**AN UPDATE ON PAEDIATRIC SEVERE ASTHMA**

Cara Bossley, MRCPCH, MD  
Respiratory Unit, Great Ormond Street Hospital, London, UK

Ranjana Suri, FRCPCH, MD  
Respiratory Unit, Great Ormond Street Hospital, London, UK

Portex Unit, UCL Institute of Child Health, London, UK

Correspondence  
Ranjana Suri, e-mail: ranjan.suri@gosh.nhs.uk

**ABSTRACT**

Children with severe asthma have recurrent exacerbations and/or persistent symptoms despite maximal treatment with conventional medication. Severe asthma in childhood is particularly difficult to treat, with substantial morbidity. There are few randomised controlled trials in these patients; evidence therefore has to be extrapolated from adult studies or paediatric studies of mild to moderate disease. The first step is often a detailed diagnostic evaluation. Patients with severe asthma can then be further categorised as one of: wrong diagnosis; significant comorbidity; difficult-to-treat; and true, therapy-resistant asthma. There are very few licensed treatments for this challenging group of children including high-dose inhaled steroids, SMART regimen and anti-IgE therapy. Many of the other treatments used (e.g. methotrexate, ciclosporin) are unlicensed. It is important, therefore, to ensure that the basics are right. Adherence must be optimised, comorbidities treated, inhaler technique regularly checked and allergen load reduced to a minimum.

Asthma is a chronic inflammatory condition of the airways characterised by variable airflow obstruction, with estimates that 300 million people suffer from it worldwide. A study of Irish 6-9-year-olds has shown a static prevalence in 2002 and 2007 of 21.7% and 23.5% respectively and similar patterns were described in the ISAAC study. However, prevalence does vary worldwide.

Most children with asthma have mild or moderate disease and are able to achieve adequate symptom control with the help of medication and/or by avoidance of triggering factors. Severe asthma affects only 4.5% of current childhood asthmatics but accounts for over 50% of healthcare costs, in terms of both morbidity and mortality, as well as the economic cost of disease. Children with severe asthma have recurrent exacerbations and/or persistent symptoms despite maximal treatment with conventional medication, such as inhaled short-acting beta2-receptor agonists (SABA), inhaled corticosteroids (ICS), long acting beta2-receptor agonists (LABA) and leukotriene receptor antagonists (LTRA). Severe asthma in childhood is particularly difficult to treat and there are few randomised controlled trials in these patients; evidence has to be extrapolated from adult studies or paediatric studies of mild to moderate disease. It is therefore important to understand and discuss all the available evidence when treating such patients.

This review reflects on the definitions of severe school-age asthma, the pathophysiology, biomarkers to investigate and monitor the disease, and treatment options.

**DEFINITIONS OF SEVERE ASTHMA**

Nomenclature is important in severe asthma. One of the first definitions of ‘difficult asthma’ was made by the European Respiratory Society (ERS) task force. This definition was based on the number of exacerbations, severity of symptoms, doses of ICS, add-on medication and SABA. Following this, an American Thoracic Society (ATS) workshop established the term ‘refractory asthma’, which required patients to fulfil at least one major and two minor criteria.

The definition of problematic severe asthma was further developed in 2008. Patients with the following were classified as having problematic severe asthma:

1. Persistent (most days for >3 months) chronic symptoms (use of SABA >3/week) of airway obstruction despite high doses of ICS (≥800 µg/day budesonide equivalent) and/or regular oral corticosteroids, LABA and current (or previous unsuccessful trial of) montelukast, OR

2. Recurrent severe exacerbations requiring >1 admission to the intensive care unit or >2 hospital admissions requiring intravenous medications, or ≥2 courses of oral corticosteroids in the past year despite therapy for persistent symptoms as described in (1) above, OR

3. At least one very sudden (≤6 hours) severe attack (requiring hospitalisation) without warning despite therapy for persistent symptoms as described in (1) above.

Patients can then be further categorised as one of: wrong diagnosis (‘Not asthma’); significant co-morbidity (‘Asthma plus’); ‘Difficult-to-treat’; and ‘Severe, therapy-resistant’ asthma (STRA). ‘Difficult-to-treat’ asthma is the label for children in whom there are issues which, when addressed, could reduce the severity of their symptoms, e.g. adherence to treatment, allergen exposure and psychosocial issues (Fig. 1). These children may not necessarily need more invasive testing or treatment; however, they may remain difficult to treat. If the basic management is optimised and other co-morbidities have been excluded, then a diagnosis of true STRA can be made. This nomenclature will be used throughout the remainder of this review.
Eosinophils are released by T-helper 2 (Th2) cells and mast cells in response to allergic stimulation. Eotaxin is also released and is a potent eosinophil stimulator. Once eosinophils are produced in the bone marrow they are released into the circulation and then migrate to the lungs. Eotaxins and eosinophil adhesion molecules mediate the transit of eosinophils across epithelial and endothelial barriers. These molecules include β integrin, very late antigen (VLA-4) and vascular cell adhesion molecule (VCAM)-1.15

Following transit through the epithelial wall the eosinophils are attracted to the site of inflammation by chemokines. Eosinophil survival is enhanced by IL-516 and apoptosis is reduced in allergy. IL-3, GM-CSF and eotaxin also lead to delayed eosinophil apoptosis.

Mast cells are important in asthma and allergy. They express cell surface receptors for IgE which when stimulated, cause type I allergic reactions. An allergen binds to this receptor and in turn stimulates the receptor. Stimulation of this receptor then causes degranulation and the production of chemokines including IL-4, IL-5, IL-3, interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α).17 They also release histamine, prostaglandins and leukotrienes, which cause airway inflammation.

Neutrophils are also produced from CD34+ progenitor cells. These undergo a number of morphological stages prior to becoming mature. They are then released into the blood, where they reside for relatively short periods of time (6-7 hours), and migrate to areas of inflammation or infection in response to chemotactic stimuli. They move into tissue by sequestration, migrating across the vascular endothelium into the lung. During the process of migration into the lung, neutrophils become activated. Their function on migration into tissue is to recognise, ingest and destroy pathogens.

**AIRWAY REMODELLING AND ASTHMA**

Airway remodelling is the change of tissue structural components that occurs during growth or in response to inflammation or injury.18 Chronic inflammation in asthma can lead on to persistent changes of airway remodelling. These are characterised by epithelial damage, thickening of reticular basement membrane and subepithelial fibrosis. It also involves mucus gland and airway smooth-muscle hypertrophy and hyperplasia.

Increased thickness of the reticular basement membrane, in particular, is an important feature of asthma. Reticular basement membrane thickening is not present at a year of age, but appears as early as 3 years in preschool confirmed wheeze.19 Increased reticular basement

---

**Fig. 1. The classification of problematic severe asthma.**

The World Health Organization (WHO) have since devised criteria that classify severe asthma into three groups: severe untreated asthma; difficult-to-treat severe asthma and treatment-resistant severe asthma.10

**MECHANISMS OF ASTHMA**

**AIRWAY INFLAMMATION AND ALLERGY**

In asthma, airway inflammatory markers do not always correlate with symptoms. Some children might have no symptoms between exacerbations but still have high levels of airway inflammatory cells on histology.11 However, other children with recurrent or persistent symptoms may have low levels of inflammatory cells.

There is a strong causal relationship between allergy and the acquisition of asthma, with up to 90% of children with severe asthma being atopic.19 Individuals may have a genetic predisposition to asthma and if environmental triggers are present, these in combination may lead to asthma. Viral infections play a part in the pathogenesis of asthma and they may increase susceptibility to allergen sensitisation in predisposed individuals.13

Allergic sensitisation is central to the pathogenesis of most childhood severe asthma, with eosinophils and mast cells playing a key role. Airway inflammation begins with the late-phase allergic reaction. Eosinophils are produced from CD34+ stem cells in the bone marrow. CD34+ stem cells mature in response to cytokines interleukin (IL)-3, IL-5 and granulocyte macrophage colony-stimulating factor (GM-CSF).14 These cytokines
membrane thickness has also been shown in school-age children with problematic severe asthma, as well as children with relatively mild asthma. Reticular basement membrane thickening probably contributes to the progressive loss of lung function seen in patients with problematic severe asthma.

Epithelial damage is also seen in severe asthma, as well as airway smooth-muscle hypertrophy and hyperplasia. This is thought to contribute to the airway hyperresponsiveness seen in such patients. Airway smooth muscle has also been shown to be increased in children with persistent obstructive severe asthma. These data suggest that airway smooth-muscle hypertrophy and hyperplasia go hand-in-hand with hyperresponsiveness and obstruction seen in severe asthma.

Finally, an increase in the size and number of bronchial vessels has been seen in paediatric asthma and this has actually been linked to fatal disease in adults. A study with persistent airflow limitation. The vascular network is more pronounced in children of paediatric problematic severe asthma has shown that the vascular network is more pronounced in children with persistent airflow limitation.

INVESTIGATION AND ASSESSMENT OF SEVERE ASTHMA
It is important to ensure that all the basics are assessed prior to making the diagnosis of asthma and during the assessment of such. History is key in making the diagnosis of asthma. It is important to establish if reported wheeze is really wheeze; this can be done using videos or demonstrating the noise. If adherence is poor, this must be addressed. If additional diagnoses are present, they should be treated (e.g. psychosocial problems) and exposure to ongoing allergen should be eliminated, if possible. In problematic severe asthma, comorbidities need to be actively investigated for and excluded (e.g. gastro-oesophageal reflux, cystic fibrosis, vocal cord dysfunction, immune dysfunction).

Biomarkers are biological markers which can be measured and give information about the individual’s asthma, including the risk of morbidity, disease activity and treatment effects. They may also identify disease or disease phenotypes. An ideal biomarker can be obtained relatively non-invasively and cheaply. Relevant biomarkers for asthma outcome that have been suggested include allergen screening to define atopy, total IgE, blood eosinophil count, sputum eosinophils, exhaled nitric oxide (NO) and urinary leukotrienes.

PULMONARY FUNCTION
Characteristic features of asthma include bronchial hyperresponsiveness and reversible airway obstruction. Studies have shown that the usefulness of forced expiratory volume in one second (FEV1) as an indicator of asthma severity remains unclear. In paediatric severe asthma, bronchial hyperresponsiveness to methacholine has been shown to correlate with markers of asthma and airway inflammation, and is reduced by anti-inflammatory treatment. Furthermore, a negative test has been shown to have a high likelihood of excluding asthma in patients who have never been on asthma treatment.

MULTIPLE BREATH WASHOUT (MBW) TEST
MBW measures the clearance of an inert gas during tidal breathing and can be performed in children using a mass spectrometer. The lung clearance index (LCI) is calculated from this, and is a reproducible marker of overall lung ventilation homogeneity. An increase in LCI denotes an increase in lung inhomogeneity. Studies have suggested that it is more sensitive than spirometry at measuring small airways disease and correlates with structural lung damage. Studies have shown that LCI is abnormal in asthma and is a better discriminant of STRA than FEV1. It has also been shown to change more dramatically than FEV1, following high-dose steroid therapy.

FRACTIONAL EXHALED NITRIC OXIDE (FENO)
FeNO has been established as a noninvasive biomarker in asthma. NO is produced by NO synthase in airway epithelial cells and diffuses into the airway lumen. The possibility of using it as a predictor of risk has been suggested. Measurement requires a series of continuous expiratory manoeuvres using an incentive device. In a recent review, all school-age children with severe asthma were able to perform the manoeuvre and had measurable levels. FeNO has been shown to correlate with airway eosinophilia in asthma, and is elevated in asthma compared with controls. However, FeNO can be elevated in patients who are atopic and not asthmatic. Recently the Severe Asthma Research Program (SARP) cohort demonstrated that high FeNO levels were identified in patients with severe asthma; however, in a smaller paediatric cohort, FeNO did not discriminate between mild and severe asthma.

It had been postulated that tracking FeNO might be helpful in managing severe asthma, as it improves after steroid treatment and may predict exacerbations in pollen-sensitive asthma. However, it has been shown not to correlate with symptoms and a meta-analysis, which included three paediatric studies, showed that FeNO-guided treatment did not improve asthma outcomes.

INDUCED SPUTUM
Sputum induction can be performed after nebulisation of hypertonic (3.5% or 7%) saline. It requires trained staff.
Adult studies in severe asthma have shown that ICS treatment guided by sputum eosinophils reduces the incidence of exacerbations and doses of ICS. However, such results were not replicated in a study of childhood problematic severe asthma and more studies in this area are required before conclusions can be made.

**EXHALED BREATH CONDENSATE**

Exhaled breath condensate is obtained by cooling exhaled air and its composition is thought to mirror the airway lining fluid. It is thus used to measure airway inflammation and lung oxidative stress. Samples are collected in a condensing device formed by two glass chambers, into which patients breathe. Different approaches and methods of analysis have been used.

Biomarkers cysteinyl-leukotriene and 8-isoprostane have been shown to be elevated in exhaled breath condensate in childhood asthma compared with controls, and also in childhood problematic severe asthma. Levels of lipoxin A4 and leukotriene B4 have been shown to be increased in asthma and the ratio of lipoxin A4 to leukotriene B4 was shown to decrease with increasing asthma severity. A recent study has used a new approach, whereby proteolytic peptides were analysed in exhaled breath condensate of asthmatics and controls. It showed that exhaled breath condensate contains proteins which may have the potential for non-invasive asthma diagnosis and follow-up, but so far this technique is confined to research rather than clinical practice.

**HIGH-RESOLUTION CT (HRCT) SCAN**

Bronchial wall thickening is the most common change seen on HRCT in problematic severe asthma. HRCT may not always distinguish bronchiolitis obliterans from severe asthma. Bronchial wall thickening on HRCT has been shown to correlate with markers of airway remodelling, namely, reticular basement membrane thickness in adults with asthma, but this has not been shown in children. There is therefore no clear evidence to recommend routine HRCT as a clinical test in true STRA.

**ALLERGY TESTING**

Allergic sensitisation can be determined either by skin-prick testing to allergen extracts or by measurement of specific IgE in serum. In children with severe asthma, allergic diagnostic characterisation can be complex and there is a discordant in 20% of patients between the two methods. It is best therefore to perform both, as if only one is performed, there is a possibility of missing sensitisation to allergens. Furthermore, avoiding trigger allergens can reduce symptoms in severe asthma, thus necessitating the need for accurate results. As the majority (80-90%) of severe asthma is atopic, it is important to ensure that other lung diseases are investigated before making the diagnosis of STRA in a non-atopic patient.

Sensitivity to fungi including Aspergillus has been shown to confer a poor prognosis and greater airflow limitation in severe asthma. A randomised trial of antifungal therapy in adult severe asthma showed some benefits, but trials in children are sparse.

**BRONCHOALVEOLAR LAVAGE (BAL)**

Studies have shown elevated BAL and sputum eosinophilia in children with severe asthma compared with controls. Interestingly, despite the eosinophilia seen in these studies, no studies have shown a clear Th2 pattern of intraluminal inflammation, which may suggest that in patients with severe disease, although such inflammation plays a part in the process, there may be another pathway, accounting for continued inflammation. In a recent study, 31 children with severe asthma were compared with adult controls. There was evidence of neutrophilia. However, this was not shown in a more recent childhood study of STRA.

**SUBMUCOSAL INFLAMMATION**

Studies investigating airway inflammation in childhood severe asthma, where endobronchial biopsy via flexible bronchoscopy have been performed, are sparse. A recent large study showed that despite high doses of inhaled and systemic steroids, patients with problematic severe asthma had significant eosinophilia in BAL and endobronchial biopsies compared with controls. Interestingly, despite submucosal eosinophilia, submucosal Th2 cytokines were not significantly elevated in STRA compared with controls. This is in contrast to the adult data which show elevation in IL-5 and IL-13 in submucosa compared with controls. This, along with the BAL data, may suggest that there is an alternative airway inflammation pathway in childhood STRA. There may be IL-17-induced inflammation, which is a cytokine secreted by Th17 cells. Recent data suggest that IL-17+ cells in endobronchial biopsies are elevated in a disease-severity-dependent manner. Th17 cells seem to function to clear pathogens inadequately addressed by Th1 or Th2 cells. They are stimulated by IL-6, IL-21, IL-23, IL-18 and transforming growth factor beta, and secrete IL-17, IL-21 and IL-22. Recently, IL-33+ cells were found to be elevated in STRA compared with controls, and this also correlated with reticular basement membrane.
In paediatric patients submucosal neutrophil numbers show no differences between severe asthma and controls. This is in contrast to adult severe asthma which exhibits submucosal neutrophilia. mast cell myositis has been described in adult asthma and has been shown to link with increased airway hyperresponsiveness (AHR). This has not so far been investigated in paediatric asthma.

**TREATMENT**

**inhaled corticosteroids**

Treatment with ICS is the mainstay of treatment for childhood asthma. A number of studies have examined the use of a single inhaled therapy in the form of a combined ICS and LABA inhaler as both maintenance and reliever therapy, for the treatment of asthma. One of the first large double-blind randomised controlled trials, inclusive of children with mild to moderate asthma, used intermittent therapy with combination of formoterol/budesonide for maintenance and reliever (Symbicort maintenance and reliever therapy (SMART)). This study showed a 45% reduction in exacerbation rate and improvements in FEV1 compared with fixed dosing. A further paediatric study showed similar results. A recent Cochrane review concluded that single inhaler therapy reduces exacerbations but reiterated that there were scanty data in childhood asthma.

Several studies point to the timing of ICS use rather than the dose per se being most important in asthma, and a recent large trial examined ICS use at the time of a viral exacerbation in children. The lowest numbers of exacerbations were in those patients on continuous ICS compared with controls, and in those on intermittent ICS therapy compared with controls, with improved growth parameters in the latter. This study suggested that intermittent ICS might be effective in mild persistent asthma as a step-down therapy.

A small-particle ICS, ciclesonide has recently been trialled and shown improved lung deposition. It is a pro-drug with a high degree of serum protein binding, low oral bioavailability, and rapid systemic elimination. However, a recent Cochrane review of its use in childhood asthma was inconclusive and recommended more trials to investigate its efficacy compared with other ICS.

**Steroid Sensitivity**

Steroid sensitivity should be assessed in severe therapy-resistant asthma. It is important to investigate and reduce potential reversible causes of steroid resistance (e.g. allergic triggers, smoke exposure, obesity). Furthermore, in some patients increasing the dose of steroids may not improve symptoms and thus steroid-sparing agents may need to be considered, such as methotrexate, azathioprine or ciclosporin, all of which have potentially significant side-effects. Some patients may benefit from additional treatments which may improve steroid sensitivity such as vitamin D supplementation (discussed later).

**Systemic Steroids**

The use of oral prednisolone is still current practice in patients in whom there are continued symptoms/exacerbations despite ICS, LABA and LTRA. Serum cortisol and prednisolone levels can be performed to assess adherence to such medications, but when adherence is in question and in severe disease, intramuscular triamcinolone has been shown to be beneficial. All children on high doses of ICS and systemic steroids should be closely monitored for side-effects, e.g. growth suppression, adrenal suppression, hypertension, diabetes and behavioural problems.

**Omalizumab**

Omalizumab is a recombinant, humanised monoclonal antibody which binds to circulating free IgE and prevents its binding to the high-affinity IgE receptor (FcεRI) on effector cells such as mast cells, basophils and also on dendritic cells. This results in a blocking of mediator release from these cells and also the inhibition of antigen presentation by dendritic cells. In addition, omalizumab downregulates FcεRI expression on these cells. Omalizumab is thus aimed at reducing the early-and late-phase asthmatic responses. It can be used in patients with ongoing symptoms despite high doses of ICS or with intermittent severe exacerbations, or who have one or more allergens to which they have IgE-mediated sensitisation. Due to its binding to IgE, it is dosed according to the serum IgE level and weight of the patient. Administration is inconvenient and requires fortnightly or monthly injections, but it is one of only a few licensed therapies for severe asthma in children.

Initial studies on children with moderate to severe asthma showed that patients on omalizumab managed ICS dose reduction, and more recently, a study demonstrated a reduction in exacerbations of 31% in children aged 6 to 12 years. Omalizumab has been shown to improve quality of life and symptom-free days in paediatric asthma. It is being used in paediatric STRA and has shown promising results.

**Low-dose Theophylline**

Oral theophylline has recently been re-assessed for its usefulness in the treatment of severe asthma. At low doses (serum levels 5-10 μg/ml) it can be helpful at improving steroid responsiveness. It down-regulates...
inflammatory gene expression by its action on histone acetylases and histone deacetylases. It also accelerates neutrophil apoptosis, but despite all of these molecular data, the clinical effects of adding oral theophylline in STRA appear to be mild.77

VITAMIN D
Recent studies have shown an association between low serum levels of vitamin D and asthma, and have suggested commencing vitamin D supplementation if levels are low. The study by Gupta et al.64 reported that increased airway remodelling correlated to levels of vitamin D in children with severe asthma, but not in children with moderate asthma or healthy controls. Furthermore, Brehm et al.78 showed that the risk of asthma exacerbation was increased in children with low levels of vitamin D. Chinellato et al.79 showed an association between exercise-induced asthma and vitamin D levels.

CONCLUSION
We have described a number of advances in our understanding, assessment, monitoring, and treatment of children with severe asthma. There are very few licensed treatments for this challenging group of children, including high-dose inhaled steroids, SMART regimen and anti-IgE therapy. It is therefore even more important to ensure that the basics are right, as often, simple measures can improve symptoms and avoid escalation of treatment. Adequacy must be optimised, comorbidities treated, allergen load reduced to a minimum and inhaler technique regularly checked.

Declaration of conflict of interest
The authors declare no conflict of interest.

REFERENCES
1. Log on to the secure members only section at www.allergysa.org by clicking ‘My Society’ and then choose the block headed ‘Update your details’.

Please follow these steps:

1. Please ensure that your details are up to date so that you will receive your journals and email updates of ALLSA events and communication.

2. Click on ‘Update your details.’ Add any relevant information (HPCSA number, email address, etc.) Click SAVE on each page as you complete it before moving to the next page (e.g. email address is on Communications page while HPCSA number is on Biographical page).

Notice to all ALLSA members — Please update your details

Please ensure that your details are up to date so that you will receive your journals and email updates of ALLSA events and communication.

Please follow these steps:

1. Log on to the secure members only section at www.allergysa.org by clicking ‘ALLSA members’ and entering your username and password (obtainable from the ALLSA office).


63. Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best