

## This Child's Asthma Appears to Be Severe: But Where Actually Is the Severe Problem?

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### Abstract

The aim of this manuscript is to outline an approach to severe asthma, which is among the most challenging problems faced by paediatric pulmonologists. A logical, protocolised approach is essential. The first step is to rule out alternative diagnoses. The next step is a multidisciplinary assessment. Severe, therapy resistant asthma (STRA) is rare, and most of those referred will improve if basic management is corrected, especially adherence to treatment. However some are unable or unwilling to make necessary changes (refractory asthma plus or refractory difficult asthma). Some, especially asthma in the obese, and those thought to have STRA, progress to bronchoscopic airway phenotyping and a parenteral steroid trial to determine an individualised treatment plan. Those with persistent eosinophilic airway inflammation should be considered for omalizumab, and mepolizumab. Pauci-inflammatory asthma remains a therapeutic challenge, with a paucity of evidence; increasing steroid therapy seems neither logical nor efficacious, but options include tiotropium and azithromycin. However the most important message to the paediatrician looking after a child with apparently severe asthma is that the answer is not uncritically escalating treatment, but finding the answer to the question, what is it about this child, and his/her environment, which means there is no response to what should be easily treated airway pathology? The answer usually requires input from a skilled and experienced multi-disciplinary team, without which management is unlikely to be successful. **Conclusion.** When managing a child with severe asthma, a detailed multi-disciplinary is essential to get the basic management right, before prescribing biologicals.

**Key Words:** Adherence ▪ Atopy ▪ Mepolizumab ▪ Obesity ▪ Omalizumab.

### Introduction

Severe asthma is amongst the greatest challenges faced by paediatric pulmonologists – get it wrong, and you will be attending the funeral of a dead child. The aim of this manuscript is to set out a systematic approach to the management of children referred with apparently severe asthma not responding to treatment.

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### What Is Severe Asthma?

In a low and middle income setting, and in pockets of some affluent societies, poor availability of basic medications is the cause of severe asthma (1). The conventional developed world definitions of severe asthma, for example the ERS/ATS Task Force (Table 1) (2), are based on levels of prescribed medication. However, it is clear that domains of risk must be incorporated, which are discussed in more detail below, the main one being risk of a severe asthma attack; a prescribed pharmacology based definition is on its own inadequate.

### What Do We Know?

Four key studies should be noted (3-6):

Table 1. ERS/ATS Task Force Definition of Severe Asthma

<ul style="list-style-type: none"> <li>• Asthma which is only controlled or uncontrolled on therapy with &gt; 800 mcg/day BDP equivalent plus additional controllers (LABA, LTRA, Theophylline) or failed trials of these agents, AND any of: <ol style="list-style-type: none"> <li>1. Poor symptom control, e.g. Asthma Control Test (ACT) &lt;20</li> <li>2. <math>\geq 2</math> bursts of systemic corticosteroids (<math>\geq 3</math> days each) in the previous year</li> <li>3. Serious exacerbations (<math>\geq 1</math> hospitalisation or PICU stay) in the previous year</li> <li>4. Airflow limitation: <math>FEV_1 &lt; 80\%</math> predicted following SABA and LABA withhold</li> </ol> </li> </ul>
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BDP=Beclomethasone dipropionate;  $FEV_{1st}$ =first second forced expired volume; LABA=Long acting beta-2 agonist; LTRA=Leukotriene receptor antagonist; PICU= Paediatric intensive care unit; SABA:Short acting beta-2 agonist.

- The BADGER (3) study posed the question, whether the best strategy for children still symptomatic on inhaled fluticasone 100 mcg twice daily is to increase the dose of the inhaled steroid (ICS), add a long acting  $\beta$ -2 agonist (LABA), or adding a leukotriene receptor antagonist (LTRA). The LABA strategy was optimal, and very few children gained benefit from an increased dose of ICS. Hence this dose should be considered 'standard dose' not 'low dose', and bigger doses are 'high dose'
- In a North American inner-city study of children with uncontrolled asthma (4), aiming to answer the question as to whether exhaled nitric oxide (FeNO) in addition to standard monitoring improved asthma control, the improvement during the 2-week run-in period was so great, that there was no scope for further improvement
- Another North American study (5), which attempted to determine whether, in children symptomatic on LABA and ICS, it was better to add LTRA or azithromycin to the regime. The study ended in futility because most of the children they attempted to recruit either did not have asthma or were not taking treatment.
- A genome wide association study comparing mild with moderate-to-severe asthma in two large cohorts showed very substantial genetic overlap between the two groups in both cohorts (6), albeit with some novel severe asthma variants. I am forced to the conclusion that it is not airway pathology that makes difficult asthma difficult, but other factors (below)

The important conclusion for those managing apparently difficult asthma is that most children have an airway disease that is easy to treat, and the

approach to a child with apparently therapy resistant asthma is not to prescribe more treatments, but rather ask, 'what is it about this child which is making him/her non-responsive to standard therapies?'

### So, Where Usually Is the Difficulty?

Table 2 sets out the three domains which should be considered in airway diseases (7). The airway disease of asthma should be easy to treat, so social/environmental factors, and co-morbidities are likely important in severe asthma. This is borne out in the UK confidential report on asthma deaths (8); important factors were poor adherence to ICS, over-use of short acting  $\beta$ -2 agonist (SABA), failure to attend regular asthma reviews and repeated emergency room visits. Most deaths were in patients who were not considered to have severe asthma! Importantly, the biggest predictor of an asthma attack is a previous severe attack (9). Hence any assessment of asthma attacks must include extra-pulmonary factors, and any definition of severe asthma based solely on levels of medication must be wrong.

### Assessment of the Patient with Respiratory Symptoms (a) Attributed to Asthma; and (b) Not Responding to Standard Therapy

Our approach is summarised in Figure 1. These children need a detailed, multi-disciplinary assessment (10, 11), before even considering beyond guidelines therapies, especially with biologicals.

**Step 1: Is the diagnosis correct?** The first question is whether the child has an airway disease at all, or is merely reporting breathlessness secondary

Table 2. Three Domains of Airway Disease to Be Considered in Severe, Therapy Resistant Asthma\*

Domain of Airway Disease	Clinical Traits	Treatment (especially what is treatable)	What treatment success would look like
Pulmonary	Airway eosinophilia	Inhaled corticosteroids Omalizumab Mepolizumab	Reduction in asthma lung attacks, better baseline control
Extrapulmonary (co-morbidities, asthma plus)	Obesity	Diet Bariatric surgery	Weight loss Improved exercise performance Reduced obesity asthma
	Exercise induced laryngeal obstruction	Identification of problem, physiotherapy and sometimes psychological intervention	Better exercise tolerance, medications weaned
Environment and lifestyle	Poor adherence	Interventions to support adherence Directly observed therapy SMART regime or other simplification	More consistent use of medications, better asthma control, fewer attacks
	Exposure to allergens to which the child is sensitized	Allergen avoidance, e.g. removing pets	Better asthma control, fewer attacks
	Active and passive nicotine exposure	Referral to smoking cessation clinic	Exposure reduced, better asthma control, fewer attacks

The problem usually does not reside in the domain of airway pathology. Examples are given, the Table is not meant to be exhaustive.

to cardiopulmonary deconditioning. In one study, around 50% of those reporting breathlessness did not have an airway disease, although many were treated for asthma (12). If the child does have a disease, the differential diagnosis is wide (Table 3), and will vary across the world; for example, airway compression from tuberculous lymph nodes is common in Cape Town, rare in London. A detailed re-evaluation, starting with a thorough history, particularly focussed on whether the child exhibits true whistling wheeze and who else has heard the wheeze, and also a physical examination, is essential. Basic investigations if not already performed should ideally include measurement of total and specific IgE and skin prick tests to determine atopic status (non-atopic school-age asthma is rare, and should prompt a complete review) (13); blood eosinophil count and FENO to explore the possibility of ongoing eosinophilic airway inflammation; spirometry before and after SABA administration, and consideration of home peak flow measurement and a test of airway hyper-responsiveness, to determine whether there is variable airflow obstruction; should all be considered. In terms of imaging, most will have had multiple chest radiographs; we reserve CT scanning for cases where the diagnosis is in doubt.

**Step 2: The child truly has asthma, so needs a multidisciplinary team assessment** This will include the determination of the contributions made by co-morbidities (“asthma plus”) and areas of basic management that have not been got right (“difficult asthma”), as well as assessment of the airway disease in terms of treatable traits, such as the presence or otherwise of eosinophilic inflammation and bronchodilator reversible airflow obstruction. Table 4 summarises this process of this Stage 1 assessment (10, 11). Visits to the home and at least a discussion with the school is an essential part of the evaluation.

- Asthma plus – obesity: the obese child should be evaluated particularly carefully. Firstly, breathlessness and wheezy breathing may be a sign of deconditioning (12), and not an airway disease. If there is any doubt, a cardiopulmonary exercise test with measurement of spirometry or peak flow after exercise should be performed. If there is an airway disease, it should not be assumed to be eosinophilic (14, 15) The airway may also be the target of systemic inflammation, mediated via Interleukin (IL)-6 (16). Dysanaptic airway growth (defined as a normal first second forced expired volume (FEV<sub>1</sub>) with greater than normal forced vital

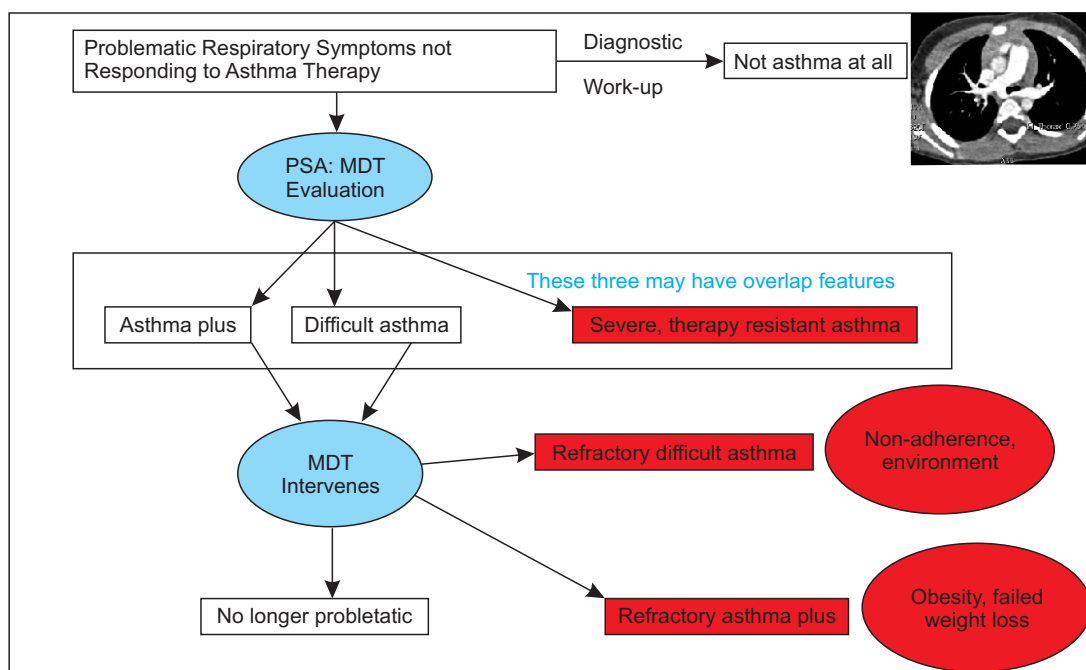


Figure 1. Approach to severe asthma. The High-resolution computed tomography (HRCT) scan shows a pulmonary artery sling, a differential diagnosis of severe asthma; MDT=Multidisciplinary team; PSA=Problematic severe asthma.

Table 3. Differential Diagnosis of Severe Asthma

Class of Diagnosis	Examples
Local (i.e. confined to the respiratory tract) immunodeficiency	Cystic fibrosis, primary ciliary dyskinesia, persistent bacterial bronchitis (cause often not found)
Systemic immunodeficiency	Any innate or adaptive immunodeficiency, including B cell and T cell dysfunction
Bronchial obstruction within the airway itself	Foreign body, carcinoid, other tumor
Obstruction arising from disease of the airway wall	Tracheobronchomalacia, complete cartilage rings, intramural tumor
Bronchial obstruction resulting from external compression	Vascular ring, pulmonary artery sling, congenital lung cyst, enlarged lymph nodes due to tumor or tuberculosis, other mediastinal masses
Direct aspiration from the pharynx	Bulbar or pseudobulbar palsy; laryngeal cleft
Aspiration by direct contamination from the oesophagus with normal pharyngeal function	H-type fistula
Aspiration secondary to gastro-oesophageal reflux	Any cause of gastroesophageal reflux, including hiatus hernia and esophageal dysmotility
Complications of 'preterm birth' or 'prematurity'	Bronchomalacia, structural secondary to intubation, vocal cord palsy secondary to surgery for patent arterial duct
Congenital or acquired heart disease	Bronchial compression from enlarged cardiac chambers or great vessels; pulmonary oedema
Interstitial lung disease	Any not presenting with neonatal respiratory failure
Dysfunctional breathing	Exercise induced laryngeal obstruction, hyperventilation syndromes

capacity (FVC) and thus a reduced  $FEV_1/FVC$  ratio) is associated with obesity and worse outcomes (17). Thus even in genuine obese asthma, ICS treatment should not be uncritically escalated, and measurement of airway inflammation at least indirectly (FeNO, induced sputum or peripheral blood eosinophil count) should be undertaken. Finally, a research area is the effects on the airway of alteration in particular in the gut microbiome in obese children (18). Treatment of obesity is of course weight loss; it may be that bariatric surgery is needed (19).

- Asthma plus – exercise induced laryngeal obstruction (EILO) (20): typically this presents as dyspnoea during rather than after exercise, which is more typical of exercise-induced bronchoconstriction. Symptoms are produced by adduction of the vocal cords, usually in inspiration. An underutilised test for EILO is a simple SMARTPHONE video recording, which typically demonstrates stridor and a tracheal tug (21). Definitive diagnosis, which is especially important if surgery is contemplated, is by laryngoscopy during exercise. A subgroup with EILO had laryngomalacia in infancy (22), or laryngeal nerve damage after ligation of a patent ductus arteriosus complicating preterm birth (23), so a detailed perinatal history should always be obtained.
- Asthma plus – rhinosinusitis: the “united airway” concept is controversial; clearly upper airway disease should be treated on its own merits, and many studies suggest this also benefits lower airway disease (24).
- Asthma plus – obstructive sleep apnoea: in our series, unless the child is also obese, this is not a feature of severe asthma.
- Asthma plus – food allergy? There is a clear association between food allergy and severe asthma (25), but whether there is causality is unclear. We do not perform blind dietary manipulations, and only diagnose food allergy with objective testing.
- Asthma plus – gastro-oesophageal reflux (GOR)? GOR is frequently detected, but there is ample evidence that treatment, whether or not there are suggestive symptoms, does not improve asthma control (26).
- Difficult asthma – adherence: this is perhaps the biggest challenge faced by Paediatric Pulmonologists. It is a waste of time to ask families if they are adherent, or ask them to fill in adherence questionnaires; the answer always is that the child takes all the treatment all the time. Sometimes this is a genuinely held be-

Table 4. Multi-Disciplinary Assessment of Severe Asthma

Issue to be Addressed	Tests Performed
Symptom pattern	Asthma control test, prednisolone bursts, unscheduled visits
Psychosocial factors	Questionnaires relating to treatment burden, anxiety and depression, quality of life
Lung function	Spirometry before and after bronchodilator
Allergic sensitization	Skin prick tests, specific IgE
• Aeroallergens	Grass and tree pollen, house dust mite, cockroach, cat and dog, and any others suggested by the clinical history
• Food allergens	Peanut, milk, egg and any others suggested by the clinical history
Fungal sensitization	See Table 6
Airway inflammation	FeNO Induced sputum cytospin if $FEV_1$ is >70% predicted
Nicotine exposure (tobacco or vaping)	Urine or salivary cotinine
Medication adherence	Prescription uptake Serum prednisolone and theophylline levels if prescribed; serum inhaled corticosteroid levels if available (usually only in a research context)

FeNO=Fractional expired nitric oxide;  $FEV_1$ =First second forced expired volume; IgE=immunoglobulin E.

lief by parents who do not realise they are not adequately supervising medication inhalation. There is a hierarchy of data and tests which lead to more objective understanding. The simplest is to access prescription records (27); of course, collecting a prescription is not the same as medications being properly used, but failure to collect definitively means none taken. A home visit is often also informative – oftentimes medications are found still in their original wrappings, or out of date, or packed away at the back of a cupboard; none of which inspires confidence that medication is actually being used (27). We increasingly use electronic monitoring using SmartInhalers™. Four patterns of use have been described (Table 5) (28), each prompting a different course of action. These inhalers only monitor activation, not inhalation, and, compared with those with a microphone to detect inhalation, overestimate adherence (29). Finally and probably the gold standard, directly observed therapy (DOTS) by video link using smartphones and Bluetooth technology (30). In one study, this technique was acceptable to the patients, but, despite multiple previous attempts at teaching, it took five weeks before the children were using their inhaler devices correctly at home. In those few children prescribed prednisolone or theophyllines, measurement of blood levels may be informative; serum cortisol should also be suppressed in those on chronic prednisolone therapy, and an elevated level suggests non-adherence. Measurement of serum levels of ICS is currently only a research technique. Other medication issues include failure of parental supervision (above), and, particularly by teenagers, using metered dose inhalers without a spacer (27).

Difficult asthma – adverse environmental factors: these include persistent active and passive exposure to cigarettes and vaping devices, detected by persistently elevated urinary or salivary cotinine; referral to a smoking cessation clinic should be offered. Another factor is persistent exposure to allergens to which the child is sensitised, usu-

ally furry pets (27). Frequent comments are that the child is no worse when near the pet cat, and was no better when the cat was sent away for two weeks. However, low dose allergen exposure can drive subacute type 2 inflammation (31), synergises with viral infection to cause acute attacks (32), and it takes at least a year for cat allergen levels to drop to low levels after removal of the animal. Another issue is mould exposure, frequently accompanied by a request for a letter to support rehousing. However, environmental fungi may cause severe asthma with fungal sensitization (Table 6), which is probably IL-33 mediated and causes more severe inflammation (33).

- Difficult asthma - Psychosocial issues: these are very common in severe asthma, and the relationship between the two is complex. Rather than trying to decide which came first, it is better to address psychosocial issues in parallel with trying to treat asthma (27). It is virtually impossible to manage severe asthma without skilled psychological support.
- Difficult asthma - Symptom perception: which may involve exaggeration or downplaying of symptoms. Exaggeration may be for financial benefits (in the UK, having a sick child allows the claiming of cash benefits), or for more serious underlying reasons, for example panic attacks after the trauma of being ventilated for asthma, or hyperventilation to escape going to school or from an abusive situation at home. Some children with asthma fail to appreciate that their airways are progressively obstructing; this situation is dangerous, difficult to address, and may rarely underlie asthma deaths.
- Difficult asthma - Asthma education: sometimes ignorance of the basics of the disease may contribute to the problem, and checking basic knowledge is an important part of the assessment (27).

**Step 3: After the assessment, a multi-disciplinary review followed by an intervention** All the data above are collated and discussed. In the minority, no potentially reversible factors are detected, and the child progresses to invasive phenotyping and beyond guidelines therapy (true Severe, Therapy



Table 5. Patterns of Non-adherence and Their Management

Symptom/Test results	Interpretation	Actions
FEV <sub>1</sub> and FeNO abnormal at start of monitoring, adherent at least in activating the inhaler during monitoring, FEV <sub>1</sub> and FeNO normalise and symptoms improve	Previously non-adherent, and became adherent during monitoring	Intervention to support adherence, with regular re-assessment and feedback
FEV <sub>1</sub> and FeNO abnormal at start of monitoring, adherent during monitoring, tests remain abnormal, still symptomatic	Severe, therapy resistant asthma Could also be activating inhaler but not inhaling	Invasive airway phenotyping
FEV <sub>1</sub> and FeNO abnormal at start of monitoring, non-adherent during monitoring, tests remain abnormal, still symptomatic	Either refractory severe asthma, or severe therapy resistant asthma who stopped medications because they do not work	Ascertain response to DOT; if no response, invasive airway phenotyping. If responds, refractory difficult asthma, consider simplifying regimes or biologicals
Poorly adherent on monitoring, but actually remains well with normal FEV <sub>1</sub> and FeNO	Previously over-treated	Wean asthma treatment but continue to follow up carefully

DOT=Directly observed therapy; FeNO=Fractional expired nitric oxide; FEV<sub>1</sub>=First second forced expired volume.

Resistant Asthma, STRA, discussed in more detail below). In most, however, assignment is to difficult asthma or asthma plus, acknowledging they may overlap, and a plan is made to try to improve control and reduce attacks. These may include:

- Difficult asthma – interventions to support adherence including DOTS at school, and simplification of the regime, for example using Symbicort™ as a single preventer and reliever inhaler, or once daily Relvar™ (fluticasone furoate/vilanterol); environmental interventions such as house dust mite impermeable bed covers, removal of pets, and addressing smoking and vaping
- Difficult asthma – an admission for evaluation to hospital (34). In particular if adherence is thought to be an issue, or symptoms are over-called, direct observation over a period time

- may be illuminating. Improved spirometry and a fall to normal in FeNO during hospital DOTS is strongly suggestive of previous poor adherence. SABAs are only permitted after evaluation by a paediatrician, and very often, the child is well and active without asking for them, suggestive of previous over-calling of symptoms. We discover safeguarding issues in adherence and overcalling symptoms in around 10% of children referred to our difficult asthma service
- Asthma plus – co-morbidities are tackled, particularly the aid of a specialist physiotherapist to tackle EILO, weight reduction under the supervision of a dietician, and consideration of a specialist referral to tackle upper airways disease
- Step 4: Has the problem been solved?** The above approaches result in many difficult asthma

Table 6. Definition of Severe Asthma with Fungal Sensitization (SAFA)

Adult Criteria	Proposed Paediatric Criteria*
Treatment with 500 µg fluticasone/day or equivalent, or continuous oral corticosteroids (less useful in the age of biologicals, since far fewer adults are prescribed oral corticosteroids on a long term basis, or four prednisolone bursts in the previous 12 months or 12 in the previous 24 months, and all of	Meets criteria for problematic severe asthma
1. IgE <1000 (exclude ABPA)	No IgE exclusion
2. Negative IgG precipitins to <i>Aspergillus fumigatus</i>	No IgG exclusion
3. Sensitization (SPT, sIgE) to at least one of <i>Aspergillus fumigatus</i> , <i>Alternaria alternata</i> , <i>Cladosporium herbarum</i> , <i>Penicillium chrysogenum</i> , <i>Candida albicans</i> , <i>Trichophyton mentagrophytes</i> and <i>Botrytis cinerea</i>	As adult criteria

There is no agreed definition in children, but given the rarity of allergic bronchopulmonary aspergillosis (ABPA) in children with asthma, we eliminate the total IgE and IgG criteria, from the diagnostic criteria.

and asthma plus patients improving dramatically, with reduction in prescribed medications, improved asthma control and reduction in attacks, and better physiological parameters (spirometry, FENO). These children need support to maintain their improvement. However, despite the best efforts of the team identifying problems and trying to support change, some families and children fail to engage, resulting in ongoing poor control and asthma attacks, i.e., are considered to have refractory disease (35).

- Refractory difficult asthma: the commonest reason is failure to support adherence; DOTS only works if the child goes to school regularly, is prepared to go to the school nurse's room for treatment, and the nurse is prepared to check obsessively that the inhaler is in date and not empty, and actually closely watches the child taking the medication. Other causes are inability or unwillingness to address environmental factors, and intractable psychosocial issues
- Refractory asthma plus: usually the issue is asthma and obesity with failed weight loss; referral for bariatric surgery should be considered, but in the meantime, asthma must be addressed.

Previously we argued (incorrectly, with retrospect) that only STRA children should be eligible for biologics (36). Given that most asthma deaths are not in STRA, we now believe that children with refractory difficult asthma should also undergo invasive airway phenotyping to develop an individualised treatment plan.

**Stage 2 and 3 assessment: What is the airway pathology?** The aim is to determine the answers to four questions:

- Is the asthma steroid responsive, or is a non-steroid based approach needed?
- Is there evidence of airway inflammation, and if so, what is its nature? For example, there seems little point in giving anti-Type 2 (TH2) agents such as mepolizumab if there is no airway eosinophilia, or increasing the dose of steroids if the airway is pauci-inflammatory?
- Is there discordance between symptoms and inflammation (37)? Either multiple symptoms

with no inflammation, or eosinophilic inflammation without symptoms, but which confers a high risk of a future asthma attack?

- Is there persistent airflow limitation (PAL), in which case escalating treatment to try to restore normal lung function will only succeed in exposing the child to the risk of side-effects?

The child attends hospital for stage 2, and is assessed with spirometry with acute response to SABA (bronchodilator reversibility, BDR), FENO, and induced sputum cytospin. The child next undergoes a fiberoptic bronchoscopy, bronchoalveolar lavage and endobronchial biopsy under general anaesthesia, during which time a single intramuscular dose of the glucocorticoid triamcinolone (40 mg if weight <40 kg, 80 mg all others) (38). The final visit, for stage 3, takes place 4 weeks later, during which all the non-invasive tests above are repeated, and the response to triamcinolone determined. We have shown that the adult definition of steroid responsiveness, namely a 15% or greater predicted increase in morning FEV<sub>1</sub> in patients with BDR of 12% or greater from baseline and an abnormal FEV<sub>1</sub> (<80% of predicted value) before a systemic steroid trial (39, 40), cannot be used in around half of children with STRA, because they have normal spirometry (38). We use a multidomain approach (Table 7), assessing symptoms, spirometry and airway inflammation (41), which is now increasingly also being adopted in adult medicine (42).

**What treatments could be considered?** For many children, there are no easy therapeutic answers.

- **Is the child eligible for omalizumab?** There is most paediatric evidence with the anti-IgE monoclonal omalizumab, which inhibits the binding of IgE to the mast cell and basophil high-affinity IgE receptor (FcεRI), thus limiting the release of those mediators driving the allergic response. There is also evidence that omalizumab may have anti-viral properties. To be eligible (43), serum IgE must be >30 and <1500 international units; and the child must unequivocally be shown to be sensitised to aeroallergens, especially if IgE is near the lower limit



Table 7. Domains of Steroid Responsiveness\*

Modality	Response
Symptoms	ACT rises to >19/25 or 50% increase
Spirometry	FEV <sub>1</sub> rises to >80% predicted or 15% increase
Inflammatory: FeNO	Falls to <24 ppb
Inflammatory: Sputum eosinophils	Falls to <2.5%

\*Note that the figures we have adopted are not evidence-based. It is accepted that FeNO and sputum eosinophils are not concordant (77) but it is often difficult to obtain paired sputum samples in this population (78); ACT=Asthma control test; FeNO=Fractional exhaled nitric oxide; FEV<sub>1</sub>=First second forced expired volume; ppb=Parts per billion.

of eligibility (although there is evidence that those without sensitisation respond equally well (44)); dosage and dosing frequency (2 vs. 4 weekly) depends on body weight and level of IgE. Unfortunately, many STRA children have an IgE above this range, making them ineligible. Although IgE determines eligibility, it is in fact a poor biomarker of response. In an adult study, a high FeNO, blood eosinophil count and serum periostin (this last is not useful in children because it is released from growing bone) were predictive of a good response (45), and in a small paediatric study (46), a fall in FeNO after triamcinolone. In our hands, asthma attacks respond better than impaired day to day control. Our practice is to assess response every 16 weeks, including asthma control test (ACT), history of attacks, FeNO, induced sputum and spirometry with BDR.

- **Is the child eligible for an anti-TH2 monoclonal?** At the moment, the only one licensed in children in the UK is the anti-IL5 mepolizumab. From the available studies, to be eligible, the child must have a peripheral blood eosinophil count of at least 150/ $\mu\text{l}$ , and preferably >300/ $\mu\text{l}$ . As with omalizumab, it is those prone to asthma attacks which respond best (47). It is worrying, however, that evidence for efficacy and safety has been uncritically extrapolated from adults; even in those studies recruiting young people over age 12, the vast majority recruited have in fact been adults. Firstly, there is evidence from two groups that airway eosinophilia in severe paediatric asthma may not be TH2 mediated (38, 48); of course, the question is ‘does it work?’ not ‘should it work?’ but we

desperately need trials in children. Secondly, the developmental biology of the eosinophil is not well understood, but at least from animal data, there is evidence that this cell has important physiological functions (49-53). For example, adipose tissue eosinophils participate in beige fat thermogenesis and glucose homeostasis through regulation of alternatively activated macrophages (49, 50); bone marrow eosinophils are required for adjuvant-induced B-cell priming and maintenance of memory plasma cells (51, 52); and resident intestinal eosinophils are distinct phenotype and constitutively express antigen-presenting cell markers (53). So it is essential that the paediatric respiratory community unite to obtain paediatric data on safety and efficacy for mepolizumab and the other upcoming anti-TH2 monoclonals (54).

- **What do we do about pauci-inflammatory asthma?** This is one of the least-understood groups. An adult proof of concept study demonstrated that this group was not steroid-responsive (55). Evidence is scant, but these children may be considered for Tiotropium (56), or given azithromycin (57) long term. Perhaps the most important is not to over-treat with steroids if there is no eosinophilic airway inflammation.

**Following up: What next?** The initial assessment is of course only the start of the process. Detailed follow up is essential, to determine progress and detect any side-effects of treatment. Regression of good adherence is notoriously common, especially when the child is feeling well. There is a good case to be made for a detailed annual assessment of these children, including assessment

of linear growth, assessment of lung function trajectories (58), reassessment of exposures (including to nicotine) and sensitization, and the performance of a short synacthen test to assess adrenal function. Of note, sputum cellular inflammatory phenotypes are much less stable than in adults (59), so an annual induced sputum and FENO should be considered. Asthma attack risk should also be determined (60), and the knowledge that the growing child has of asthma and treatment should be checked.

### **A (Literally) Deadly Issue: The Asthma Attack Prone Child**

The word exacerbation implies a mild inconvenience that is readily reversible. In fact, what we prefer to call asthma lung attacks (61, 62) may be fatal, are a warning sign that further attacks are imminent unless something is done (9), and are associated with an impaired lung growth trajectory (63, 64). Asthma lung attacks should be a 'never event' like cutting off the wrong leg in the operating room (65).

- Firstly, determine the basis on which the asthma lung attack was diagnosed; what objective measurements were made? We have often seen that a history of so-called severe asthma who were over-treated in the emergency room; one child was given intravenous salbutamol for 'asthma' despite an oxygen saturation in air of 100%! The child was hyperventilating.
- A true asthma attack needs to be treated effectively. There is no place for a standard 3- or 5-day course of prednisolone, with no review to ensure the child has responded. The child must be reviewed to ensure that recovery is complete.
- An asthma attack must not be treated as an isolated event, like lobar pneumonia (66); it should be seen as a serious occurrence on the asthma journey, and taken really seriously
- The asthma plan should be reviewed; was it followed, should it be changed?
- Medication issues: can the child use the medication delivery device? How many ICS canis-

ters have been accessed (67)? How many SABA canisters have been dispensed (68)? Do the child and family understand the dangers of non-adherence? Should the child have SABAs removed and substituted with Symbicort™ (69-71), or prescribed a SMART regime (72), so the combination of underuse of ICS and overuse of SABA is taken out of the equation? Should a biological (omalizumab, mepolizumab) be prescribed to reduce future lung attack risk?

- Are there environmental issues? The combination of sensitization to allergens, allergen exposure and respiratory viral infection is strongly predictive of an asthma attack (32), of which only allergen exposure can be modulated. A proof of concept, randomised double blind study demonstrated that, in children sensitised to house dust mite and who had been admitted to hospital had improved asthma outcomes if they were randomised to mite impermeable bedding covers (73). It may be that the intervention was too focused; other studies have shown the efficacy of a more multifaceted intervention (74, 75).
- The evidence relating Vitamin D deficiency to asthma attacks has a sound experimental basis but clinical evidence is less secure (76). However, it is not unreasonable to measure Vitamin D levels and prescribe supplementation if the levels are suboptimal.
- Future work should determine if a single dose of mepolizumab as part of the management of the acute attack will reduce the risk of future attacks.

### **Summary and Conclusions**

Severe asthma is challenging, and requires a focused, protocolised approach to management. Most severe asthma relates to extrapulmonary comorbidities and social/environmental factors rather than difficult airway pathology. A systematic multi-disciplinary assessment must be used which will often resolve the problem, or place the child into one of the three categories of STRA, refractory difficult asthma, and difficult asthma

plus. Many in these categories will require bronchoscopic airway phenotyping and assessment for biologicals such as omalizumab and mepolizumab. Asthma lung attacks are a sentinel, never-event, which should prompt a detailed response to prevent recurrence. However, the over-arching final message is that almost all children with asthma can have their disease controlled well by low dose ICS if taken regularly and correctly, and adverse environmental factors are dealt with. There is no substitute for getting the basics right!

**Conflict of Interest:** The author declares that he has no conflict of interest.

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