



Severe asthma in childhood: diagnostic and management challenges

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Purpose of review

Problematic severe asthma is a heterogeneous disease with multiple phenotypes. It is rare (<5% of children with asthma), but accounts for 30–50% of all pediatric asthma healthcare costs. This review looks into the currently used management strategies and the innovative treatments, considering both conventional medications and innovative biological therapies for targeting airway inflammation.

Recent findings

Patients with problematic severe asthma should be seen by pediatric asthma specialists using a stepwise approach. The first step is to exclude alternative diagnoses; the second is to consider and exclude comorbidities, and assess adherence to medication; the third step involves identifying the pattern of inflammation; and response to treatment in the fourth. Innovative biological therapies are emerging and healthcare professionals should know how to handle them. Patient phenotyping is the main step towards a targeted therapeutic strategy.

Summary

A careful management is important for children with severe asthma, who form a small but challenging group of patients. More research efforts are needed to enable a personalized medicine and a biomarker-driven approach.

Keywords

asthma phenotypes, childhood asthma, problematic severe asthma, therapy-resistant asthma

INTRODUCTION

Problematic severe asthma (PSA) is a heterogeneous disease and PSA can be considered an ‘umbrella term’ [1] used to identify children with many different symptom patterns and different disease phenotypes. Symptoms can range from a few acute severe attacks in between periods of good asthma baseline control to chronic daily symptoms and airflow limitation despite high-intensity treatment. PSA is rare (0.5% of the general pediatric population, <5% of children with asthma), but it accounts for 30–50% of all pediatric asthma healthcare costs [2].

As emphasized in the National Review of Asthma Deaths [3^{••}], a nationwide investigation into asthma deaths in the UK and the largest such study worldwide to date, ‘asthma still kills’. Twenty-eight (14%) of the 195 asthma-related deaths recorded in the UK between February 2012 and January 2013 involved young people under 20 years of age. The expert panels identified factors suggesting that these deaths might have been avoided. These factors were related to patients, their families and the environment in 126 (65%) cases,

and to health professionals’ implementation of asthma guidelines in 46% of cases. Particularly in children and young people, an inadequate awareness of the risk of adverse outcomes emerged as an important avoidable factor in both primary and secondary care. This highlights the need for a correct approach to PSA.

We can distinguish between two main entities coming under the label of PSA: difficult-to-treat asthma and severe therapy-resistant asthma (STRA) (children that are still symptomatic even when the basic management needs are resolved) [1]. Cases of difficult-to-treat asthma are children whose poor

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KEY POINTS

- PSA is a rare, heterogeneous and costly disease and the management of children with PSA is often very challenging.
- The evaluation of the child with PSA should be done by a pediatric asthma specialist and implies a stepwise approach, to exclude alternative diagnoses and comorbidities, identify inflammatory patterns, and assess adherence to medication and response to treatment.
- Novel strategies and biological drugs are emerging and biomarker-driven approaches may pave the way to more personalized treatments.

symptom control is because of one or more associated diagnoses, comorbid conditions, poor adherence to treatment regimens, or adverse psychological and environmental factors. The latter children should not be candidates for innovative therapies, unless their asthma severity persists after such problems have been solved. STRA is diagnosed when factors that make the child difficult to treat have been excluded or treated, or cannot be identified (by definition, a diagnosis of STRA excludes individuals with difficult-to-treat asthma).

In 2014, a task force supported by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) reviewed the terminology and produced guidelines on the treatment of severe asthma in children and adults [4²²]. This task force underscored the need for a complete, stepwise diagnostic assessment of children referred for severe asthma. The guidelines stress that patients should be managed by asthma specialists for more than 3 months before the diagnosis can be confirmed [4²²]. The first step in patient assessment involves excluding other possible diagnoses. Then the specialist should consider and exclude any comorbidities and assess the patient's adherence to medication. As a third step, it is important to identify the pattern of airway inflammation, and the fourth step involves assessing response to steroids treatment [5,6].

When a diagnosis of asthma has been confirmed and any comorbidities have been addressed, the definition of severe asthma depends on the patient's therapeutic needs. According to the ATS/ERS, for children over 6 years of age, asthma is classifiable as severe when it requires treatment with high daily doses of inhaled corticosteroids (ICS) (>800 µg/day of budesonide or equivalent) and a second controller (long-acting beta-agonists or a leukotriene modifier/theophylline) for the full previous year and/or systemic corticosteroids for more than 50% of the

previous year to prevent it from becoming 'uncontrolled', or which remains 'uncontrolled' despite this therapy.

The definition of a high daily dose of ICS can unfortunately be misleading, however, when it comes to diagnosing severe asthma in children. This definition varies considerably between the ATS/ERS guidelines [4²²] and the Global Initiative for Asthma (GINA) guidelines [7²³], the 'high dose' of ICS being twice as high in the former (800 µg/day of budesonide as opposed to 400 µg/day) [4²²,7²³].

Severe asthma is termed 'uncontrolled' if any one of the following four criteria is met: (1) poor symptom control: ACQ (asthma control questionnaire) score consistently more than 1.5; ACT (asthma control test) less than 20; (or 'not well controlled' according to the National Asthma Education and Prevention Program/GINA guidelines); (2) frequent severe exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous year; (3) serious exacerbations: at least one hospitalization, ICU stay or need for mechanical ventilation in the previous year; (4) airflow limitation: after withholding appropriate bronchodilator, forced expiratory volume in the first second (FEV₁) less than 80% predicted (in the face of reduced FEV₁/forced vital capacity (FVC) defined as less than the lower limit of normal).

For children with 'uncontrolled' severe asthma, the diagnosis of STRA can be considered and innovative medication can be proposed. Such a diagnostic classification should not be considered definitive: children with PSA need to be continuously reassessed [6].

THE FIRST STEP: EXCLUDING AN ERRONEOUS DIAGNOSIS

Many different diseases may mimic asthma. Tuberculosis, cystic fibrosis, interstitial lung disease, primary ciliary dyskinesia, bronchopulmonary dysplasia and prematurity, foreign body aspiration, bronchiolitis obliterans and airway malformations, such as tracheobronchomalacia, should all be ruled out. Dysfunctional breathing, such as vocal cord dysfunction, should be considered too in the differential diagnosis in older children [8].

Some diagnostic tests can facilitate the differential diagnosis. Lung function assessment with spirometry and acute bronchodilator reversibility should always be performed. Bronchial obstruction can be documented using several spirometric parameters [FEV₁, forced expiratory flow at 25-75% of forced vital capacity (FEF₂₅₋₇₅) and FEV₁/FVC] and correct reference values. Compared with adults, children with PSA have a less impaired lung function than

adults, and many children may have normal spirometric findings when asymptomatic [5]. Spirometry is nonetheless an important part of the diagnostic work-up, enabling an objective assessment of lung function that is useful for monitoring response to treatment and should also be used to check lung growth over time.

Assessing bronchial hyperresponsiveness with a bronchial challenge test and exercise limitation should also be part of the routine assessment of patients suspected of having PSA [9].

High-resolution computed tomography scanning is helpful in the differential diagnostic process, but is not routinely recommended. Bronchoscopy with bronchoalveolar lavage (BAL) analysis is indicated to dispel diagnostic doubts concerning any anatomical anomalies or infections, and to examine the type of airway inflammation involved, but is also not routinely recommended [5,9].

SECOND STEP: CONSIDERING COMORBIDITIES AND ADHERENCE TO MEDICATION

Difficult-to-treat asthma may be associated with comorbidities, adverse psychological and environmental factors, and poor adherence to treatments. These factors have to be investigated.

Skin-prick testing and specific immunoglobulin E (IgE) measurements should be performed [10]. High allergen exposure in the home in sensitized children may be one of the causes of acute exacerbations in children, and allergic factors (especially food allergies) have been associated with asthma deaths [11,3²²]. There is sufficient evidence, especially in sensitized children with PSA, to support the recommendation that allergens be avoided wherever possible [5,9].

Allergic bronchopulmonary aspergillosis should be considered in the differential diagnosis [5].

Viral infections have a major role in children because they can induce asthma exacerbations. The majority of asthma exacerbations coincide with seasonal peaks in viral respiratory infections. In early autumn (September asthma epidemic), rhinovirus is the most commonly involved in children [12]. For the time being, there are no therapies available for controlling viral infections and specifically inhibiting the mechanisms by which respiratory viruses trigger asthma exacerbations [13].

In sensitized children, we must also consider possible interactions between viral respiratory infections and exposure to allergens [14]. Exacerbations triggered by viral infections associated with allergen exposure are characterized by a mixed eosinophilic and neutrophilic inflammation [9].

Upper airway assessment should be a routine part of the patient's clinical assessment, checking for allergic rhinitis and chronic rhinosinusitis [5]. Allergic rhinitis often coexists with asthma, but to what extent treating the allergic rhinitis can improve the asthma symptoms is still a matter of debate [5]. De Groot *et al.* suggested, in their cross-sectional study, that the treatment of allergic rhinitis with nasal corticosteroids improves asthma control in children, but randomized controlled trials are needed to confirm this [15]. Chronic rhinosinusitis may be a comorbidity, especially in adults, whose asthma symptoms improve after treatment for rhinosinusitis [5]. Whether it is effective in children too is still not clear. Studies on the effects of treating sinusitis in children with PSA are lacking [5].

Gastroesophageal reflux is another common associated comorbid condition. There is still little evidence to indicate that reflux can cause asthma, and that treating reflux can improve the disease, and the relationship between these two conditions is sometimes overemphasized [16]. It is nonetheless appropriate to check for reflux as a potential comorbidity during the PSA patient's diagnostic work-up.

Tobacco smoke correlates with more severe asthma [4²²] and with the disease's persistence. It can also impair response to asthma treatment [5]. Passive exposure to tobacco smoke is one of the strongest domestic and environmental risk factors for children developing recurrent coughing/wheezing or asthma symptoms at any age [17]. In adults with asthma, cigarette smoke induces steroid resistance, and exposure to second-hand smoke could have the same effect in children too [1]. Tobacco smoke has particularly detrimental effects in younger children because their airways are smaller. Smoking cessation should be encouraged, and parents should be aware of the smoke-related health risks for themselves and their children.

The interactions between obesity and asthma are complex. Obesity can cause steroid resistance. On the contrary, asthma treatment might in itself contribute to obesity [1]. Weight loss should be encouraged to improve asthma symptoms and quality of life, but it may be difficult to achieve [1].

An association has been demonstrated between vitamin D deficiency and asthma severity [18], but controlled studies on the benefit of vitamin D supplementation are still lacking [19].

Psychological and mental health issues are among the factors that raise the risk of asthma attacks and asthma-related deaths. The importance of acute and chronic stress as triggers of asthma exacerbations is well recognized [9]. Asthma is often associated with functional impairment in daily life, and children with severe asthma have a worse

quality of life than their healthy peers due to their frequent school absences, limited physical activity, and high risk of severe exacerbations [4²²,5]. The Paediatric Asthma Quality of Life Questionnaire and the Paediatric Asthma Caregiver's Quality of Life Questionnaire should be completed as part of a PSA patient's assessment. Where necessary, psychological interventions should also be considered on an individual basis.

Failure to take prescribed treatments properly is the most common reason for persistent symptoms. Fifty percent of children referred for severe asthma have persistent symptoms and poor asthma control due to inadequate disease management (poor adherence, incorrect use of inhalers) [20,4²²]. Even multiple teaching sessions may not suffice to ensure a good technique in using inhalers, and this aspect should be checked regularly. Emphasis on 'how', 'why' and 'when' to use asthma medications is fundamental to asthma management [2].

THIRD STEP: IDENTIFYING PATTERNS OF AIRWAY INFLAMMATION

The basic mechanisms and airway pathology in children with severe asthma are still largely unknown. The heterogeneity of PSA makes it necessary to characterize the different underlying inflammatory patterns in order to customize patients' treatment and identify potential responders to innovative therapies [9]. The following techniques can be used to study airway inflammation: induced sputum analysis, exhaled nitric oxide measurement, exhaled breath condensate analysis, bronchoscopy with BAL and bronchial biopsy.

Induced sputum analysis can reveal different patterns of inflammation – eosinophilic, neutrophilic, mixed (eosinophils and neutrophils), and paucicellular – but the clinical usefulness of sputum markers in children has yet to be ascertained and sputum induction is not possible in at least 20–30% of children [9].

The exhaled nitric oxide fraction (FeNO) correlates with eosinophilic inflammation and may be reduced by steroid treatment [5], but the clinical role of FeNO measurement in cases of PSA is still being investigated.

Exhaled breath condensate can be collected in children and may reflect the composition of the airway lining fluid. Few biomarkers have been validated for clinical use, and considerable methodological challenges remain [5].

Bronchoscopy with BAL and bronchial biopsy may be indicated for the purposes of differential diagnosis, or to assess structural anomalies, remodeling and patterns of inflammation.

It is important to bear in mind that pediatric asthma differs from adult asthma. Children with severe asthma are highly atopic and show no gender bias [8]. Unlike adult cases, STRA in children is more often characterized by eosinophilic, and not by neutrophilic airway inflammation. There may be different mechanisms driving pediatric and adult severe asthma, and this means that adult therapeutic strategies should not be applied uncritically to children [21,22]. Hence, the importance of individualized treatment. There is currently no firm evidence of the clinical usefulness of assessing patterns of inflammation, but improvements in this field are mandatory. In this regard, the recent advent of 'omic' technologies (proteomics, metabolomics) may have great potential [5,21]. The metabolomic approach, in particular, can be applied to the study of different body fluids (breath condensate, urine, blood) with the potential for contributing to the characterization of specific metabolite fingerprint associated with asthma severity, risk of exacerbations, or response to treatments.

TREATMENT

There is little evidence for the various treatment options for children with STRA. The available data have been extrapolated from studies conducted in children with mild or moderate asthma, or from adults with severe asthma.

Standard therapies include high-dose inhaled corticosteroids, long-acting beta-agonists, leukotriene receptor antagonists, oral prednisone, the single maintenance and reliever therapy (SMART) regimen, the anti-IgE antibody omalizumab, low-dose oral theophylline and intramuscular triamcinolone acetonide [7²²,20]. First of all, it is important to ensure that these standard therapies are optimized. Innovative treatments can be used for STRA, or for children with difficult-to-treat asthma who, despite the successful treatment of comorbidities, continue to have asthma symptoms. Corticosteroids remain the mainstay of treatment for asthma, but – by definition – STRA involves a persistent lack of control despite corticosteroid therapy.

In children with asthma uncontrolled by ICS, long-acting beta-agonists and leukotriene receptor antagonists, oral corticosteroids are considered the next step and prednisolone therapy should be tried. If significant clinical benefits are seen, the dose should be gradually tapered to the lowest effective dose. Side-effects should be monitored but there is no clear evidence to support how this should be done.

There are no well established methods for assessing systemic steroid response in children, and there

is no consensus on the type and dosage of the drug, its form of administration (oral versus intramuscular triamcinolone acetonide), and the duration of the treatment [20]. The definition of steroid resistance in adults (an increase in FEV₁ <15% after 2 weeks of oral prednisolone in a patient who can bronchodilate more than 15% with the use of beta-2 agonists) is inappropriate for children, who may have normal spirometric findings despite severe asthma. In children, steroid response might be reflected mainly by their symptoms improvement, as measured with: an asthma control test; reduced bronchodilator use for symptom control; improved prebronchodilator FEV₁; and normal cellularity of induced sputum/normal FeNO [5]. It is now recognized that many factors can contribute to reducing responsiveness to corticosteroids, including obesity and exposure to tobacco smoke, and eliminating such factors may improve response to treatment.

The SMART regimen, that is, using budesonide/formoterol in a single inhaler for maintenance and rescue therapy has proved effective in adults. A trial in children might be considered, but its use and efficacy are still controversial [20,23].

The anti-IgE antibody omalizumab is indicated for children with truly severe, therapy-resistant atopic asthma. Good-quality, randomized, placebo-controlled studies in children aged 6–12 years with moderate-to-severe asthma showed a significant reduction in ICS dose, fewer exacerbations and a better asthma-related quality of life in children treated with omalizumab [24[¶]]. The drug has a safe profile. There is currently no clear evidence to support a threshold level of baseline serum IgE for optimum efficacy [24[¶]]. Omalizumab has recently demonstrated a significant role in the treatment of severe nonatopic asthma too [25]. The high cost of the drug makes it essential to identify biomarkers capable of predicting response [24[¶]].

There has been a renewed interest in theophylline (with its immunomodulatory properties), and a low-dose trial could be conducted in patients with neutrophilic asthma. The appropriate duration of such a trial is not known (probably some months).

The experimental therapies include macrolides, cyclosporine, methotrexate, immunoglobulins, antifungal agents, subcutaneous terbutaline infusion, and bronchial thermoplasty [9]. Numerous other biological therapies have been developed (interleukin-13, interleukin -4, interleukin -9). Macrolides have immunomodulatory properties as well as antibacterial effects, and are safer than other toxic agents, so it would be reasonable to test macrolides, particularly in patients with neutrophilic asthma and children with suspected atypical respiratory infections (judging from evidence obtained in

adults) [20]. Cyclosporine and other cytotoxics (e.g., methotrexate and azathioprine) cannot be recommended for the time being. Itraconazole (or voriconazole if symptoms persist) might be considered in patients sensitized to fungi. Bronchial thermoplasty was approved by the Food and Drug Administration in 2010 for the treatment of severe adult asthma: results have been promising, but no experiences in children have been reported to date [26,9]. Anti interleukin-5 is effective against eosinophilic inflammation, and it reduces the risk of exacerbations in adult patients with severe eosinophilic asthma [27]. There are no reports of its use in children. Injectable adrenaline should be considered for the emergency treatment of children with catastrophic asthma [20].

Patient phenotyping may be useful for orienting the choice of treatment, and an accurate clinical and biological phenotyping will be essential to any usage of innovative biological therapies targeting airway inflammation [28[¶]]. To give an example, the best treatments for eosinophilic inflammation (which can present as an exacerbating phenotype, judging from studies conducted in adults) are high-dose inhaled steroids, corticosteroids or triamcinolone. In children with this phenotype, it has also been suggested that high-dose ICS or leukotriene receptor antagonists, or both, be administered at the first sign of exacerbation in an effort to contain the severity of the episode [20]. Corticosteroids are less effective in patients with neutrophilic patterns of inflammation, whereas macrolides have been shown to reduce this type of inflammation, and theophylline to accelerate neutrophil apoptosis [9,20].

Although the innovative approaches are interesting, getting the basics right for children with apparently severe asthma will remain fundamentally important to their management.

CONCLUSION

Every patient's asthma has particular characteristics and trigger patterns, and their response to treatment may vary. PSA, in its various forms, is increasingly recognized as a major problem, also accounting for considerable asthma-related healthcare costs. PSA patients form a small but very challenging group and demand a multidisciplinary approach. Research efforts to carefully characterize children with PSA and improve phenotyping will help us to provide an effective personalized treatment (ATS/ERS). In children, special concern should be paid to long-term respiratory outcome. Acute asthma exacerbations can cause substantial morbidities and are an independent risk factor for an accelerated decline in lung function. Further research to enable a personalized

medicine and a biomarker-driven approach is mandatory.

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