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Review

An approach to the management of children with problematic severe asthma

Valentina Fainardi [1], *Sejal Saglani* [2]

[1] Department of Medicine and Surgery, Pediatric Respiratory Unit, Pietro Barilla Children's Hospital, Parma University Hospital, Parma, Italy; [2] Department of Respiratory Paediatrics, Royal Brompton & Harefield NHS Foundation Trust, London, UK

Summary. Children with poor asthma control despite high levels of prescribed treatment are described as having problematic severe asthma. Most of these children have steroid sensitive disease which improves with adherence to daily inhaled corticosteroids and after having removed modifiable factors like poor inhalation technique, persistent adverse environmental exposures and psychosocial factors. These children are described as having "difficult-to-treat asthma" while children with persistent symptoms despite above-mentioned factors having been addressed are described as having "severe therapy-resistant asthma". In this review, we will describe the 6-step approach to the diagnosis and management of a child with problematic severe asthma adopted by The Royal Brompton Hospital (London, UK). The role of a multidisciplinary team is crucial for identification and treatment of modifiable factors and comorbidities in order to avoid invasive examinations and useless pharmacological treatments. The current knowledge on add-on therapies will be discussed.

Key words: Severe asthma, problematic asthma, steroids, children, allergy, multidisciplinary, management

Introduction

Asthma is the most common chronic disease in childhood affecting up to 20% of children depending on geographical area (1). Asthma in children aged 6 years and older is characterised by symptoms of wheeze, breathlessness and/or cough, with associated aero-allergen sensitisation, eosinophilic airway inflammation and remodelling. Low doses of inhaled corticosteroids (ICS) are usually successful in achieving good symptom control and minimising acute attacks in the majority of children. However, there is a small subgroup that remain symptomatic, have frequent exacerbations and/or persistent airflow obstruction despite maximal recommended prescribed therapy, including high dose ICS, long-acting beta$_2$ agonists (LABA) and/or leukotriene receptor antagonists (LTRA) (2). Children with poorly controlled asthma despite maximal prescribed therapy are considered to have "problematic severe asthma" (3) which is estimated to include approximately 5% of all asthmatic children aged 6 years and older (4). The definition of maximal prescribed therapy varies in different guidelines. The definition and cut-off according to ERS/ATS guidelines of high dose therapy for school-aged children is summarised in Table 1 (5). Uncontrolled asthma can affect the child's daily activities including limitations in physical exercise, night awakenings, absence from school and frequent use of reliever medications such as bronchodilators (6). In addition, persistent asthma and

recurrent exacerbations are associated with long-term consequences like impaired growth, side-effects due to the pharmacological treatment (7) and reduced lung function which may persist into adulthood (8). Among children with problematic severe asthma it is crucial to distinguish those with "difficult-to-treat asthma" because of wrong diagnosis or modifiable underlying factors (asthma plus co-morbidities) from those with true "severe, therapy-resistant asthma" (STRA) who have persistent symptoms despite optimization of the basics of asthma management.

Definitions

Difficult-to-treat asthma

Children with difficult-to-treat asthma have persistent poor asthma control because of underlying reversible or modifiable factors, which if addressed, will result in improved control and potential reduction in the amount of treatment needed. The reversible factors causing symptoms can be environmental factors like persistent exposure to tobacco smoke, or to aero-allergens that the child is sensitised to. There may be subject-related factors contributing to poor control, such as poor inhaler technique, poor adherence to treatment and the presence of other comorbidities (gastroesophageal reflux, obesity, breathing pattern disorders, psychosocial issues). Up to 60% of children referred for further investigation with a diagnosis of severe asthma were found to have difficult-to-treat asthma due to modifiable factors. Poor adherence to maintenance ICS treatment is one of the most common causes of poor control (9).

Once the modifiable factors are addressed (details of how to identify and treat modifiable factors are given below), children with difficult-to-treat asthma usually achieve better asthma control without the need for escalating therapy because they are not truly resistant to the medications. However, difficult asthma can become refractory because of ongoing poor adherence despite all efforts or due to persistent environmental exposures such as pet allergens and tobacco (10).

Severe therapy-resistant asthma (STRA)

STRA describes those children with persistent symptoms and/or frequent exacerbations despite high-dose ICS and LABA, after the exclusion of any underlying factors and after that the basics of asthma management have been addressed. These patients require detailed assessments in order to phenotype their airway disease as they will require escalation of therapy and can be the right candidates for novel biologicals.

A Structured Approach to the Management of Problematic Severe Asthma

All children meeting the criteria for problematic severe asthma and on high doses of treatment (Table 1) should be referred to a tertiary paediatric respiratory centre for a full multidisciplinary assessment and further investigations and management. Here we describe the 6-step protocol for school-aged children with problematic severe asthma followed by the Paediatric Difficult Asthma team at the Royal Brompton Hospital (London, UK) (Fig. 1).

Step 1. Confirm the Diagnosis of Severe Asthma

The initial step is to confirm the diagnosis of asthma and consider alternative or associated diagnoses (differential diagnoses are described in Table 2). The key features of childhood severe asthma are confirmed wheeze, reversible airflow obstruction, allergic sensitisation and airway eosinophilic inflammation. Each of these must be considered in turn and the evidence upon which a diagnosis of asthma has been made must be clearly documented in each case.

Include a detailed medical history and examination, skin prick tests for aero and food allergen sensitisation, spirometry with bronchodilator response, measurement of airway inflammation with exhaled nitric oxide (FeNO) (2). A chest X-ray is also usually performed.

Table 1. Definition of "uncontrolled asthma" for patients aged >6 years [(adapted from Chung KF et al. (5)]

Definition of "uncontrolled asthma" for patients aged ≥6 years

Asthma which is uncontrolled on therapy with:

- High daily dose ICS

	6-12 yrs	**>12 yrs**
Fluticasone propionate	≥500 (DPI or HFA MDI)	≥1000 (DPI or HFA MDI)
Beclomethasone dipropionate	≥800 (DPI) or ≥320 (HFA MDI)	≥2000 (DPI) or ≥1000 (HFA MDI)
Budesonide	≥800 (DPI or MDI)	≥1600 (DPI or MDI)

PLUS

- additional controller (LABA, LTRA, theophylline) OR systemic CS for ≥50% of the previous year to prevent it to become uncontrolled

AND

presence of at least one of the following:

- Poor symptom control according to the published questionnaires (ACQ >1.5, ACT <20)
- Frequent severe exacerbations: >2 courses of systemic CS for >3 days in the previous year
- Serious exacerbations: at least 1 hospitalisation, ICU stay or mechanical ventilation in the previous year
- Airflow limitation: FEV_1 <80% predicted after bronchodilator (with reduced FEV_1/FVC)

ICS, inhaled corticosteroids; DPI: dry powder inhaler; HFA: hydrofluoroalkane; MDI: metered-dose inhaler; LABA, long-acting beta$_2$ agonist; LTRA: leukotriene receptor antagonist; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CS, corticosteroids; ICU, Intensive Care Unit; FEV_1, forced expiratory flow in 1 second; FVC, forced vital capacity.

History and examination

Medical history is essential to assess symptom onset, child growth, previous wheezing episodes confirmed by a doctor, clinical response to bronchodilator and symptoms characteristics (wheeze, cough, chest tightness, shortness of breath).

The presence of unusual features like persistent nasal polyps, wet cough or recurrent middle ear infections should alert the clinician to consider additional investigations such as nasal epithelial cell brushing or sweat test to exclude primary ciliary dyskinesia or cystic fibrosis.

Assessment of atopic status

The majority of children (>85%) with severe asthma are atopic, have a positive family history for asthma and show a certain degree of eosinophilic inflammation with multiple aero-allergen sensitization (11). Skin prick tests for aeroallergens (house dust mites, trees, grass pollen, pet dander), food (cow's milk, eggs, peanuts, tree nuts, fish) and moulds (A*spergillus fumigatus*, *Alternaria alternata*), serum total IgE and specific IgE tests are performed to determine the atopic status. If a child is non-atopic, then it is essential that any alternative diagnoses are considered and excluded.

Evidence of airflow obstruction (reduced FEV_1/FVC ratio <0.80)

Although most children with asthma will have a normal baseline spirometry when they are well (12), the presence of reversible airway obstruction after bronchodilator (increase in FEV_1>12% predicted and at least 200 ml following short-acting beta$_2$ agonists) needs to be demonstrated to confirm the presence of asthma. If bronchodilator reversibility is not apparent, then it may be necessary to undertake tests of airway hyperresponsiveness such as a histamine or methacholine challenge to support the diagnosis.

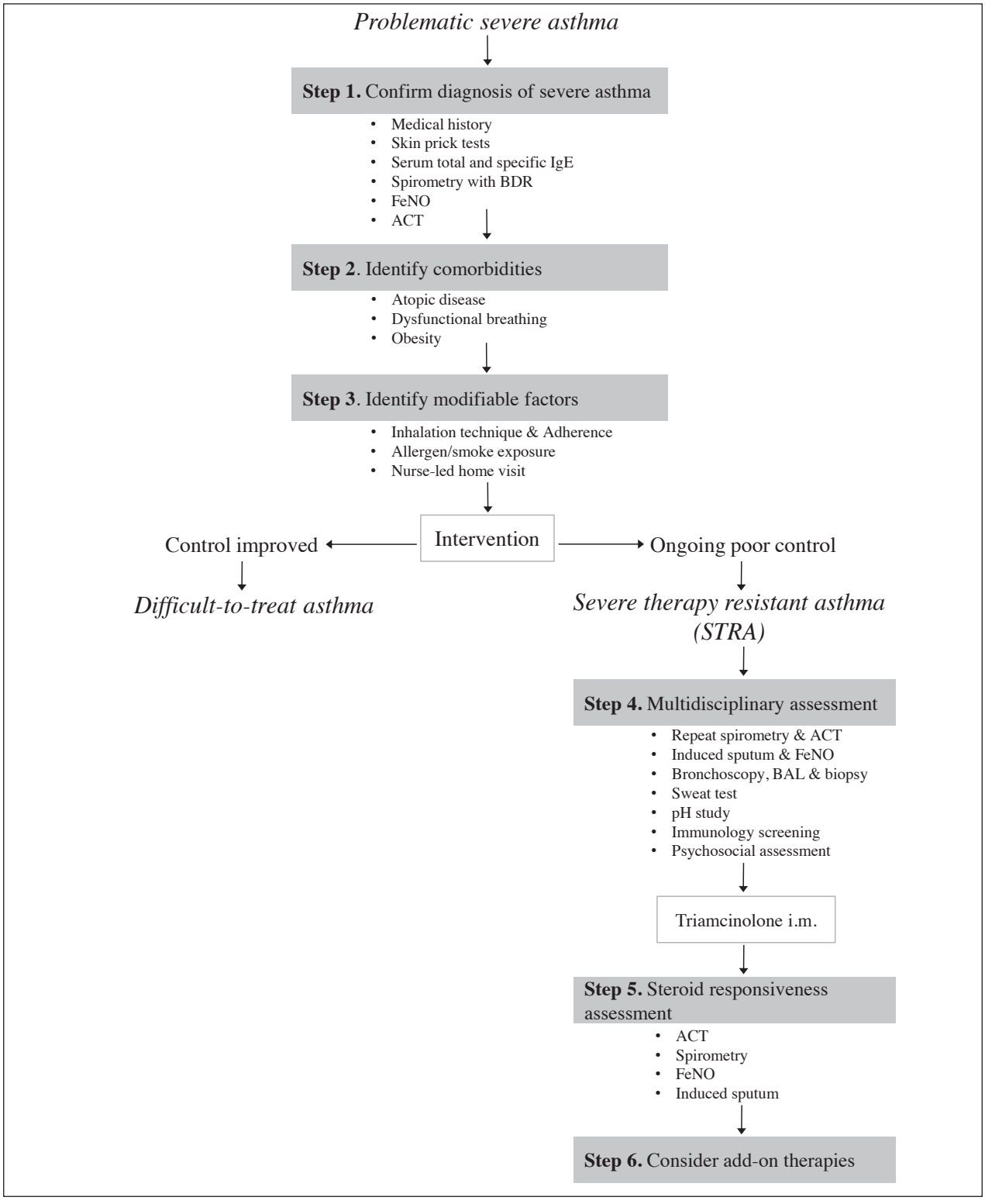

Figure 1. Six-step protocol followed by the respiratory team at the Royal Brompton Hospital for children with problematic severe asthma.
BDR, bronchodilator responsiveness; FeNO, fractional exhaled nitric oxide; ACT, Asthma Control Test; BAL, bronchoalveolar lavage.

Table 2. Differential diagnosis of severe asthma.

Differential diagnosis of severe asthma
Respiratory disease • cystic fibrosis • primary ciliary diskinesia • BPD due to prematurity • protracted bacterial bronchitis
Immunodeficiency
• Airway obstruction • tracheo or bronchomalacia • laryngeal or tracheal web • vascular ring or vascular compression • enlarged lymphonodes • foreign body • congenital lobar emphysema • tumor
Airway aspiration • laryngeal cleft • vocal cord palsy • tracheoesophageal fistula • gastroesophageal reflux disease • neurological disease
Congenital heart disease
Interstitial lung disease
Dysfunctional breathing • exercise induced laryngeal obstruction (EILO) • hyperventilation syndrome

BPD, bronchopulmonary dysplasia.

Airway inflammation

Children with STRA have airway eosinophilia despite high dose steroid therapy (11, 13). Eosinophilic airway inflammation may be assessed indirectly by peripheral blood eosinophil count and by FeNO (elevated if ≥35 ppb in steroid naïve children) and directly by induced sputum and bronchoscopy. However, it is important to remember that in children whose adherence to maintenance therapy has been optimised, peripheral eosinophilic inflammation can be difficult to identify. Sputum eosinophils provide a better reflection of lower airway eosinophilia, but induced sputum can be difficult to obtain and processing for cytology may be a challenge (11) and blood eosinophils rarely account for airway eosinophils (14). FeNO can be useful to assess response and adherence to steroid treatment and to identify patients with steroid refractory asthma. However, FeNO may be very variable in children with STRA, some may have normal levels with poor control, and others may have very persistently elevated FeNO which may be because of their significant atopy, or because airway inflammation. The FeNO trend longitudinally over time may be useful to identify those children who have stopped taking their treatment and there is some suggestion that children with high FeNO despite good adherence may respond best to biologics targeting type$_2$ immune pathways (omalizumab or mepolizumab) (15).

Step 2. Identify Comorbidities

During the first medical assessment the presence of comorbidities should be identified.

Atopic diseases such as rhinosinusitis, dermatitis or food allergies can be associated with severe asthma and poor control and deserve appropriate treatments. Obesity is a recognized risk factor for problematic severe asthma. Asthma in obesity can be non-eosinophilic and instead mediated by IL-6 driven inflammation (16). In these cases assessment of airway inflammation via FeNO or peripheral blood eosinophil count is recommended. Furthermore, cardiopulmonary deconditioning is often associated with obesity and may contribute to difficult asthma.

When evaluating a child with persistent dry cough, gastroesophageal reflux can be suspected but it is demonstrated that treatment with protonic pump inhibitors does not influence asthma control (17, 18). Gastroesophageal reflux should only be treated if the child is symptomatic, as treatment is unlikely to influence asthma control.

Dysfunctional breathing can contribute to poor asthma control. It has been found in up to 5% of children with severe asthma followed-up in the outpatient clinic (19) and in 23% of a cohort of children with problematic severe asthma admitted to the hospital for an intensive inpatient stay (20). Symptoms include dyspnoea with normal pulmonary function, deep sighing, chest pain, chest tightness, frequent yawning, hyperventilation and breathlessness during exercise. It is often associated to emotional stress and when addressed with breathing and relaxation exercises (nose breathing, appropriate use of the diaphragm) under the supervision of a physiotherapist can improve asthma symptoms and overall quality of life (QoL) (21). However, the majority of studies have been conducted in adults and at present we do not have a valid screening instrument for dysfunctional breathing in children.

Step 3. Identify Modifiable Factors

Ensuring that the basics of asthma management are addressed is crucial to identify patients with true STRA. Basic modifiable factors include adherence to therapy, inhaler administration technique and allergen and smoke exposure.

Adherence to maintenance therapy

After confirming the diagnosis of asthma, the next essential step is to ensure the child's maintenance treatment is being taken correctly. Good adherence is defined when ICS are administered for at least 80% of the prescribed dose (22). Adherence is a major problem in patients with asthma. In 2014 80% of asthma deaths in the United Kingdom occurred in people who had picked up less than the expected number of prescriptions for maintenance ICS while up to 40% had picked up more than 12 prescriptions for acute bronchodilators in the previous 12 months (23).

- *Monitoring adherence:* Adherence needs to be checked at every out-patient visit although self and parental-reported adherence usually overestimates the treatment taken (24). In the Royal Brompton Respiratory unit adherence assessment is performed by a specialist nurse who visits the home of the patient to ensure the medicines are available, in date and that there is no excessive stock piling. Also prescription uptake from the general practitioner or from the hospital is calculated for the previous 12 months. Errors in medication use can be found in 20-25% of children with difficult asthma (9).

Electronic monitoring devices which record date and time of therapy administration are also used as an objective assessment of monitoring adherence. In a study conducted at the Royal Brompton Hospital almost a quarter of the children monitored with an electronic device showed improved adherence with improved asthma control. Interestingly, persistent poor control despite electronically recorded good adherence to treatment revealed a cohort of children with true severe asthma deserving further investigations (25).

- *How to optimise adherence:* To enhance adherence an attempt can be made simplifying the therapeutic regime through the SMART therapy with Symbicort (budesonide/formoterol: both preventer and reliever inhaler) or prescribing a single dose inhaler like Relvar (fluticasone furoate/vilanterol).

The family environment must be aware of the importance of taking asthma medications. The beliefs that families have about asthma and the prescribed medications have a significant impact on treatment adherence. Social and psychological support may be required to improve asthma education (how to manage asthma, use the medications, recognize triggers and when to appropriately seek further medical advice), make and maintain positive behavioral changes in the daily life. To limit mistakes a written, personalised asthma management plan with the prescribed medications (when and how to take them, dosage, therapy duration) and about the signs of an exacerbation should be provided to all patients (Fig. 2) (26).

Inhaler reminders are another possible option. Associated to electronic monitoring, they have been proven to improve adherence, reduce exacerbations and admission to the hospital (27, 28).

When family needs further support directly observed administration of ICS at school can be a valid alternative to improve adherence. Directly observed therapy (DOT) at school has been associated to improvement in asthma symptom control and decrease in exacerbations (29) suggesting that integration with community can be recommended when dealing with high risk children.

If there are significant concerns about adherence, a hospital admission where treatments are given by nursing staff as DOT can be useful to demonstrate poor adherence as a reason for the asthma being difficult to treat. If adherence is optimized, asthma symptoms improve, spirometry normalizes and FeNO decreases, this demonstrates previous non-adherence to treatment in the home environment as a reason for poor control (20, 30).

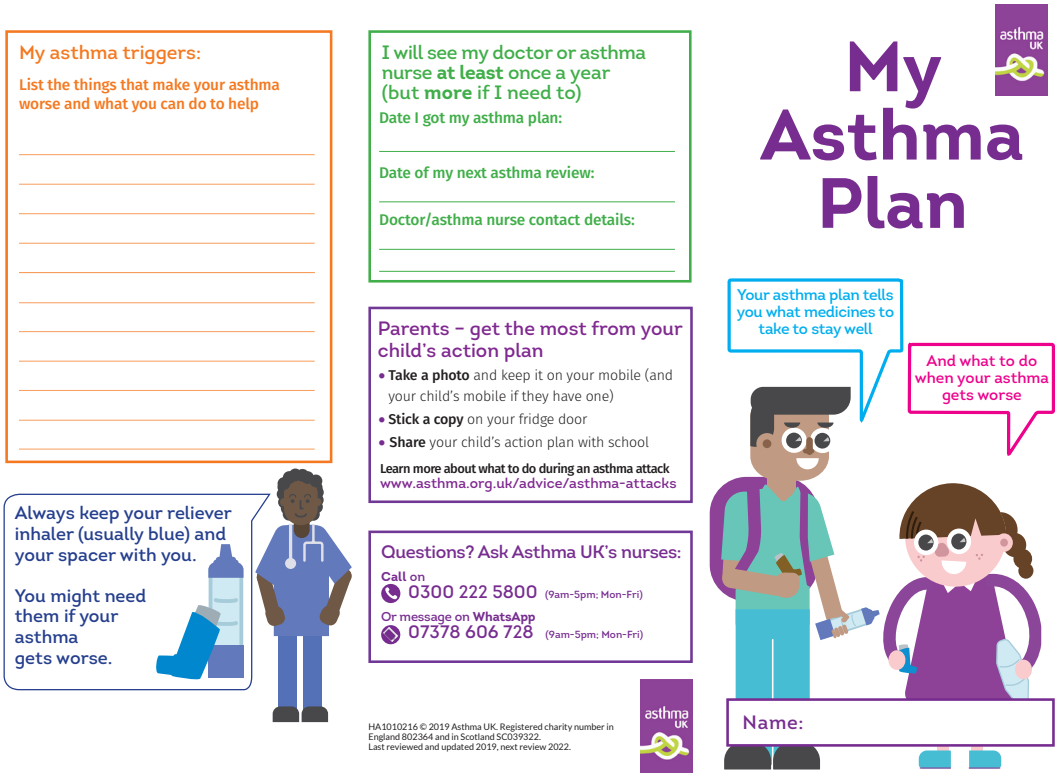

Figure 2. Example of children's asthma plan (26).

Inhaler technique and device

Regarding the inhalation technique, this needs to be checked at every out-patient visit. The family should bring their inhalers and spacer and demonstrate how the medicine is taken and the technique should be corrected at every opportunity (31). According to the team experience, poor inhaler technique can be found in up to 40% of children assessed for severe asthma (9). All metered dose inhalers must be used with a spacer and children aged 4 years and older should use the spacer via mouthpiece and not with a mask. Dry powdered devices should be reserved for those children able to hold breath and to take a forceful inhalation, this is usually limited to children aged approximately 9 years and older.

Environmental exposures

In addition, the specialist nurse considers the home environment including smoke and allergen exposure (especially dust and pets, if the child is sensitised to these). Advice about minimising house dust is given (avoid carpets, curtains and stuffed toys, wash bedding weekly in hot water, use house dust mite-impermeable bedding if possible), as there is evidence of improved control and fewer attacks in children with more severe disease (32), and families are counselled about pets especially if a child is having frequent attacks when exposed to a pet that they are sensitised to. Urinary or salivary cotinine levels are measured as objective markers for both active and passive smoking. This is important since smoke exposure is associated with increased resistance to steroids (33). Discussing the results with the parents can be very useful to convince the parents to seek advice for smoking cessation.

Step 4. Multidisciplinary Assessment

Once it is confirmed that the child has asthma and any basic associated factors that could have prevented the patient from achieving asthma control have been modified (i.e. adherence and inhalation technique, exposure to allergens or smoke), the respiratory team discuss the case in multidisciplinary meetings (a doctor, a nurse, a psychologist and a physiotherapist are always present) to decide for further investigations to identify more complex comorbidities and to phenotype airways.

Psychosocial factors can significantly contribute to asthma control. In a retrospective review of the Royal Brompton Hospital management of problematic severe asthma up to 39% of patients had psychosocial issues (9). These can be assessed with specialists through appropriate questionnaires with the aim of exploring and understanding the factors that may affect asthma management. Anxiety about asthma, family relationships, poor adherence, difficulty about understanding the disease, school problems and refusal of symptoms are all issues that can be encountered when assessing problematic severe asthma.

Breathing pattern disorders like vocal cord dysfunction, hyperventilation and exercise induced laryngeal obstruction (EILO) are often associated with asthma and anxiety. For this reason when assessing problematic severe asthma a psychologist and a physiotherapist should always be part of the multidisciplinary assessment. EILO typically presents as dyspnoea during physical exercise and is determined by the adduction of the vocal cords in inspiration. The gold standard diagnosis is the laryngoscopy during exercise and, when confirmed, the help of a physiotherapist is required. In cases where dysfunctional breathing is identified, children are taught to normalise breathing using breathing exercises, nose breathing and appropriate use of the diaphragm (34).

When complex comorbidities are assessed, fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial biopsy are undertaken to characterize airway inflammation, to exclude underlying airway infection and eventually tailor the treatment. Bronchoscopy allows direct visualization of the airways including structural anomalies, airway compressions or foreign bodies; BAL analysis gives information on the presence of pathogens while cell count and airway biopsy depict the type and the level of inflammation and remodelling.

Additional blood test are performed to exclude deficits in immune system activity (serum IgA, IgG, IgM, IgG subclass concentrations and lymphocyte subpopulations) and to better define the allergic status

(total IgE, IgG precipitins to *Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum, Penicillium Chrysogenum, Candida albicans*). The identification of severe asthma with fungal sensitization may lead to a trial with a specific anti-fungal therapy and total serum IgE can be very important if anti-IgE antibody therapy is being considered.

Patients usually undergo a pH study during a 24-hour admission to assess the presence of gastroesophageal reflux. However, published studies report that in children with asymptomatic acid reflux and uncontrolled asthma daily treatment with lansoprazole does not improve asthma control , (17, 18).

When excessive use of short-acting bronchodilator is reported or in case of discrepancy between symptom reporting and objective markers of disease severity, a multidisciplinary assessment may need to be undertaken during an in-patient stay. Most patients significantly improve in terms of lung function, FeNO and exacerbations during a 2-week admission demonstrating poor compliance with the therapy at home or suggesting a distorted perception of symptoms (20).

Step 5. Steroid Responsiveness Assessment

If the investigations show eosinophilic airway inflammation the decision of undertaking an intramuscular injection of triamcinolone (40 mg for age <12 years; 80 mg for age >12 years) to assess steroid response can be made. Corticosteroids may have a role in identifying steroid responsive asthma and triamcinolone can be particularly useful in patients with poor adherence to inhaled and/or oral CS. A multidomain assessment is used to evaluate CS response and therefore the presence of CS resistance. This includes the assessment of asthma symptoms with the Asthma Control Test (ACT), airways inflammation with sputum induction and FeNO and spirometry. Triamcinolone administration is considered effective if the patient shows: a) increase of 50% or more in the ACT score or a score >19/25; b) a FEV_1 of 80% or more predicted, or an increase of at least 15%; c) normalization of the sputum eosinophils (<2.5%) and FeNO (<24 ppb). On the basis of the multidomain assessment the respiratory team decides whether or not to reduce the CS therapy and consider add-on therapies such as anti-IgE antibodies. Data of the Royal Brompton cohort showed that a decrease in airway inflammation after triamcinolone administration was associated to a good clinical response to omalizumab (35).

Step 6. Consider Add-on Therapies – according to Phenotype

Tiotropium bromide, a long-acting muscarinic antagonist, is an attractive option for children aged >12 years not responding to usual therapy with ICS. It acts by inhibiting smooth muscle contraction and mucus secretion through the block of the muscarinic acetylcholine receptor. In phase III trials tiotropium improved lung function in adolescents on continuous ICS (36). This may be considered in children with persistently low lung function and those with persistent airflow limitation.

Omalizumab is widely used in children >6 years with STRA meeting certain criteria (39). Omalizumab is a recombinant DNA-derived humanized monoclonal anti-body against IgE which reduces IgE and downregulates high-affinity IgE receptors FcεRI on mast cells, basophils and dendritic cells. Omalizumab is prescribed according to local guidelines. In the UK this is determined by the National Institute for Clinical Excellence (NICE) guidance. It can be prescribed in children who are sensitised to aero-allergens (positive specific IgE or skin prick test to at least one aeroallergen) and have a total IgE between 30 and >1500 IU/mlml. However, the difficulty is that approximately one-third of children with STRA have an IgE >1500 IU/ml, and are not eligible for omalizumab, and only approximately 50% respond to the treatment.

In three randomized controlled trials omalizumab to reduce the dose of ICS, improve QoL and showed to reduce the number of exacerbations without any serious adverse events (38). The main outcome that improves following omalizumab is asthma exacerbations, however, it is difficult to predict which child will respond best to the treatment and often a trial of treatment is needed. In a recent retrospective French study in pediatric patients, mean annual exacerbation rate and hospitalizations were reduced by 70.4% and

73.2% respectively but omalizumab efficacy was similar in patients with high and low blood eosinophils (39). If blood eosinophils can be the only biomarker to predict the response to omalizumab is a matter of debate. In addition, long-term safety and efficacy have been evaluated in adults (40) but not yet in a paediatric population. At the Royal Brompton Hospital the response to omalizumab is assessed every 16 weeks with ACT, history of asthma attacks, FeNO values, induced sputum eosinophils and spirometry with bronchodilator response. A 16-week period off omalizumab is usually considered after 12-18 months of treatment; lung function, symptoms and airway inflammation are then monitored monthly to determine the need to restart the therapy. Since most asthma deaths are in children who do not adhere to maintenance therapy and have Refractory Difficult Asthma (41), children with persistent poor adherence and at high risk of asthma death should undergo airway phenotyping and be considered for biologics.

Considering most children with STRA have a Th_2-high eosinophilic airway inflammation, a promising add-on therapy may be the monoclonal antibody to interleukin (IL)-5 that reduces circulating eosinophils. Mepolizumab was licensed in Europe for use in children with severe asthma aged 6 years and older (with peripheral blood eosinophils of at least 300 cells/ul) in August 2018 based only on safety data from a single study of 36 subjects aged 6 to 11 years (42). In adults the DREAM trial showed that mepolizumab resulted in a significant reduction in exacerbations in adults and adolescents with severe asthma and no adverse effects (43).

Subcutaneous administration of mepolizumab in children 6 to 11 years of age with severe eosinophilic asthma was associated with a significant reduction in blood eosinophils, reduced rate of exacerbations and improved asthma control (42).

However, the real benefit on lung function is still unclear and more trials are needed to confirm the efficacy of this therapy in children (44). Moreover, the relationship between peripheral blood eosinophils and airway eosinophils is still controversial since elevated airway eosinophils may persist despite a normal blood eosinophil count obtained with high dose ICS (14).

Follow-up

Once the patient is diagnosed with STRA, clinicians should consider regular follow-up, ideally every 3-4 months or more depending on clinical conditions. The goals are: reduction of the maintenance therapy until the minimal amount needed to achieve control and promote self-management and medication adherence.

Control visits and annual review

Every 3-4 months each patient with STRA should be reassessed in the out-patient clinic in order to evaluate asthma control, QoL, airway inflammation with FeNo, lung function, inhalation technique, treatment adherence and medical history.

Asthma control is evaluated with the childhood ACT (c-ACT), developed for children aged 4-11 years, or the ACT, developed for children aged >12 years. The test consists of five items and assess symptoms in the past 4 weeks including night awakening, limitation of activities and use of short acting $beta_2$ agonists. A score ≤19 suggests uncontrolled or partly controlled asthma. However, this cut off has been questioned since it might underestimate the proportion of children with uncontrolled asthma (45).

In children with severe asthma, poor control and airway obstruction are associated with poor QoL (46). In the follow-up of STRA patients QoL is regularly assessed with the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) which evaluates symptoms, activity limitation and emotional function. A score ≥5.87 on total QoL is considered to reflect adequate QoL (47).

Regular measurement of FeNO is recommended. Values of FeNO >35 ppb are likely connected with Th_2-mediated airway inflammation, airway eosinophilia and responsiveness to ICS. The use of FeNO to tailor the dose of ICS is not recommended but it may be helpful for tapering, rather than for stepping up, the treatment (48). Its utility has been recognized as an indicator of the child's compliance with the prescribed therapy. However, contradictory results have been reported on the role of FeNO as biomarker to assess

asthma control and as predictor of asthma exacerbations (49, 50). FeNO may provide useful information about airway inflammation and playing a complementary role in the management of asthma especially when combined to lung function tests (51).

Lung function with spirometry with bronchodilator response should to be performed at each visit to track the patient over time and investigate the presence of persistent airway obstruction which can be a risk factor for exacerbation. Inhaler technique and adherence to medications have to be regularly checked. When on biologics, every 16 weeks eosinophils need to be assessed via blood test and induced sputum.

A detailed medical history needs to be recorded in order to evaluate the patient for asthma attacks, environment exposure and treatment adverse effects.

Long-term therapy with ICS may cause suppression of the hypothalamo-pituitary adrenal axis leading to adrenal suppression in 24-32% of children (52-54).

During the annual review, a short Synatchen test can be considered in patients on ICS >400 mcg/day for more than 2 years and especially in those also treated with nasal steroids (52, 53). Furthermore, complete clinical examination including weight and linear growth should be done. Reassessment of sensitisation with prick test can be considered yearly.

Conclusions

The management of a child with problematic severe asthma is challenging and starts with the confirmation of the diagnosis. The respiratory clinician must exclude any differential diagnosis, recognise comorbidities and intervene on any underlying modifiable factors that may contribute to difficult-to-treat asthma in order to avoid invasive examinations and useless pharmacological treatments. Most children with asthma can be controlled with low doses of ICS and if environmental factors are solved. Additional investigations and therapies must be reserved for patients with true STRA or, in selected cases when parents cannot address environmental issues or will not follow the indications, to patients with refractory difficult asthma (55). Adherence is a major problem that can present at any stage of the follow-up and also in a child with STRA and needs to be systematically addressed. The contribution of different professionals able to perform a multidisciplinary assessment is essential for a 360 degrees-approach to our patient's asthma.

Both patients with difficult asthma and STRA should be followed-up every 3-4 months to ensure that the asthma basics (adherence to therapy, inhalation technique, allergen and smoke exposure) continue to be addressed and to monitor any progression of the disease and the need for additional therapies.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:
Dr. Valentina Fainardi
Pediatric Respiratory Unit, Pietro Barilla
Children's Hospital, Department of Medicine and Surgery,
Parma University Hospital - 43126 Parma, Italy
+39 0521 702198
E-mail: vfainardi@ao.pr.it