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EUROPEAN RESPIRATORY UPDATE

An update on paediatric asthma

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In this Update we will discuss aspects of the definitions, epidemiology, diagnostics, asthma-associated comorbidities, assessment and treatment of asthma including a specific focus on severe asthma in school children. The Update will mainly cover data published during the last 3 yrs.

In 2009, an expert panel was tasked to propose a World Health Organization definition of asthma severity and control. The result of this Task Force was a uniform definition of asthma severity, control and exacerbation [1]. As we will discuss later in an overview of asthma outcomes [2], symptom evaluation is the key to the diagnosis and outcome measures in clinical studies.

Airway inflammation is one of the pathophysiological characteristics of asthma, which is mediated through infiltration of inflammatory cells, including mast cells, and eosinophilic and neutrophilic granulocytes in the airway wall. This cell infiltration subsequently leads to bronchial hyperresponsiveness (BHR) and, in the case of chronic inflammation, persistent changes of the airways, *i.e.* airway remodelling [3, 4].

Immunoglobulin (Ig)E-mediated allergy leading to allergic inflammation is common among children with persistent asthma. There are ongoing studies worldwide (the MeDALL initiative) aiming to identify allergic phenotypes [5] and understand the complexity of the IgE related phenotypes in children and adults [6].

The purpose of paediatric asthma treatment is for the child to control symptoms, to be able to lead a normal active life, to have normal lung function and to prevent asthma exacerbations [7, 8]. The care of asthmatic children does not only include the prescription of asthma medication. The families need to be convinced and educated to actually make the parents give the medication as prescribed and in a proper manner [9]. Furthermore, healthcare providers must teach the families how to avoid or handle triggering factors, including exercise; recognise signs that asthma is worsening; and seek medical advice when needed [10].

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NOTES ON EPIDEMIOLOGY

Wide variations exist in the symptom prevalence of children with asthma. While severe symptoms among children in less affluent countries are more common, there are more children with any symptoms of asthma in wealthy countries [11]. In a systematic analysis of the global burden of disease in people aged 10–24 yrs [12], where the disease risk was assessed by calculating years lost because of disability, respiratory disorders were the sixth main cause of disability worldwide. Most of the years lost because of disability were caused by asthma, which was the fourth most common cause of disability-adjusted life years for children aged 10–14 yrs. Another approach to estimating the burden of asthma was reported from Ontario, Canada, in a study of the lifetime risk of physician-diagnosed asthma [13]. One in three individuals had physician-diagnosed asthma. Even more interesting is that one in five was diagnosed before 20 yrs of age. This demonstrates the life-long pattern of asthma compared with other chronic diseases such as diabetes and coronary heart disease [13]. In a 5-yr follow-up study of Irish children, the prevalence of asthma remained stable in 6–9-yr-old children at 21.7% in 2002 and 23.5% in 2007 [14]. This illustrates and confirms the findings of the International Study of Asthma and Allergies in Childhood (ISAAC) study of the varying prevalence of asthma in Europe.

DEFINITIONS AND DIAGNOSIS OF SEVERE ASTHMA

Problematic severe asthma

The majority of children with asthma have mild or moderate disease and can obtain adequate control of symptoms through avoidance of triggering factors and/or with the help of medications, such as inhaled short-acting β_2-receptor agonists (SABA), inhaled corticosteroids (ICS) and, when needed, the addition of long-acting β_2-receptor agonists (LABA) and leukotriene receptor antagonists (LTRA) [15, 16]. Asthma control is defined as ''to which extent the manifestations of asthma have been reduced or removed by treatment'' [17], a concept that not only includes assessment of daytime and nocturnal symptoms and need for reliever medication, but also an estimation of future risk of severe exacerbations. However, ~5% of all asthmatic children have chronic symptoms and/or recurrent exacerbations despite maximum treatment with conventional medications [18]. These children are referred to as severe asthmatics, and due to the lack of specific biomarkers of this disease, severe asthma is currently being defined on the basis of the intensity of treatment required to improve asthma control, and the level of control achieved [7, 17, 19]. Thus, the definition of severe asthma combines evaluation of medication, chronic symptoms and exacerbations. These criteria are developed from the Global Initiative for Asthma (GINA) guidelines and other studies or reviews on severe childhood asthma [20–22]. Children with such severe and therapy resistant symptoms are heterogeneous with

respect to triggering factors, pulmonary function, inflammatory pattern and clinical symptoms [22–25]. These children have a reduced quality of life [26] and represent a continuous clinical challenge to the paediatrician [24, 27].

A Global Allergy and Asthma European Network (GA^2LEN) Task Force, the Problematic Severe Asthma Initiative, has proposed the term problematic severe asthma to define all children who suffer from chronic symptoms and/or severe exacerbations despite prescription of high doses of ICS with additional LABA and/or LTRA [21, 22]. This concept has been incorporated in the recent WHO definition of severe asthma [1]. The concept is a reflection of how children with problematic severe asthma are presented to the paediatric allergist, *i.e.* having troublesome symptoms despite maximum conventional medications, step 4 and 5 according to GINA.

The advantage of the newly introduced term problematic severe asthma is that it encompasses two groups of children: 1) children who, after a thorough work-up, can be classified as difficult to treat because of identified exacerbating factors; and 2) children who, following a thorough work-up, do not have any identifiable aggravating factors but are still severely resistant to therapy (fig. 1).

Clinical presentation of problematic severe asthma in school-age children

We diagnose severe therapy-resistant asthma when differential diagnosis is excluded (table 1), and we cannot identify factors that make the child ''difficult-to-treat''. Severe therapy-resistant asthma may take a number of different forms that are not mutually exclusive.

Exacerbation phenotype

Exacerbation phenotype refers to children with problematic severe asthma who have received more than one burst of oral corticosteroids in the preceding 12 months, without experiencing daytime or night-time symptoms between exacerbations.

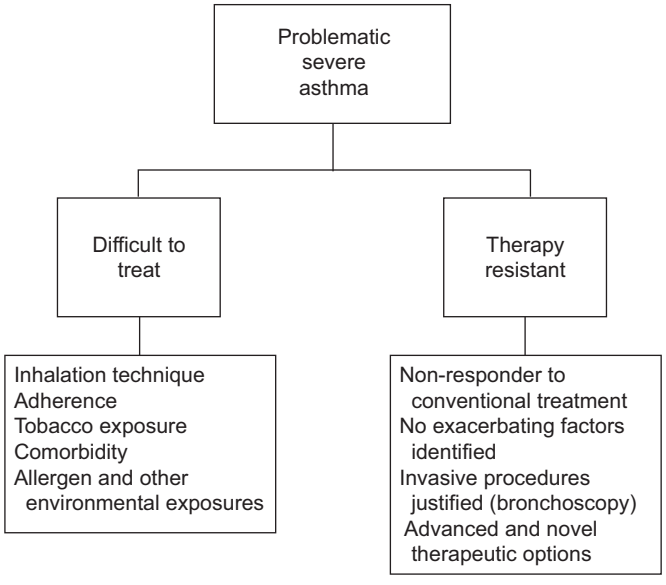

FIGURE 1. Clinical classification of children presenting with problematic severe asthma.

Chronic symptoms phenotype

Chronic symptoms phenotype refers to children with problematic severe asthma that have experienced daytime and/or night-time symptoms more than twice per week in the preceding 3 months.

We diagnose difficult-to-treat-asthma when poor control is due to one or more of the following: associated diagnoses (comorbidities), poor adherence to treatment regimens, or adverse psychological and environmental factors.

Difficult-to-treat asthma versus *therapy resistant asthma*

In a study of Swedish school children with problematic severe asthma, 39% of the children with problematic severe asthma were exposed to exacerbating factors that could be treated or at least partially eliminated. This finding provides support for the clinical utility of the definition of problematic severe asthma [23]. Moreover, these exacerbating factors were not disclosed in connection with routine care by experienced paediatric allergists, emphasising the usefulness of an extensive and standardised clinical protocol. Home visits [28] and assessment of steroid response with, for example, triamcinolone injection [20, 29] could have further improved the classification of children with problematic severe asthma.

The Swedish results and the results from other studies indicate that children with problematic severe asthma who have a low socioeconomic background and a high exhaled nitric oxide fraction (F_{ENO}) have an increased probability of having asthma that is difficult to treat because of identifiable aggravating factors [23, 30]. This finding suggests a shortcoming of the profession to educate these families on how to avoid or handle triggering factors. Furthermore, although impaired asthma control and risk of exacerbations are related, the respective predictors are different [31].

ASTHMA COMORBIDITIES AND/OR ASSOCIATED DIAGNOSIS

Other conditions may co-exist with asthma, and continuing respiratory symptoms may be wrongly attributed to asthma alone. These children may be difficult to treat. The most common comorbidities are chronic rhinosinusitis, gastro-oesophageal reflux and obesity.

Rhinitis and rhinosinusitis

It has long been recognised that diseases of upper and lower airways may co-exist. The co-morbidity between childhood

TABLE 1 Possible differential diagnosis in a child presenting with severe asthma

Tracheomalacia
Congenital disorders
Primary ciliary dyskinesia
Oesophageal fistula
Foreign body
Bronchiolitis
Immunodeficiency
Cardiac disease

asthma and rhinoconjunctivitis is well established. The relationship between the nose and the lung, however, is complex and it has been reviewed in several studies [32, 33]. 76% of patients with asthma have rhinitis and up to 15% of patients with allergic rhinitis have asthma [34]. CHAWES *et al*. [35] further report that children with allergic and non-allergic rhinitis have a similar risk of asthma. It is still unclear whether sinusitis worsens asthma, or whether both are manifestations of the same underlying disease process. However, the observation that patients with problematic severe asthma report clinical symptoms of rhinoconjunctivitis more often than those with controlled asthma was found in a Swedish study [23]. The fact that untreated rhinitis contributes to reduced symptom control in asthmatic children has become increasingly evident [34]. In children, chronic rhinosinusitis is possibly also an underestimated disease [36].

Gastro-oesophageal reflux

The relationship between the oesophagus and the lung is also multifactorial [37]. Lung disease can cause gastro-oesophageal reflux, reflux can cause lung disease, or reflux may be of no clinical significance. Depending on the criteria used for diagnosis, 20–80% of children with chronic respiratory disease have gastro-oesophageal reflux [37]. To date, a precise mechanistic link between gastro-oesophageal reflux and decline in asthma control has not been established [38]. The results of trials of anti-reflux therapy are often disappointing [39], especially in older children, but an empirical trial is reasonable in younger children if the history is suggestive.

Vocal cord dysfunction

Some breathing problems can be confused with asthma. In particular, vocal cord dysfunction may co-exist with asthma and may be a differential diagnosis, leading to inappropriate asthma treatment. LOW *et al*. [40] report a noninvasive method for quantification of laryngeal movement by using computed tomography (CT) of the larynx. A 320-slice CT was used to monitor laryngeal behaviour. A specific pattern of laryngeal dysfunction was demonstrated, which was observed in patients with difficult-to-treat asthma. The importance in the awareness of ''considering the total airway'', particularly in severe asthma, is further stressed by AYRES *et al*. [41].

Obesity

The relationship between obesity and asthma is complex. There are a number of confounding factors, including gastro-oesophageal reflux (as mentioned previously), and the effects of obstructive sleep apnoea could be confused with asthma. The debate on obesity and asthma is about to what degree obesity has metabolic effects that contributes to airway inflammation. The latter has been shown in the Childhood Asthma Management Program (CAMP) study [42]. In addition, an association was found in the Severe Asthma Research Program study, although it was age dependent. Children with early onset asthma became obese, whereas there was no significant relationship between increasing body mass index and asthma duration among obese children with late onset asthma [43]. Furthermore, CIBELLA *et al*. [44] reported that being overweight was not a risk factor for asthma and allergic sensitisation, but was a risk factor for airway inflammation measured by *F*eNO. Based on a study of 32,321 children aged 5–17 yrs, QUINTO *et al*. [45] conclude that childhood obesity is associated with worse asthma control and exacerbations. Obesity may cause steroid resistance, in part, by reducing steroid-induced mitogen activated protein kinase phosphatase-1 [46]. Finally, COTTRELL *et al*. [47] found an association between an abnormal lipid and glucose metabolism and asthma regardless of prevalence of obesity.

Vitamin D deficiency and asthma

The impact of low serum levels of vitamin D in relation to lung disease and to asthma, in particular, is a subject of discussion. The study by GUPTA *et al*. [48] showed that increased airway remodelling, as measured by smooth muscle in biopsies, correlated to levels of vitamin D in children with severe asthma. This relationship did not exist for children with moderate asthma and in healthy controls [48]. Other evidence of the association between vitamin D and asthma severity was reported from the CAMP study [49]. Risk of exacerbation was increased in children with low levels of vitamin D. In addition, CHINELLATO *et al*. [50] reported an association between exercise-induced asthma and vitamin D levels.

UPDATE ON MECHANISMS OF ASTHMA IN CHILDREN

Inflammation

The level of symptoms and markers of inflammation do not always correlate; some children might have persistent symptoms without any inflammatory cells on histology, whereas other children might have no symptoms between exacerbations but still have increased markers of airway inflammation [51].

The aetiology of airway inflammation in asthmatic children varies depending on age. Whereas viral infections, including rhinovirus and respiratory syncytial virus, are linked to obstructive bronchitis in infancy and early childhood, and considered by some to be a combined risk factor with allergen sensitisation [52], sensitisation and exposure to allergens is the major cause of allergic airway inflammation in older children. Interestingly, recent evidence also points to a synergistic effect between viral infections and aeroallergen exposure, and subsequent sensitisation in genetically predisposed children [53, 54]. Furthermore, viral infections have been shown to be the most important cause of asthma exacerbations in all age groups [55, 56]. Rhinovirus and respiratory syncytial virus are shown to damage the respiratory epithelium, making it less resistant to inhaled allergens and subsequently leading to enhanced T-helper (Th)2 responses in predisposed children and the development of allergic inflammation [57].

Starting with the late phase allergic reaction, airway inflammation includes recruitment and migration of inflammatory cells, eosinophils, in particular, and neutrophils to the site of allergen exposure within 4–6 h. These cells are recruited and developed from a pluritpotent stem cell in the bone marrow *via* the circulation to the airways. Interleukin (IL)-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted by Th2 cells and mast cells are the most important interleukins for eosinophilic development and recruitment, although only IL-5 is specifically targeted towards the eosinophils. Once matured and recruited to the circulation, eosinophils adhere to the endothelial wall, connecting with adhesion molecules expressed on the eosinophil (very late antigen-4) and endothelial cells (vascular cell adhesion molecule-1) [58–60]. After transmigration through the endothelial wall, the eosinophils are guided to the site of inflammation by chemokines and

release several stored toxic mediators, including free acid radicals, eosinophilic cationic protein, eosinophilic peroxidase and eosinophilic protein X [61].

Neutrophils are attracted by GM-CSF and interferon (IFN)-γ. Neutrophilic pathogenic excretions include elastase, which causes hypersecretion and hyperreactivity. Matrix metalloproteinase-9 breaks down collagen causing hypersecretion and the release of free oxygen radicals, which also induce BHR [62]. The relative contribution of each of these cell types to asthma severity is not clear. In a recent published study on children with therapy-resistant asthma, there was a huge variability in eosinophil counts in bronchoalveolar lavage (BAL) and biopsy [4]. This important study in children with therapy-resistant asthma did not demonstrate neutrophilic airway inflammation on BAL and biopsy [4].

Airway remodelling and asthma

Airway remodelling refers to structural changes in the bronchial wall causing reduced lung function [63] in asthmatic patients. These structural changes are diagnosed by histology and are characterised by epithelial damage, thickening of reticular basement membrane and, subepithelial fibrosis, as well as mucus gland and airway smooth muscle hypertrophy and hyperplasia. Remodelling is found in the majority of school age children with problematic severe asthma [4, 20] and the progressive loss of lung function found in these patients is probably caused by remodelling [64].

Allergy and asthma

Every allergen has several epitopes, and similar epitopes might occur in allergens from different sources; this is the biological explanation behind cross-sensitisation [65, 66]. Some allergens are unique markers of a specific allergen source whereas allergens with similar structure and function are found in different species, *e.g.* lipocalins are a group of proteins arising from cat, dog, horse and mice, and cross-reactivity within these groups of proteins is common [67, 68].

Basophils

Basophils share important features with mast cells; however, basophil development is stimulated by IL-3, whereas mast cells are stimulated by IL-9. Basophils are a main source of IL-4 and IL-13, which are important for the production of IgE and the development of Th2 lymphocytes. Furthermore, basophils are found in the circulation, which has led them to be considered accessible surrogate makers of mast cells [69]. However, recent evidence indicates that basophils are not only markers of mast cell function, but could also function as initiators of allergic inflammation and contribute to the development of chronic allergic inflammation [70].

ASSESSMENT AND BIOMARKERS OF ASTHMA

A biomarker reveals information about the investigated disease, and can be used in one or more of the following settings to: assess the risk of morbidity; identify disease or disease phenotypes; and monitor disease activity as well as treatment effects [71]. The ideal biomarker is attained noninvasively, is reproducible, easily measured and provides information about essential pathophysiological processes with high performance characteristics including sensitivity, specificity, and negative and positive predictive values. Using biomarkers in childhood airway disease is particularly challenging. Imaging and spirometry, although providing relevant information, also have significant limitations. Biological events that occur episodically (bronchoconstriction) might not be captured and in early or mild disease these evaluations might be normal despite the patient having symptoms [71]. A US working group proposed the most relevant biomarkers for asthma outcome, namely multi-allergen screening to define atopy, blood counts to measure total eosinophils, $F_{E}NO$, sputum eosinophils, urinary leukotrienes and total and allergen specific IgE. They also concluded that system-wide studies (proteomics and genomics) are emerging but are not yet ready for clinical use [72].

Pulmonary function and BHR

Reversible obstruction of the airways and BHR are characteristic features of asthma [73]. In relation to asthma severity, some studies found no difference in forced expiratory volume in 1 s (FEV_1) on average [18, 20], but there were large individual variations [74] and the results from these studies implicate that the usefulness of FEV_1 as an indicator of severity in childhood asthma remains questionable. BHR to methacholine has been shown to correlate with asthma in specific studies on children with problematic severe asthma [18, 75]. BHR to methacholine is reduced by anti-inflammatory treatment and has been shown to correlate with markers of airway inflammation, including nitric oxide (NO) in exhaled air in severe asthmatics [76]. However, a negative test has a greater value to rule out asthma, at least in the treatment naïve patient [73]. The clinical relevance of direct and indirect tests is still being debated [77, 78]. The direct challenge with methacholine is a sensitive test for BHR although less specific than the indirect tests such as mannitol and exercise. The latter could be considered more ''real life'' appropriate.

Biomarkers in BAL and sputum

Invasive methods such as biopsy and analysis of BAL are possible in specialised centres, but in most circumstances they are not considered feasible in children. Induced sputum, a semi-invasive method, has been found to be safe in children but does require specially trained staff [79]. Cross-sectional studies have shown different cell patterns in sputum from non-allergic and allergic asthmatic children [80]. Furthermore children with asthma and food allergies were demonstrated to have more eosinophils in sputum than children with asthma but without food allergies [81]. In adults, treatment guided by the presence or absence of sputum eosinophils has been shown to reduce asthma exacerbations. There is one study in severe asthmatic children in which this has not been proven effective [82]. In a recent meta-analysis the utility of sputum eosinophils was confirmed in adults but studies in children are needed [83].

Exhaled NO

NO is produced by NO synthase in airway epithelial cells. The NO that is produced easily diffuses into the airway lumen. $F_{E}NO$ has been established as a noninvasive biomarker in asthma. The possibility to use it as a predictor of risk has been suggested [84].

In a cross-sectional study, ZEIGER and co-workers [85, 86] found that $F_{E}NO$ was a complement to symptom evaluation in that higher $F_{E}NO$ was associated with an increased use of SABA and the need for oral corticosteroids. Nevertheless, the clinical situation in which $F_{E}NO$ provides the most useful information is currently under debate [73] and the relationship between $F_{E}NO$

and asthma severity is unclear [76]. A meta-analysis [83] included three paediatric studies of the utility of *F*eNO in guiding treatment in children with asthma [87–89] and it was concluded that asthma treatment guided by *F*eNO did not improve asthma outcomes. One of the studies in which treatment was adjusted according to *F*eNO showed that the children in the NO-guided group increased their daily dose of ICS [89]. In the aforementioned study comparing asthmatic children with and without food allergies, *F*eNO was significantly higher in the children with food allergies [81] indicating increased bronchial inflammation caused by the food allergy. One could speculate that airborne food allergen exposure might be an underestimated problem in children contributing to insufficient anti-inflammatory therapy. Likewise, children who spend a lot of time indoors and are exposed to allergen like dust mite and/or dander have been shown to have increased levels of *F*eNO, especially if not sensitised to the allergens; thus, sedentary behaviour might increase airway inflammation as measured by *F*eNO. The correlation between *F*eNO and the evaluation of symptoms according to the Asthma Control Test can be weak or absent [26, 90]. Finally, *F*eNO fluctuation measurements in combination with methods that quantify cross-correlations with symptoms can be used as indicators of risk of exacerbations as opposed to the use of single measurements of *F*eNO [91].

Biomarkers in exhaled breath condensate

Analysis of exhaled breath condensate (EBC) is another noninvasive method that has been proposed to reflect airway inflammation. Different approaches and methods of analysis have been used during the last 3 yrs. In a review by AUJILA *et al.* [92], EBC is mentioned as a possibility but the conclusion is that this method requires further study before it can be applied in any clinical setting. A recent study by CABALLERO BALANZA *et al.* [93] found increased concentrations of leukotriene B_4 and 8-isoprostane in children aged 6–14 yrs with asthma compared to healthy controls. Furthermore, children with persistent asthma had higher concentrations than children with episodic asthma. Leukotriene B_4, prostaglandin E2 and 8-isoprostane in breath condensate from the nose and the mouth were analysed in an attempt to study the relationship between persistent allergic rhinitis and asthma; possible correlations were reported [94]. In two other paediatric studies, eoxin and eotaxin were measured in EBC along with 8-isoprostane, all three were significantly increased in children with problematic severe asthma [95, 96]. Finally, a new and advanced approach to utilising EBC was reported by BLOEMEN *et al*. [97]. By using a proteomics approach, the authors conclude that EBC contains proteins of interest for asthma diagnosis and follow-up, which is also supported in studies by DOMPELING and JÖBSIS [98] and SINHA *et al*. [99].

Biomarkers in urine

Urine is the most accessible noninvasive biofluid sample that can be obtained, but its utility is still questionable in diagnosing and monitoring asthma and airway inflammation. There are, however, new approaches that seem promising. For example, metabolomic profiling of asthma by magnetic resonance spectrometry of urine. SAUDE *et al*. [100] applied this technique to discriminate between acute and stable asthma in children in relation to healthy controls with some promising results. In a similar group of children with asthma, liquid chromatography coupled with mass spectrometry was used for analysis of urine samples with similar results [101]. The measurement of urinary leukotriene excretion has been investigated in order to find a marker for response to leukotriene antagonists and some promise of the utility has been found in the ratio of urinary leukotriene E_4/*F*eNO [102]. In children with exercise-induced asthma, the change of urinary leukotriene E_4 was significantly higher after an exercise test than in healthy children and tended to be higher than in mild asthmatics, thus, leukotriene E_4 might have some association in controlling exercise-induced asthma [103]. At present, analysis of leukotriene E_4 seems to be the most useful measurement relevant to asthma. Eosinophil activity markers such as EPX have not been shown to be useful in monitoring asthma; however, bromotyrosine, a marker of eosinophil-catalysed protein oxidation in urine, has been shown to be associated to asthma control and risk of asthma exacerbation in children [104].

Chitinases

A group of proteins recently discovered to be potential biomarkers of asthma are the chitinases. Chitin is a tough structural polysaccharide, the second most abundant biopolymer in nature after cellulose and is used by a variety of organisms including insects, crustaceans, parasites, fungi and bacteria to protect against harsh environmental conditions [105]. Although chitin is not present in the human body, we express enzymes capable of its degradation. Two members of this family, the enzymatically active chitotriosidase and the enzymatically inactive chitinase-like protein YKL-40, are increased in the serum of asthmatic patients [106, 107] and levels of YKL-40 have also been shown to correlate with markers of asthma severity [107]. It has been suggested that the chitinases may be involved in the development of fibrosis and remodelling of the airway [108]. YKL-40 has also recently been shown to increase the proliferation and migration of human bronchial smooth muscle cells [109]. Another noteworthy finding regarding the chitinases is the close correlation between YKL-40 and blood neutrophils. Previous studies have indicated that alveolar macrophages are a major source of YKL-40 in the airways [110], although it is not known whether YKL-40 can be stored in the specific granules of neutrophils and released upon activation of these cells. A recent study of sputum YKL-40 levels in adults with asthma also demonstrated a strong correlation with sputum neutrophil count [111].

Imaging

The relationship between CT findings in children with asthma and markers of remodelling has been investigated. In a report on findings when investigating wet cough by high-resolution CT (HRCT) and bronchoscopy it was concluded that HRCT detected airway wall thickening and the finding correlated with duration of clinical symptoms and neutrophilic inflammation as evaluated by BAL [112]. In adult studies of severe asthma, CT scans are suggested to demonstrate possible bronchial wall changes [113, 114]. Little is known of the possible role of magnetic resonance imaging for evaluation of airway remodelling and/or severity of asthma, although a combination of HRCT and magnetic resonance imaging could help in identifying regional distributions of asthma in the lungs [115, 116]. This could help in investigating regional effects of bronchial/small airway obstruction in children with asthma.

Diagnosing allergy

Sensitisation is usually determined by using allergen extracts to identify the disease eliciting allergen source by *in vivo* skin-prick testing. An update and practical guide to skin-prick testing using aeroallergens was recently published [117]. *In vitro* testing, *i.e.* measurement of specific IgE in serum, is the alternative way of diagnosing allergic sensitisation. However, some disadvantages are associated with these extract-based methods. These methods only give information about the possible sensitising allergen source, but no information about sensitisation towards specific allergens is provided. Thus, it is not possible to differentiate between the primary source of sensitisation and cross-reactivity between allergens from different allergen sources [65]. Moreover, it is not possible to determine whether the patient is sensitised to an allergen causing severe reactions or allergens causing mild reactions. In children with severe asthma the allergy diagnostic characterisation can be complex and often requires both *in vivo* and *in vitro* testing [118].

IgE component resolved diagnostics

Today, the only commercially available component-based microarray platform for allergy is the immunosolid-phase allergen chip (ISAC; Thermo Fisher Scientific, Uppsala, Sweden). Although the ISAC chip lacks some minor allergens, the most common species-specific and cross-reactive allergens are represented. Some allergens are specific markers of an allergen source [119], and by identifying these allergens it is possible to determine which are sensitising allergen sources and which are cross-reactive allergen sources [120]. Furthermore, it is possible to predict whether the patient is at risk for a severe or mild reaction, based upon which allergen the patient is sensitised to. Children allergic to peanuts and sensitised to the allergens Ara h 1, Ara h 2 and Ara h 3 are at risk for significantly more severe symptoms upon peanut exposure compared to children sensitised to Ara h 8 [121], which is a homologue to the major Birch allergen, Bet v 1. Assessment of allergic sensitisation by the established extract-based methods has diagnostic limitations with respect to concordance [11], cross-reactivity and prediction of severe allergic reactions. There can be an added value of performing this analysis in children with persistent asthma, as shown by NORDLUND *et al*. [122] who report that children with severe asthma have higher levels of the animal-derived components lipocalin, secretoglobin and kallikrein compared to well-controlled children with asthma.

Basophil allergen threshold sensitivity

Assessment of allergen specific IgE antibodies does not necessarily predict the effector cell response and the subsequent clinical symptoms upon allergenic stimulation. For this purpose allergen provocation tests are needed but as they are potentially harmful, especially in severe asthmatic children, few studies have been performed and published on *in vivo* allergen challenge tests. Basophil allergen threshold sensitivity (CD-sens) is an attractive *in vitro* alternative to the clinical allergen provocation tests [123] and correlates well with *in vivo* allergen provocation [124]. CD-sens is based on the detection of CD63 on basophils following *in vitro* allergen titration. CD-sens is calculated from the allergen concentration causing 50% of maximum basophil activation and reflects the sensitivity of basophils to the particular allergen. This has been shown as a difference between cat allergic children with severe or mild asthma in spite of comparable levels of cat-specific IgE [125]. It may be speculated that the higher allergen sensitivity in children with problematic severe asthma could be due to skewing of a basophil phenotype, since basophils are a heterogeneous cell population with varying degranulation properties depending on the genetic background and surrounding cytokine environment at the stage of basophil precursor development [126].

RECENT ADVANCES IN THE TREATMENT OF ASTHMA IN CHILDREN

Detailed recent reviews of the treatment of pre-school wheeze and severe asthma [27, 127] have recently been published. In this section we update these publications and also discuss studies relevant to more mild asthma. A stepwise therapeutic approach is usually applied to adjust the medications to the symptoms and several guidelines have been published to support the physician in these treatment decisions [15, 128–130].

Treatment of pre-school wheeze

The European Respiratory Society Task Force [131] proposed that pre-school children with episodic viral wheeze should be treated with intermittent therapy. A more recent paper [132] randomised 278 children with a positive asthma predictive index aged 12–15 months to either 1 mg nebulised budesonide for 7 days with any clinically diagnosed viral upper respiratory tract infection (n=139) or 0.5 mg nebulised twice daily regular budesonide (n=139). Unfortunately there was no placebo limb. There was no significant difference in any outcomes, specifically including frequency of exacerbations, time to first exacerbation, frequency of treatment for respiratory illness and time to first treatment for respiratory illness. From these data, it is clear that, in the setting of episodic viral wheeze, continuous budesonide does not prevent exacerbations, does not make them any less severe and does not result in any less treatment for acute symptoms, but does lead to an increase in the steroid dose taken. Unfortunately, in the absence of a placebo group, we do not know whether either treatment was at all helpful. We can certainly use this study to refute the need for pre-school children to be treated with ICS for episodic viral wheeze.

Treatment of school-age asthma

Intermittent therapy

The clinical reality is that adherence is poor even in very severe asthma [28], and it is likely that children with mild asthma are deliberately treated intermittently at home. The TREXA (TReating Children to Prevent Exacerbations of Asthma) study assigned 288 children aged 5–18 yrs to one of four regimes in a 44-week study [133]. The children had well-controlled, mild, persistent asthma such that treatment could be discontinued. The regimes are shown in the table 2, and the primary outcome was time to first prednisolone burst. The frequency of exacerbations was lower in all three beclomethasone diproprionate groups compared with the placebo group (group 4). Linear growth was 1.1 ± 0.3 cm less in the two continuous beclomethasone diproprionate groups (groups 1 and 3; $p<0.0001$), but not in the rescue group (group 2; $p=0.26$) compared with the placebo group. This study suggests that rescue therapy with ICS during tapering may be a beneficial strategy, and adds to the evidence that ICS at the time of viral infections may be beneficial in children with asthma. This study agrees with the Finnish data which suggests that intermittent ICS may be as effective, and

TABLE 2 Treatment regimens for the TREXA study

Group	Subjects n	Regular therapy	Exacerbation therapy
1	71	BDP 50 μg twice a day	BDP 100 μg/β_2-rescue
2	72	Placebo	BDP 100 μg/β_2-rescue
3	71	BDP 50 μg twice a day	Placebo/β_2-rescue
4	74	Placebo	Placebo/β_2-rescue

TREXA: TReating Children to Prevent Exacerbations of Asthma; BDP: beclomethasone diproprionate.

with fewer side-effects, than continuous ICS in children with mild asthma [134–136].

Add-on therapy

The BADGER study [129] enrolled 182 children who were symptomatic despite being prescribed fluticasone 100 μg twice daily. The investigators used a triple cross-over, unblinded design to assess whether additional therapy with high dose ICS, LABA or LTRA was better. The salient features of the results were: 1) that additional LABA therapy performed best for the group, although many children performed better with the other alternatives; 2) no biomarker predicted best response to LABA, the children who were more likely to respond had better baseline asthma control; and 3) the peak of the ICS dose response curve for most of the children was observed during administration of low dose fluticasone. So we need better biomarkers, and LABA is probably the first-line add-on therapy, but LTRA and high dose ICS can be tested in non-responders.

Beyond guidelines therapy: currently available treatment

There is increasing evidence that background eosinophilic inflammation and viral infections interact to produce acute asthma attacks [137, 138]. Two recent studies have shown that strategies likely to have reduced airway eosinophilia also reduce acute asthma attacks [139, 140]. The anti-IgE monoclonal antibody omalizumab is a well-established therapy for asthma in childhood. A randomised, double-blind, placebo-controlled study of more than 400 inner city children and young adults aged 6–20 yrs demonstrated that omalizumab did not just merely improve the number of symptom free days, but also significantly reduced the number of children having an exacerbation from 48.8% to 30.3% [139]. In a *post hoc* analysis, the seasonal peak of exacerbations was abolished. Response was better in the children with higher *F*eNO and blood eosinophils [141, 142]. A study in younger children aged 6–<12 yrs showed that omalizumab therapy led to a 31% reduction in exacerbation rates [140]. Taken together, these studies suggest that background airway eosinophilic inflammation may contribute significantly to exacerbations.

Beyond guidelines therapy: future treatment

A large adult study showed that the addition of tiotropium to the regime of patients who were symptomatic despite ICS therapy was superior to doubling the dose of ICS and equivalent to adding a LABA [143]. There is no paediatric study of tiotropium, but there is an urgent need to explore its role.

Possible new treatment alternatives

Several new treatment alternatives are in the pipeline, including pitrakinra (IL4-/IL-13 antagonist) [144], lebrikizumab (IL-13 antagonist) [145] and reslizumab (antibody against IL-5) [146], all of which predominantly target allergic asthma. As these are, or are likely to be, expensive treatment alternatives, detailed characterisation of patients in order to identify those most likely to benefit from these interventions will be increasingly important. A novel marker of potential clinical relevance is periostin, a protein suggested as a marker of excessive Th2-type inflammation in asthma [147]. The expression of periostin in airway epithelial cells is regulated by IL-13 [148]. The effect of lebrikizumab treatment has been shown to be greater in severe asthmatics with high periostin levels compared to those with low periostin levels, as demonstrated by an improvement in FEV1 and a reduction in *F*eNO [145], thus providing an entirely new example of biomarker-guided treatment in severe asthma.

New treatment alternatives for asthma, particularly in children, should probably not just focus on suppressing the inflammatory response. The idea of primary prevention of asthma is becoming an option [54] and in this regard combining vaccines for allergy and rhinovirus infections are a novel and interesting approach [149]. Another novel approach is intralymphatic immunotherapy which may turn out to be a ''fast-track'', effective alternative to subcutaneous immunotherapy [150]. Finally, vitamin D supplementation could be a straightforward treatment alternative to strengthen the immune response in children with therapy resistant asthma [48], although more trials are needed.

ADHERENCE TO TREATMENT

Reliable assessment of adherence to prescribed treatment is a challenge in clinical practice, as well as in research on patients with asthma. KRISHNAN *et al*. [151] compared subjective and objective measurements of children's adherence to ICS therapy in a sub-study to the CAMP study [151]. They compared reported intake of ICS, as reported in diary cards, to the number of doses left in the study inhalers. The difference was striking. Adherence of <80% of the prescribed doses was seen in 75% of the children by objective measures while this lack of adherence was only reported in 6% of the children by self-report in the diary cards. The parents' perception of the child's asthma is crucial for adherence to recommended therapy. This has been shown in several studies from the Netherlands. KLOK *et al*. [152] reported on the importance of follow-up and discussion with parents on their perceptions of the child's asthma. KOSTER *et al*. [30] reported how parents concern about side-effects affected their adherence to prescribed therapy and also that under treatment was associated with lower maternal education. CAUDRI *et al*. [153] reported from the 8-yr follow-up of the PIAMA cohort that under treatment was common but also over treatment was found in children who continued regular use of ICS while symptom free for >1 yr.

CONCLUSION

We have described a number of very exciting advances in paediatric asthma. However, the overall message for clinicians is timeless: it is essential to get the basics right. More mistakes are made through neglecting this principle than by failing to deploy the latest sophisticated treatments. Finally, it should be emphasised that childhood asthma also could be treated at the

community level, as shown in a study by MACKAY *et al.* [154]. A reduction of hospital admissions because of childhood asthma was seen after smoking was prohibited in public places in Scotland, UK. Another example of the impact of air pollution on asthma morbidity was provided by RENZETTI *et al.* [155], who report reduced markers of airway inflammation and improved pulmonary function in asthmatic children who were relocated from a highly polluted urban area to a less polluted rural area. These studies should remind all healthcare providers to take every opportunity to advocate measures to improve indoor and outdoor air quality.

STATEMENT OF INTEREST

None declared.

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