Clinical assessments	• Asthma control test • Nurse lead home visit • School visit • Access GP records • Psychological assessment as appropriate	• Asthma control test • Assess symptoms, new peak flow diary	• Asthma control test • Assess symptoms, new peak flow diary • Allocate as steroid responder, partial responder, or non-responder
2. Physiological measurements	• Spirometry including response to β-2 agonist	• Spirometry, including response to β-2 agonist	• Spirometry, including response to β-2 agonist
3. Non-invasive inflammatory and other markers	• Induced sputum • FeNO (variable flow) • RAST or skin prick tests as appropriate • Measure prednisolone and theophylline levels if appropriate	• Induced sputum • FeNO (variable flow)	• Induced sputum • FeNO (variable flow)
4. Invasive studies		• Bronchoscopy, bronchoalveolar lavage, and bronchial biopsy • Intramuscular triamcinolone • pH study	

unless it leads to useful action. It must be stated that, as yet, the value of this approach has yet to be proven. There is a real need for multi-centre studies, with very careful and uniform protocol-driven assessments, to confirm or otherwise the value of these phenotypes.

The phenotypes we have described, and the approach we take to them, are summarised in Table 6. 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 identical eosinophilic inflammation to that seen in age-matched patients with ongoing symptomatic asthma.[40] 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:[41]

- 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, in 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

Table 6 Summary of proposed management, at the conclusion of the protocol studies

Clinical scenario	Presumptive diagnosis	Suggested action
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 CT scan if not already performed • Consider viral and autoimmune studies • Use minimum treatment which maintains lung function
2. Continued airflow obstruction, no inflammation, but with reversibility to β-2 agonists	• Presumed steroid resistant, non-inflammatory bronchial reactivity	• Continuous subcutaneous terbutaline treatment • High dose eformoterol by inhalation
3. Persistent eosinophilic inflammation, with either or both of airflow obstruction and symptoms	• Presumed steroid partial or complete resistance	• Look for causes of secondary steroid resistance • Treat with either prolonged high dose steroids or steroid sparing agent • Consider omalizumab
4. Persistent eosinophilic inflammation, with no airflow obstruction or symptoms	• ?Lagging of clearance of inflammation • ?Risk of ongoing remodelling despite no symptoms	• Observe closely with repeated spirometry and non-invasive measures of inflammation
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 • Steroid sparing agent (often less effective in this phenotype) • Consider omalizumab
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. 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

- 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 salivary 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.[30-33] 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).[42] Data in children is 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[29] and a Lancet editorial[43] 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 sensitised, via an interleukin (IL)-2 and -4 dependant mechanism.[44,45] The detailed mechanisms are unclear, a change in isoforms of the glucocorticoid receptor has been implicated by some,[46] but by no means all[47] workers.
- Experimental studies: repeated low dose inhalant allergen challenge, in a dose too low to lead to a change in FEV_1 leads to worsening of bronchial responsiveness and airway inflammation (as judged by induced sputum).[48]
- Observational studies: children who are cat sensitive, and are in a school class in which more than 18% of their class mates are cat owners develop a pattern akin to occupational asthma, progressively worsening during the week, improving at the weekend and in school holidays.[49]
- Interactions with viral infections: in a study of children hospitalised for an acute attack of asthma, much the most significant odds ratios for admission were for the combination of isolation of a respiratory virus, together with the combination of sensitisation 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,[50] and so could cause airway damage independent of any IgE effects. In a study of adult asthmatics, non-sensitised 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.[51] An epidemiological study in Europe showed a dose effect for cat allergen exposure leading to worse bronchial responsiveness in atopic, non-cat sensitised people.[52] 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.[53,54]

Thus, pending further intervention studies in severe, therapy resistant asthma, it is and remains right to advise stringent avoidance measures for all allergens to which the child is sensitised. Thus any such 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 bedding) should be put in place. Even in the absence of IgE mediated sensitisation, there is a case for allergen avoidance.

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™). This expensive and inconvenient monoclonal antibody has been advocated as treatment for sever atopic asthma. In the UK, it is licensed for use in children over age 12 years,[55] who have a total IgE of less than 700 iU/ml, but there is substantial clinical experience in the 6-12 years age groups,[56] 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 they may still benefit from the top recommended dose.[57] 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 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,[58-60] and have been shown to be of proven benefit in cystic fibrosis.[61-64] Hypothetically, they may be useful in neutrophilic asthma,[65] but convincing evidence of long term benefit is lacking. They also have activity in suppressing eosinophilic chemo-attractants, and thus might have wider application.[66] 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.[67] If BAL culture are positive for bacteria, I would investigate for causes of chronic suppurative lung disease such as CF and PCD (above), and, if none is found, treat presumed persistent bacterial bronchitis[68,69] 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. Other to be considered include low dose theophylline (anti-inflammatory level), which accelerates neutrophil apoptosis,[70] as well as potentially restoring steroid sensitivity by an effect on nuclear histone deacetylase activity.[71] A future option might be reduction of leukotriene B_4 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.[72] Choices include monthly intravenous immunoglobulin infusions (at least a six month trial), oral low dose methotrexate or azathioprine, and cyclosporin[73-75] (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[76] 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[20,21] or etanercept.[37] The recent serious adverse events due to a cytokine storm with human monoclonals is a warning of the dangers of these approaches.[77] 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.[78] 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 7), to eliminate the large potential placebo effect of such treatment. The pharmacist prepares the syringes, and the child and family know that neither they, not 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 independent 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,

Table 7 Timetable for the double-blind, placebo controlled trial of subcutaneous terbutaline. The two treatments are subcutaneous terbutaline and normal saline

Day of admission	Intervention
1-3	Baseline, no therapy
4-6	Treatment A infused
7, 8	Washout period
9-11	Treatment B infused
12, 13	Washout period
14-16	Treatment A infused
17, 18	Washout period
19-21	Treatment B infused
Out-patient review one week later	Decision as to future treatment

spirometry and acute bronchodilator reversibility is 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 out-patient 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[79,80]) may also partially 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 8 – sadly, none such exists. Trials using FeNO,[81-83]

Table 8 The characteristics of the perfect 'inflammometer'

CHEAP
Easy to maintain and calibrate
Completely non-invasive
Easy to use, no co-operation needed
Direct measurement of all relevant aspects of inflammation
Rapid availability of answers
Evidence of beneficial clinical outcomes

sputum eosinophils[84,85] and BHR[86,87] have all shown benefit, but it is fair to say that even in moderate asthma, the exact place of which method is unclear. A recent cluster analysis in adults[88] suggests it is in those patients in which there is discordance between symptoms and inflammation (either severe but asymptomatic inflammation, or multiple symptoms without evidence of inflammation) are most likely to benefit from 'inflammometry'. The data in 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.[89] This is another area for future research. However, it is also very complex; in this severity-group, in our hands phenotypes may be inconstant[90] (below), and the relationship between FeNO and sputum eosinophils may vary between individuals, and within the same individual over time, illustrating the complexity of the problem.[91]

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 has 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,[40] 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.[92,93]

By contrast, data from anti-IL5 studies suggests 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.[94] 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.[95]

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 ignoring symptoms, which has been successfully employed in adults, is the assumption that cellular phenotypes remain stable over time. This is not the case in severe, therapy resistant asthma in children. In one study, more than 40% children showed at least one switch in sputum cellular phenotype over a one year period.[90] It is certainly not right to assume that assigned phenotypes will remain stable over time. What is unclear is how frequently children should be re-phenotyped; and what these changes actually mean, whether they represent a real change in the fundamental nature of the disease, or reflects transient environmental influences such as viral infection, allergen load or pollution.

Proximal Versus Distal Inflammation: What Matters?

Adult studies have utilised transbronchial biopsy (TBB) to determine alveolar inflammation in asthmatics.[96-98] Distal inflammation with CD4 positive lymphocytes correlated with nocturnal asthma. TBB has a significant risk of bleeding and pneumothorax in children,[99] 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.[100] This approach could be followed in asthma, but as yet 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 (J_{NO}) and alveolar (C_{ALV}), by measuring NO production at different expiratory flow rates.[101] We have shown that in children J_{NO} and $FeNO_{50}$ correlate closely. As has been described before both J_{NO} and $FeNO_{50}$ are elevated in atopic asthmatics but also atopic, non-asthmatics. However, C_{ALV} was only elevated in atopic asthmatics. Both J_{NO} and C_{ALV} were elevated in poorly controlled asthmatics. Another approach might be to study distal airway function, albeit acknowledging that 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 including 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 (S_{COND}) and the acini (S_{ACIN}).[102-104] More data is needed before we can determine whether these measurements will enable us to determine 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; that 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[105] and ciclesonide,[106] 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.

Summary

We have a long way to go before we understand phenotyping 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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