

REVIEW ARTICLE

Management of severe asthma in childhood – State of the art and novel perspectives

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Abstract

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. There is still a group of children with severe asthma in whom symptom control is poor depending either on identifiable aggravating factors or on true therapy resistance. These children have a poor quality of life and are limited by the severity of their disease. There is a need for a staged approach to the assessment and treatment of this small but vulnerable and resource-consuming group. The current review will provide an overview of a possible standardized approach to characterize this heterogeneous group of severely sick children including some newly developed ways of assessing asthma severity and potentialities of new asthma therapies. Furthermore, the umbrella term 'problematic severe asthma' is described. The term encompasses children whose severe asthma is due to identifiable exacerbating factors, as well as children who are resistant to any conventional therapeutic approach. Characteristics of these two groups of children are described, as are possible biomarkers and current and emerging diagnostic tools for allergy evaluation. Some recent advances and future possibilities for treatment of severe asthma are also presented in this review.

Childhood asthma encompasses several and different states of bronchial obstruction depending on age of presentation, cause of symptoms, severity of symptoms, persistency of symptoms, comorbidities, response to treatment and short- and long-term prognosis. In view of this heterogeneity, numerous guidelines and consensus reports have been produced. In 2009, an expert panel was requested to propose a WHO definition of asthma severity. The result of this task force was a uniform definition of asthma severity, control and exacerbations (1). The Global Initiative for Asthma management and prevention (GINA) has produced recommendations for the diagnosis, assessment and treatment of asthma in general (2). However, severe asthma is still a challenge, and proposals for the definition and management of this diverse, debilitating and resource-consuming disease are needed. Children that suffer from severe, often uncontrolled asthma are not capable of leading a normal life. Their quality of life is low due to the numerous school days missed, limited physical activity and high risk of severe exacerbations (3–6). A GA²LEN task force, the Problematic Severe Asthma Childhood Initiative, has suggested a uniform approach to this problematic group of paediatric patients. The umbrella term *problematic severe asthma* was adapted by the

GA²LEN task force (7, 8). The definition was described and a proposal for assessment was presented as were possible treatment options (8–10). The ICON position paper that was launched recently (11) provides an extensive and instructive overview of current knowledge on diagnostic procedures and mechanisms of paediatric asthma of varying severity.

Problematic severe asthma

As stated in the ICON document and other reports, 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 short-acting inhaled β_2 -receptor agonists (SABA), inhaled corticosteroids (ICS) and, when needed, long-acting β_2 -receptor agonists (LABA) and leukotriene receptor antagonists (LTRA) (11, 12). Approximately 5% of all asthmatic school children are referred to as severe asthmatics. They have chronic symptoms and/or recurrent exacerbations despite maximum treatment with conventional medications (13). Due to the lack of specific biomarkers, these children are still being defined on the basis of the intensity of treatment

Asthma severity according to the GINA guidelines(2010)

Level of asthma control				Treatment steps				
Characteristics	Controlled	Partly Controlled	Uncontrolled	Step1	Step 2	Step 3	Step 4	Step 5
Daytime symptoms	twice or less/week	> twice/week	Three or more	SABA as needed	SABA as needed	SABA as needed	SABA as needed	SABA as needed
Limitations of activity	None	any	more		Low dose ICS or	Low dose ICS + LABA or	Medium/high dose ICS + LABA	Oral GCS
Nocturnal symptoms	None	any	features					
Rescue medication	twice or less/week	> twice/week	of partly		LTRA	Low dose ICS + LTRA	+ LTRA	Anti-IgE
Lung function	normal	< 80% personal best	controlled					
Exacerbations	none	≥ one/year	>1/month				+ theophylline	

Figure 1 (a) GINA classification of asthma control. (b) Treatment steps according to GINA (2).

required to improve asthma control and the level of control achieved (8, 14). GINA guidelines (2) define three levels of asthma control: controlled, partly controlled and uncontrolled (Fig 1a), in relation to six different characteristics (Fig 1a). This evaluation is further considered in relation to the five treatment steps (Fig 1b). Severe asthma is defined by a lack of control despite treatment steps 4 and 5. Those who achieve control by step five treatment or 'beyond guidelines therapy', but would suffer an exacerbation if treatment was stepped down (2, 15), are also included in the definition of severe asthma. These children represent a continuous clinical challenge to the paediatrician (9, 15).

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

Difficult-to-treat asthma vs. Therapy-resistant asthma

In the UK, studies have shown that more than 50% of children referred for severe asthma could be identified as 'difficult to treat' due to aggravating factors (16). In a study of Swedish school children with problematic severe asthma, 39% were exposed to exacerbating factors that could be treated or at least partially eliminated. These findings provide support for the

clinical utility of a PA definition (4) (Fig 2). Moreover, these exacerbating factors were not disclosed during the routine care provided by an experienced paediatrician, which emphasizes the usefulness of an extensive and standardized clinical protocol.

Clinical presentation of Severe Asthma in school-age children

The first step in caring for a child that has been referred for severe asthma must be to eliminate the possibility of an incorrect diagnosis. As illustrated in Table 1, there are a number of diseases of the respiratory tract that need to be excluded before the stepwise approach to problematic severe asthma can begin.

Problematic severe asthma may include different subtypes, two such distinctive phenotypes can be defined but they are not mutually exclusive.

Exacerbation phenotype

Children with problematic severe asthma who have suffered one or more severe exacerbations during the preceding 12 months, without experiencing day- or night-time symptoms in between.

Chronic symptoms phenotype

Children with problematic severe asthma that have experienced day- and/or night-time symptoms more often than twice a week during the preceding 3 months.

Although impaired asthma control and risk of exacerbations are related, their respective predictors are different (17).

Severe asthma in children with preschool wheeze

The definition of severe asthma in preschool children is less established. So far, the best approach has been described in the ERS preschool wheeze task force report (18). Severity in this age group is often dependent on the nature of the airway infection that has induced the bronchial obstruction. These children are classified as having episodic wheeze, while those who wheeze between infections are classified as having multi-trigger wheeze. It is still not known whether/or to what degree an existing airway allergy aggravates the viral-induced bron-

Table 1 Differential diagnoses that need to be considered in children with severe asthma

Vocal cord dysfunction (VCD)
Tracheomalacia
Congenital disorders
Primary ciliary dyskinesia
Foreign body
Bronchiolitis
Immunodeficiency
Cardiac disease
Cystic fibrosis

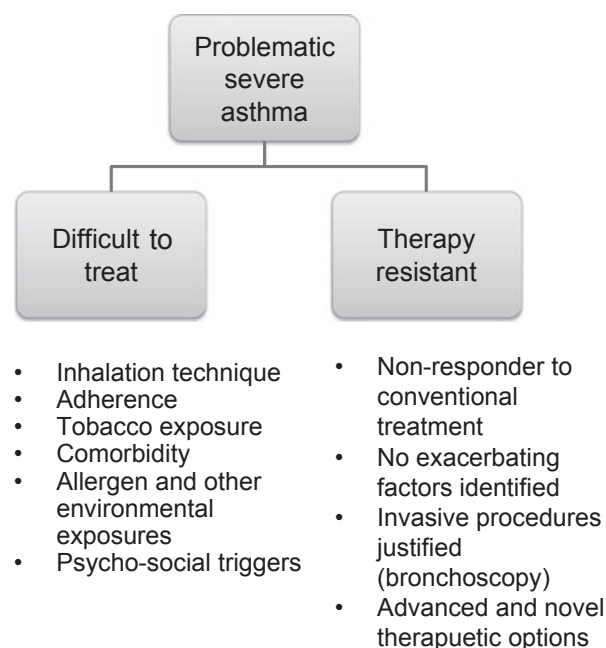


Figure 2 Clinical classification of children presenting with problematic severe asthma (7, 8).

chial obstruction or starts a chronic asthma disease (19), or whether the reverse is more likely (20). A variable response to inhaled corticosteroids is another characteristic of children with preschool wheeze.

Characteristics and assessment of severe asthma

Comorbidities

Some of the alternative diagnoses may also play a role as comorbidities such as tracheomalacia and vocal cord dysfunction (Table 1).

Chronic rhinosinusitis The comorbidity of childhood asthma and rhinitis is well established (21) and rhinosinusitis may be an underestimated disease, even in children (22). Rhinitis and rhinosinusitis should be treated even if there is still controversy surrounding the effects of nasal corticosteroids on the lower airways.

VCD should be recognized as it is treatable, although not with asthma drugs. VCD and asthma can coexist and confuse the evaluation of response to treatment. Low et al. (23) report a potentially useful, non-invasive method for the quantification of laryngeal movement using computed tomography (CT) of the larynx.

Gastro-oesophageal reflux should be confirmed if the patient is symptomatic, however, controlled treatment studies are disappointing regarding beneficial effects on asthma symptoms (24).

Vitamin D deficiency shows an association with asthma severity as reported both in the elegant study by Gupta et al., as well as in the CAMP study (25, 26). Risk of exacerbation was increased in children with low levels of Vitamin D.

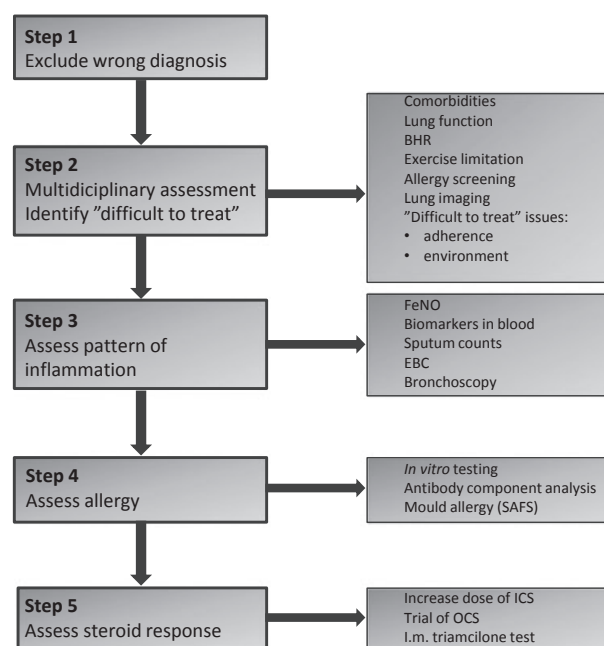


Figure 3 Stepwise assessment plan for problematic severe asthma, as adapted from ref 10 (Loedrup-Carlsen KC et al.). BHR – bronchial hyper-responsiveness, FeNO – exhaled nitric oxide, EBC – exhaled breath condensate, SAFS – severe asthma with fungal sensitization, ICS – inhaled corticosteroids, OCS – oral corticosteroids.

However, controlled studies regarding the benefit of vitamin D treatment are lacking.

Obesity has a complex relationship with severe asthma, contributing both to decreased corticosteroid responsiveness (27) and mechanical impairment of lung function, but on the other hand, obesity can also be a consequence of sedentary behaviour due to severe asthma (28).

Inflammation

Airway inflammation is one of the pathophysiological characteristics of asthma. This infiltration of inflammatory cells subsequently leads to bronchial hyper-responsiveness, and in the case of chronic inflammation, persistent changes to the airways, i.e. airway remodelling (29). The aetiology of airway inflammation in asthmatic children varies depending on age and trigger factors. Viral infections, including rhinovirus and respiratory syncytial virus, are linked to bronchial obstruction in infancy and early childhood and are considered by some to be a risk factor along with allergen sensitization (30). The development of allergic inflammation may be caused by a damaged respiratory epithelium, which is less resistant to inhaled allergens and subsequently leads to an enhanced Th₂ response in liable children (31). Sensitization and exposure to allergens are a major cause of allergic inflammation in older children, although viral infections have been shown to be the most important cause of asthma exacerbations in all age groups (32). In a French study, two clusters of severe asthma in children were identified – one characterized by multiple allergies, severe exacerbations and

increased blood eosinophils, the other by bronchial obstruction and elevated blood neutrophils (33).

Airway remodelling

Airway remodelling refers to structural changes in the bronchial wall causing reduced lung function in patients with asthma. These structural changes are diagnosed histologically and include epithelial damage, thickening of the reticular basement membrane, 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 PA (34) and is likely to underlie the progressive loss of lung function found in some patients (35).

Lung function/impairment

Reversible airway obstruction is a characteristic feature of asthma. However, the relationship between lung function and asthma severity may be complex. Some studies show no difference in FEV₁ between patients with severe and moderate asthma (36), but the results from these studies and our own (37) show large individual variations, implicating that the usefulness of FEV₁ as indicator of severity in childhood asthma remains questionable.

Bronchial hyper-responsiveness

Bronchial hyper-responsiveness (BHR) to methacholine has been shown to correlate with asthma severity in specific studies on children with PA (13, 38). BHR to methacholine has also been shown to correlate with markers of airway inflammation, including exhaled nitric oxide in severe asthmatics. The clinical relevance of direct and indirect testing of bronchial responsiveness is still debatable, and in those with poor lung function, it is not safe to perform a bronchial challenge test. An exercise test can add important information on both BHR and lack of control. A standardized exercise test can be performed also in those with impaired lung function under careful surveillance. Exercise-induced asthma can also be aggravated by allergy like the seasonal deterioration in children with pollen allergy and severe asthma (39).

Allergy

IgE-mediated allergy leading to allergic inflammation is common among children with persistent severe asthma (38). Seasonal differences in allergen exposure may result in periodic variations of asthma control and both current and long-term asthma control need to be evaluated (40). Worldwide studies (e.g. the MeDALL initiative) that aim to identify allergic phenotypes and understand the complexity of IgE-related phenotypes in children and adults are ongoing (41).

Imaging

The relationship between CT findings in children with asthma and markers of remodelling has been investigated in studies of

severe asthma, high-resolution CT (HRCT) scans are suggested to demonstrate bronchial wall changes (42). Little is known about the possible role of MRI in the evaluation of airway remodelling and/or asthma severity, although a combination of HRCT and MRI could help to identify regional distributions/effects of bronchial/small airway obstruction in children with asthma (43).

Biomarkers for airway inflammation

A biomarker may be used in one or more of the following settings: to assess risk of morbidity, identify disease phenotypes and to monitor disease activity as well as treatment effects (44). The ideal biomarker is obtained non-invasively, is reproducible, easily measured and provides information about essential pathophysiological processes. The acquisition and use of biomarkers in childhood airway disease are particularly challenging.

Bronchoalveolar lavage and sputum

Invasive methods such as performing bronchoscopies to obtain biopsies and bronchoalveolar lavage are possible in specialized centres, but in many circumstances, they are not considered feasible in children. In severe therapy-resistant asthma, a bronchoscopy may be required to obtain a more detailed picture of the degree of inflammation and/or airway remodelling (45). The relative contribution to asthma severity made by the different cell types found in such samples is not clear. In a recent study of children with therapy-resistant asthma, there was a huge variation in BAL and biopsy eosinophil counts (34). Furthermore, Ullman et al. (46) have shown that there is no agreement between these two measurements in children with severe asthma.

Induced sputum, a semi-invasive method, has been found to be safe in children but does require specially trained staff (47). Cross-sectional studies have shown different patterns regarding the cellular composition of sputum samples from children with non-allergic and allergic asthma (48). In a recent meta-analysis, the utility of sputum eosinophils was confirmed in adults (49), but further studies in children are required.

Exhaled nitric oxide

The fraction of NO in exhaled air (FeNO) has been established as a non-invasive biomarker in asthma. In a cross-sectional study, Zeiger et al. (50) showed that FeNO could be used as a complement to symptom evaluation as higher FeNO was associated with an increased use of SABA and the need for oral corticosteroids. Nevertheless, the clinical situation in which FeNO provides the most useful information is currently under debate, and the relationship between FeNO and asthma severity is unclear (51). In a recent meta-analysis (49) including three paediatric studies examining the benefit of FeNO in guiding treatment in children with asthma, it was concluded that FeNO did not improve asthma outcomes. Finally, measurements of FeNO fluctuation in combination with methods that quantify cross-correlations with symptoms can

be used as indicators of exacerbation risk, as opposed to the use of isolated FeNO measurements (52).

Exhaled breath condensate

Analysis of certain metabolites in exhaled breath condensate (EBC) is another non-invasive method proposed to reflect airway inflammation. Various different approaches and analytical methods have been suggested over the past years. In a recent study, LTB₄ and 8-isoprostane were found to be increased in children with asthma aged 6–14, compared to healthy controls (53). In another two paediatric studies, eosin, eotaxin and 8-isoprostane were measured in EBC and all three were significantly increased in children with problematic severe asthma (54). Interestingly, in a prospective study, IL-5 and condensate acidity were able to predict asthma exacerbations (55). Finally, metabolomic profiling of EBC, an advanced approach to mediator measurement in this matrix, was reported to identify patients with severe asthma (56).

Urine

Urine is the most accessible and non-invasive biofluid, yet, its utility is still questionable regarding the diagnosis and monitoring of asthma and airway inflammation. There are, however, new approaches that seem promising. Metabolomic profiling of asthma by magnetic resonance spectrometry of urine is an example. Saude et al. (57) applied this technique to discriminate between children with acute and stable asthma, as well as healthy controls, with promising results. In a similar group of children with asthma, liquid chromatography coupled with mass spectrometry was used to analyse urine samples, and the results obtained were in agreement with the Saude et al.'s study (58). The measurement of urinary leukotriene excretion has also been investigated to find a marker of the response to leukotriene antagonists, and the ratio of urinary LTE₄/FeNO has shown some promise for this purpose (59). Markers of eosinophil activity such as EPX have not been found to be useful in the monitoring of asthma; however, a urinary marker of eosinophil-catalysed protein oxidation, bromotyrosine, has been found to associate with asthma control and risk of asthma exacerbation in children (60).

Possible new biomarkers in blood

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 (61). Although chitin is not present in the human body, we express enzymes capable of its degradation. The enzymatically inactive chitinase-like protein YKL-40 is increased in the serum of patients with asthma (62), and levels of YKL-40 have also been shown to correlate with markers of asthma severity (62). It has been suggested that the chitinases may be involved in the development of fibrosis and remodelling of the airway (63). In the previously mentioned

Swedish study of children with PA, our results show a correlation between serum YKL-40, blood neutrophils and bronchial wall thickening as measured by HRCT of the lungs (64).

Periostin

Periostin is a systemic biomarker of airway eosinophilia, and it is found to be elevated in the serum of about half of all patients with asthma, particularly in those with severe eosinophilic asthma. It is a protein suggested to be a specific marker of a Th₂-type inflammation in asthma. It has also been shown that adult patients with high periostin levels respond to IL-13-directed therapies (65). Periostin in serum may also be useful in identifying children with severe asthma suitable for IL-13-directed therapies.

Diagnosing allergy

Allergy testing

Sensitization is usually determined by extract-based methods, by *in vivo* skin prick testing and/or *in vitro* testing, i.e. the measurement of specific IgE in serum. These methods only provide information about the possible source of the sensitizing allergen, but no information regarding sensitization towards specific allergenic components. Thus, it is not possible to differentiate between the primary source of sensitization and cross-reactivity between allergens from different sources (66). Moreover, it is not possible to determine whether the patient is sensitized to an allergen causing severe reactions or allergens causing mild reactions. In children with severe asthma, it is important to characterize the allergy diagnosis. It often requires both *in vivo* and *in vitro* testing (67). Furthermore, children with asthma and food allergies were demonstrated to have more sputum eosinophils than children with asthma without food allergies (68), implying that the impact of food allergy in severe asthma may be underestimated.

IgE component-resolved diagnostics

Every allergen has several epitopes, and similar epitopes might occur in allergens from different sources, which is the biological explanation of cross-sensitization (66). Some allergens are unique markers of a specific source, whereas other allergens may arise from different sources, yet share a similar structure and function. Component-specific methods are currently available and may help us to identify these allergens, making it possible to determine the sources of the sensitizing allergens, as well as the sources of the cross-reactive allergens (69). Furthermore, it is possible to predict whether a patient is at risk of a severe or mild reaction, based upon the allergen towards which the patient is sensitized. Children with severe asthma who are allergic to peanut and sensitized to the allergens Ara h 1, Ara h 2 and Ara h 3 are at risk of life-threatening asthmatic reactions upon peanut exposure, compared to birch allergic children only sensitized to Ara h 8 (70), which is a homologue of the major Birch allergen, Bet v 1.

IgE component microarray-based diagnostics

Today, the only commercially available component-based microarray platform for allergy diagnostics 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. Performing this analysis may be of additional value in children with severe asthma as Nordlund et al. (71) report that children with severe asthma display increased sensitisation towards the animal-derived components lipocalin, secretoglobulin and kallikrein compared to children with well-controlled asthma.

Basophil allergen threshold sensitivity (CD-sens)

Assessment of allergen-specific IgE antibodies does not necessarily predict the effector cell response and the subsequent clinical symptoms upon allergenic exposure. For this purpose, allergen provocation tests are needed, but as they are potentially risky, especially in children with severe asthma, they cannot be performed. Basophil allergen threshold sensitivity (CD-sens) is an *in vitro* alternative to clinical allergen provocation tests and correlates well with *in vivo* allergen provocation (72). CD-sens is based on the detection of CD63 on basophils following an *in vitro* allergen titration and reflects the sensitivity of basophils to a particular allergen. A difference in CD-sens has been demonstrated between cat-allergic children with mild and severe asthma, despite comparable levels of cat-specific IgE (73).

Recent advances in the pharmacotherapy of asthma in children

There are reviews of treatment of preschool wheeze and severe asthma in school children (9, 18). A stepwise therapeutic approach is generally applied to adjust medication according to the symptoms present, and several guidelines have been published to support the physician in these treatment decisions (11, 12, 74).

Treatment of preschool wheeze

The ERS Task Force (18) proposed that preschool children with episodic viral wheeze (EVW) should be treated with intermittent therapy. However, the results of previous trials of intermittent treatment strategies have been mixed. One study of 238 randomized children between 1–4 yr of age found no significant effects of either inhaled budesonide or montelukast as compared to placebo (75). On the other hand, another study examining the episodic use of high-dose fluticasone in children aged 1–6 yr reported a reduction in the need for oral corticosteroids, and some effect on symptoms and SABA use (76). A third approach, comparing intermittent and continuous treatment with budesonide in children aged 12–15 months did not report significant differences in any outcomes, including frequency of exacerbations (77). From these data, it is clear that the treatment of preschool children with ICS for EVW has

to be individualized and with a careful follow-up. On the basis of a review by Kaditis et al. (78), the task force recommends that children with multi-trigger wheeze use low-dose continuous ICS therapy and/or a LTRA. In the ICON position paper, it is concluded that there is a need for more studies of new strategies with existing medications especially in the youngest age group.

Treatment of school-age asthma

There are few studies focused on school-age children with severe asthma. The GA²LEN task force has reviewed the current literature and concluded that most studies of asthma therapy have been conducted in adults and that there is a great need for paediatric studies in these severely sick children (9). The results of a selection of recently performed studies are summarized below.

Inhaled corticosteroids

The dose–response curve to ICS in children is a matter of debate. In some children, doses of ICS higher than those conventionally used (>800 µg per day beclomethasone equivalent) may be beneficial. A Cochrane review (79) found few studies on high-dose ICS therapy that were of relevance to severe asthma in children. However, there was some evidence that those taking oral prednisolone were able to reduce their prednisolone dosage if they used a higher than conventional dose of ICS. Again, a clear need for more data was identified. Another recent Cochrane analysis of intermittent versus daily ICS concluded that daily treatment was superior to intermittent regarding indicators of lung function, airway inflammation, asthma control and reliever use, although a similar efficacy on the risk of severe exacerbations was observed (80). It is noteworthy that continuous ICS can have a dose-dependent effect on children's growth. In the CAMP study, children in the budesonide group reached a final height that was 1.2 cm shorter than those in the placebo arm of the study (81).

The molecular mechanisms of steroid resistance in children with severe, therapy-resistant asthma are not known and may be different to those in adults. A trial with parenteral or oral corticosteroids may be recommended and has proven effective in ruling out true corticosteroid resistance (36).

Inhaled corticosteroids and LABA or LTRA

The study by Lemanske et al. (82) enrolled 182 children who were symptomatic despite being prescribed fluticasone 100 mcg twice daily. The investigators used a triple crossover, unblinded design to assess the benefit of additional therapy with high-dose ICS, long-acting β -2 agonist (LABA) or leukotriene receptor antagonist (LTRA). The main findings were that (a) additional therapy with LABA was best for the group as a whole, although many children did better with the other alternatives; and (b) the peak of the ICS dose–response curve was at a low dose of fluticasone for most of the group. These findings further highlight the need for individualized therapy in those children with severe disease.

Small airways and severe asthma. It is not clear whether distal inflammation is an intrinsic part of severe, therapy-resistant

asthma or reflects poor distal airway deposition of conventional ICS. There are two strategies whereby treatment may reach the small airways, involving either the use of oral corticosteroids or small particle ICS such as ciclesonide, which may have enhanced distal airway deposition (83). A recent comparison of efficacy of ciclesonide compared to other ICS could however neither confirm nor refute any significant difference between ciclesonide and budesonide or fluticasone (84).

The symbicort maintenance and reliever therapy (SMART) regimen. This regimen involves the use of a single inhaler (containing budesonide and formoterol) for both regular therapy and to treat exacerbations. The optimal SMART daily dose for children with severe asthma has not been studied, and data proving its efficacy compared to conventional regimes are lacking (85).

Low-dose theophylline

Theophylline has again been discussed as a potentially beneficial agent in asthma, and low-dose theophylline (blood levels of 5–10 instead of 10–20 M) may have some immunomodulatory properties. It is suggested that at least some forms of acquired steroid resistance may be reversed by low-dose theophylline. However, the clinical effects of adding theophylline to inhaled corticosteroid therapy have been small (86).

Omalizumab – anti-IgE

The anti-IgE monoclonal antibody omalizumab is a well-established therapy for childhood asthma. A randomized, double-blind, placebo-controlled study of more than 400 inner city children and young adults aged 6–20 yr demonstrated that omalizumab, not merely improved the number of symptom-free days, but also significantly reduced the numbers of patients suffering an exacerbation from 48.8% to 30.3% (87). In an additional analysis, the seasonal peak in exacerbations was abolished. Furthermore, the response was improved in children with higher FeNO and blood eosinophils (88). A study in younger children aged 6 to <12 yr showed that omalizumab caused a 31% reduction in exacerbation rates (89). Taken together, these studies suggest that allergic inflammation may significantly contribute to exacerbations.

New treatment possibilities

Tiotropium

A large adult study showed that the addition of tiotropium to the regime of patients symptomatic despite ICS therapy was superior to doubling the dose of ICS and equivalent to adding LABA (90). There is no paediatric study on tiotropium therapy in asthma, but there is an urgent need to explore its role.

Macrolide antibiotics

Macrolides have a number of immune modulatory activities, in addition to their antibacterial effects (91). There is still very

little evidence supporting an effect in true severe, therapy-resistant asthma. Azithromycin or montelukast have been tested as corticosteroid sparing agents in moderate-to-severe asthma in children (92). Only 55 of 292 children could be randomized and results showed no effect of either of the added drugs. The study was underpowered, but the authors considered a benefit unlikely, even if the recruitment targets had been met. Another study of clarithromycin in children with asthma showed some effect on severity and duration of exacerbations (93).

Anti-fungal therapy

In adult practice, yet to a lesser extent in paediatrics, the concept of severe asthma with fungal sensitization (SAFS) is becoming more established. The possibility of clinical benefit and IgE reduction with itraconazole therapy in children is not known.

Th₂ cytokine antagonists

Several other new treatment alternatives are in the pipeline, so far only studied in adults, including Lebrikizumab (IL-13 antagonist) (94) and Reslizumab (antibody against IL-5) (95) all of which predominantly target allergic asthma. As these are, or are likely to be, expensive treatment alternatives, a detailed characterization of patients to identify those most likely to benefit from these interventions will be important. As mentioned – a novel marker of potential clinical relevance in this context is periostin (96). The effect of Lebrikizumab treatment has been shown to be greater in severe asthmatics with high levels compared to those with low periostin levels, as demonstrated by an improvement in FEV₁ and a reduction in FeNO (94), thus providing an entirely new example of biomarker-guided treatment in severe asthma.

Allergen avoidance

This is still a controversial issue particularly in relation to the clinical impact of decreasing dust mite exposure. A new device to reduce allergen exposure in the bedroom has recently been tested whereby allergen exposure is decreased by a technique involving temperature-controlled laminar airflow above the bed. It has been reported that the use of this device is able to improve airway inflammation and quality of life (97).

Prevention

New treatment alternatives for asthma, particularly in children, should not only focus on suppressing the inflammatory response. The idea of primary prevention of asthma by combining vaccines for allergy and rhinovirus infections is a novel and interesting approach (98). Another novel approach is that of intralymphatic immunotherapy, which may be a ‘fast-track’, effective alternative to subcutaneous immunotherapy (99). It is important to stress that immunotherapy for allergic asthma is not safe in children with uncontrolled asthma. Finally, Vitamin D supplementation could strengthen the

immune response in children with therapy-resistant asthma (25), although clinical trials are required.

Exacerbations

The most common triggers of exacerbation include viral infections, allergen exposure, non-adherence to controller therapy, exposure to pollutants, smoke and psychological stress (11, 18, 100). Recent exacerbation history is a strong predictor of future exacerbation risk (101). There is some support that a symptom-based written action plan may prevent acute care visits (102). Treatment and care of a child with an acute exacerbation is best guided by standardized management strategies as illustrated by the ICON document and other reports and guidelines (11, 103–105). It is beyond the scope of this review.

Adherence to interventions and perception of disease

Reliable assessment of adherence to prescribed treatment is a challenge in clinical practice, as well as in research on patients with asthma, particularly with a view to prevent and recognize risk of exacerbation (106). Krishnan et al. (107) compared subjective and objective measurements of children's adherence to inhaled corticosteroid therapy in a CAMP substudy. The reported intake of ICS as reported on diary cards was compared to the number of doses remaining in the study inhalers. The difference was striking. Adherence to less than 80% of the prescribed dose was seen in 75% of the children, as detected by objective measures, while this lack of adherence was only self-reported by 6% of children on the diary cards.

The parents' perception of a child's asthma is crucial for adherence to recommended therapy. This has been shown in studies from the Netherlands. They reported the importance of follow-up and discussion with parents regarding their perceptions of their child's asthma and concern about side effects (108, 109). Caudri et al. (110) reported from the 8 yr follow-up of the PIAMA cohort that undertreatment was common, but overtreatment was also found in children who continued with regular ICS use despite being symptom free for more than 1 yr. It is not unusual that children and parental-reported asthma control by, e.g. the asthma control test (C-ACT), does not agree with a paediatricians' assessment of asthma control by the GINA guidelines, and both might be needed for an accurate report of asthma status (111).

Last but not least, the home environment is of fundamental importance, particularly in children with 'difficult-to-treat' severe asthma. A home visit can add important information and also contribute to improved communication and adherence to both the avoidance of triggers and prescribed therapy (16).

In summary

Children with severe asthma require a standardized and individualized approach including reassessment for differential diagnoses, comorbidities, aggravating factors in their environment, careful work-up on airway inflammation/remodelling (invasive when required), allergy, response to therapy and last but not least evaluation of quality of life. There is a great need for extensive collaborations between specialist centres in finding new ways of preventing and treating these very sick children.

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