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SERIES "HOT TOPICS IN PAEDIATRIC ASTHMA"
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Problematic severe asthma in children, not one problem but many: a GA^{2}LEN initiative

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ABSTRACT: Although most children with asthma are easy to treat with low doses of safe medications, many remain symptomatic despite every therapeutic effort. The nomenclature regarding this group is confusing, and studies are difficult to compare due to the proliferation of terms describing poorly defined clinical entities.

In this review of severe asthma in children, the term problematic severe asthma is used to describe children with any combination of chronic symptoms, acute severe exacerbations and persistent airflow limitation despite the prescription of multiple therapies.

The approach to problematic severe asthma may vary with the age of the child, but, in general, three steps need to be taken in order to separate difficult-to-treat from severe therapy-resistant asthma. First, confirmation that the problem is really due to asthma requires a complete diagnostic re-evaluation. Secondly, the paediatrician needs to systematically exclude comorbidity, as well as personal or family psychosocial disorders. The third step is to re-evaluate medication adherence, inhaler technique and the child's environment.

There is a clear need for a common international approach, since there is currently no uniform agreement regarding how best to approach children with problematic severe asthma. An essential first step is proper attention to basic care.

KEYWORDS: Child, genes, problematic severe asthma, prognosis

Most children with asthma respond well to treatment with safe and evidence-based medications. However, those children who do not appear to respond to standard therapy show considerable morbidity and even mortality, and consume a disproportionate amount of health resources [1]. The prevalence of severe asthma in childhood is largely unknown, since there is no general consensus regarding the definition, and severe childhood asthma has rarely been studied in a general population. One birth cohort study reported the prevalence of severe asthma in a general population of 10-yr-old children to be 0.5%, and 4.5 % among children with asthma [2], using a definition of poor asthma control despite prescription of 800 μg budesonide equivalent and at least a long-acting β-agonist and/or a leukotriene antagonist. However, there may be disparate underlying problems, including wrong diagnosis, poor adherence to therapy, adverse environmental conditions and comorbid conditions, such as gastro-oesophageal reflux and rhinosinusitis, as well as various forms of genuine therapy-resistant asthma. Hence randomised controlled trials of treatment or searches for asthma genes must be preceded by a rigorous elimination of all extraneous factors causing poor control, followed by description and characterisation of those with genuine therapy-resistant asthma.

Age is an important modifier of the clinical characteristics and presentation of problematic severe asthma (see definitions later on) and the treatment response, which may differ considerably from infancy to teen age. Lack of asthma control is, in all age groups, related both to the frequency and severity of the attacks, as well as to the persistence of recurring symptoms of airways

For editorial comments see page 6.

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obstruction. During the first 3 yrs of life, frequently recurring asthmatic attacks often require hospitalisation and the exacerbations are most often precipitated by respiratory virus infections. Viral infections remain the major cause of exacerbations in all age groups, and the treatment response may differ according to age; this will be discussed in a later article in the present series.

The aims of the present article are, first, to describe and define appropriate terminology; secondly, to consider which asthmatic children should be investigated; and, lastly, to summarise what is currently known about factors contributing to poor response to treatment. Treatment response will be discussed further in the next article in the present series, on the assessment of problematic severe asthma, and is not discussed here in any detail.

TERMINOLOGY

When a child is referred to a specialist because asthma treatment is apparently not working, it is initially unclear whether this is due to true therapy-resistant asthma, or whether the child is simply not taking treatment or adhering to the prescribed treatment. We suggest that, before evaluation by a specialist, all of these children are categorised as having problematic severe asthma [3]. The first aim of specialist evaluation is to subcategorise them into difficult-to-treat asthma and true severe therapy-resistant asthma (see below).

AGE-RELATED PRESENTATION OF PROBLEMATIC SEVERE ASTHMA

1) School-age children who, despite prescribed therapy of $\geqslant$800 $\mu g \cdot day^{-1}$ inhaled corticosteroid (budesonide or equivalent), have undergone trials of at least two of three controllers (long-acting β-agonist, leukotriene receptor antagonist and oral theophylline) and still have symptoms as described below would be considered to have problematic severe asthma. Any controller may have legitimately been discontinued because of lack of benefit.

2) Pre-school children. Any child falling into one or more of the following categories despite trials of maximal guideline-recommended treatment should be considered as having problematic severe asthma [4].

Categories of symptom patterns in problematic severe asthma in children

1) Persistent (most days; for $\geqslant$3 months) chronic symptoms of airways obstruction with poor quality of life. This group includes type 1 brittle asthma (chaotic swings in lung function, with a very labile peak flow) [5]. However, this type 1 brittle asthma may not necessarily be the same as asthmatics with milder persistent symptoms.

2) Acute exacerbations with or without associated interval poor control, which may be very severe. They may have required any or all of: 1) at least one admission to an intensive care unit, 2) at least two hospital admissions requiring intravenous medication(s), and 3) at least two courses of oral steroids during the previous year.

3) Persistent airflow obstruction following steroid trial, with post-bronchodilator Z score of $<$-1.96 using appropriate reference equations [6].

4) The need for prescription of alternate-day or daily oral steroids in order to achieve control.

SUBGROUPS OF PROBLEMATIC SEVERE ASTHMA

The recognition that a child has problematic severe asthma is the prelude to an attempt to dissect out the reasons for failure to achieve well-controlled asthma. The next step is to assess reasons for treatment failure, by separating difficult-to-treat-asthma from severe therapy-resistant asthma (fig. 1). This is preceded by an appropriate work-up in order to exclude other diagnoses (wrong diagnosis, not asthma at all). This is not discussed further in the present article. We accept that there is a spectrum, for example children with severe therapy-resistant asthma often have consequent psychosocial issues, and the importance of these *versus* genuine steroid unresponsiveness requires continuous re-evaluation. Nonetheless, we believe the concept of problematic severe asthma is a useful one, since the child who is not being given any therapy at all clearly requires a different approach.

We diagnose severe therapy-resistant asthma when factors that make the child difficult to treat cannot be identified. Severe therapy-resistant asthma may take a number of different forms, which are not mutually exclusive.

The phenotypes related to lack of response to the available therapies will be dealt with in the next article in the present series, on the assessment of problematic severe asthma. However, this is the group that may be eligible for toxic steroid-sparing agents, such as cyclosporin, or novel molecular-based therapies, such as anti-immunoglobulin-E or anti-interleukin (IL)-5 [7].

We diagnose difficult-to-treat-asthma when poor control is due to one or more of the following: associated diagnoses (comorbid conditions), poor adherence to treatment regimens, or adverse psychological and environmental factors. Such children may still be difficult to treat but they would not be candidates for innovative therapies, unless these problems have been solved and asthma severity persists. It would be difficult to justify the high cost of administering, for example, omalizumab, cyclosporin or anti-IL-5, together with the inconvenience to the family, if there is no willingness to take even basic steps to reduce allergen exposure and take standard therapies. Furthermore, such children should not be included

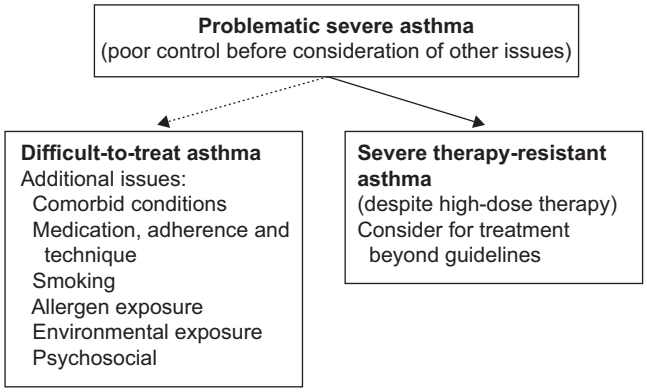

FIGURE 1. Problematic severe asthma can be divided up into difficult-to-treat asthma and severe therapy-resistant asthma.

in studies to determine genetic factors for severe therapy-resistant asthma.

Difficult-to-treat asthma

Associated diagnosis (asthma plus)

That other conditions may coexist with asthma should always be borne in mind, since continuing respiratory symptoms may be wrongly attributed to asthma alone. These children may be difficult to sort out. The two most common comorbid conditions are chronic rhinosinusitis and gastro-oesophageal reflux. It has long been recognised that diseases of the upper and lower airways may coexist. The relationship between the nose and the lung is complex (reviewed in [8]). Up to 80% of patients with asthma have rhinitis, and up to 15% of patients with allergic rhinitis have asthma [8]. It is unclear whether sinusitis worsens asthma, but both can be manifestations of the same underlying disease process. There is evidence that neglecting to treat rhinitis increases asthma morbidity [9, 10].

The relationship between the oesophagus and the lung is also complex [11]. Lung disease can cause gastro-oesophageal reflux, reflux can cause lung disease or reflux may be of no clinical significance. Depending upon the criteria used for diagnosis, 25–80% of children with chronic respiratory disease have gastro-oesophageal reflux [11]. To date, a precise mechanistic link between gastro-oesophageal reflux and decline in asthma control has not been established [12]. The results of trials of anti-reflux therapy are often disappointing, especially in older children, but an empirical trial is reasonable in younger children if the history is suggestive. Finally, diagnoses that can be confused with asthma, in particular vocal cord dysfunction, may coexist with asthma and be missed, leading to inappropriate asthma treatment [1].

Likewise, the relationship between obesity and asthma is complex. There are a number of confounding factors, including gastro-oesophageal reflux (above) and the effects of obstructive sleep apnoea. There are also sex differences, including lung development with growth and puberty, which affect the interactions between obesity and the airways [13]. Being overweight *per se* is also known to induce respiratory symptoms, such as dyspnoea and wheezing, which can mimic asthma. In the Childhood Asthma Management Program (CAMP) study, no significant association was found between body mass index (BMI) and many markers of asthma control; however, there was a decrement in the forced expiratory volume in 1 s/forced vital capacity ratio with increasing BMI [14]. It has also been reported that overweight children with asthma are more likely to be admitted to hospital when presenting at the emergency department with exacerbations [15]. Furthermore, obesity may cause steroid resistance, in part at least, by reducing steroid-induced mitogen-activated protein kinase phosphatase-1 [16].

Medication adherence and technique

Problems with medication are common, even in tertiary centres. Failure to take prescribed treatment is the commonest reason for continuing symptoms in patients with problematic severe asthma [17–19]. The first step is to obtain a prescription printout from the child's general practitioner or local paediatrician, and to check whether or not the prescribed medication has been obtained from the pharmacy. Another helpful way of assessing medication use and attitudes to medication is a home visit by a respiratory nurse [19]. Very young children are frequently and inappropriately left to take their asthma medications unsupervised [20]. Finally, repeated checking of inhaler technique is important.

Contributory factors

Home environment

It is difficult to evaluate the home environment without visiting. Families rarely give accurate descriptions of the degree of social deprivation, passive smoking, house dust and pet allergen exposure, and any damp and mould in their homes. Fireplaces, wood-stoves, kerosene heaters and gas for cooking have been associated with increased asthma morbidity [21]. Installation of more effective nonpolluting heating in the homes of children with asthma may significantly reduce symptoms [22]. Smoking cessation should be encouraged, pets removed, house dust mite prevention measures instituted and damp dealt with. There is ample evidence from adult studies that active smoking causes steroid resistance [23–25], and it is likely that passive smoke exposure has the same effects. In addition to house dust mite and pet allergens, mice and cockroaches may be important [26]. Allergen exposure may cause a sensitised subject to become steroid-resistant *via* an IL-2 and IL-4-driven mechanism [27, 28]. Furthermore, allergens cause more than allergy, and there is suggestive evidence that high levels of cat, dog and house dust mite allergens may worsen asthma even in the nonsensitised population [29, 30]. It is, however, often not possible to change the home environment.

Symptom perception, stress and other psychosocial issues

Psychological risk factors are prominent in children and young adults who subsequently die of asthma [31, 32]. Similarly, in near-fatal asthma episodes in children, the children also showed significant denial, psychosocial pathology and delay in seeking treatment [33]. There is a growing body of evidence linking psychological stress in the caregiver to both the onset of asthma and asthma-related morbidity [34]. In contrast, wheeze in children does not predict subsequent caregiver stress [34].

There is evidence that stress worsens asthma in children [35], which could be counteracted by life events with a definite positive effect [36]. Little is known about the biological mechanisms responsible for these effects. Asthma management behaviours, such as lack of concordance with prescribed medication due to psychosocial factors in chaotic families, influence asthma control. However, psychological distress may also influence asthma through neuroimmunological mechanisms and the induction of steroid resistance [37, 38]. This last factor is particularly significant because resistance to asthma therapy is so characteristic a feature of children with problematic severe asthma.

PROBLEMATIC SEVERE ASTHMA: PHENOTYPES AND AGE

The manifestations of problematic severe asthma in children vary with age. For practical and possibly aetiological purposes, the following age groups could be considered: 0–2, 3–5, and 6–12 yrs, and adolescents (12–17 yrs), each deserving specific consideration (table 1).

TABLE 1 Characterisation of problematic severe asthma at different ages (which may hamper recognition of asthma severity)

Infancy
Underlying pathophysiology and clinical characteristics poorly understood
Viruses are the most common precipitating factors
Many conditions to be considered in the differential diagnosis
Difficulty in objective documentation of bronchial obstruction
Many with problems in the first year of life remit long term in the second year
Pre-school age
Viruses are the most common precipitating factors
Compliance with management largely dependent upon carers
Some difficulty in objective documentation of bronchial obstruction or airway inflammation
School age
Allergy is frequent
Symptoms often precipitated by exercise
Compliance with management still dependent upon carers
Evaluation of lung function easy
Indirect evaluation of airway inflammation relatively easy
Adolescence
Clinical expression is variable
Tendency to deny symptoms
Risk-taking behaviour common
Low compliance
Psychological problems
Treatment may be difficult

There is little agreement regarding the criteria for severe asthma in the first 2 yrs of life. The underlying pathophysiology, as well as the clinical characteristics of severe asthma, is poorly understood. First, there are difficulties in objective documentation of asthma, such as with lung function measurements, and reversibility tests are difficult. Secondly, the younger the child the higher the risk of more severe episodes of bronchial obstruction due to the small airways. Thirdly, many differential diagnoses, as well as comorbid conditions and complications in the upper airways, are more likely to occur in the youngest children compared to older children.

At an age of 3–5 yrs, the difficulties in performing objective measurements remain. Compliance largely depends upon the parents. All through childhood, respiratory virus infections, especially rhinovirus, are the most common precipitant of acute asthma exacerbations [39–41]. However, sensitisation to inhalant allergens often becomes more important [42]. From pre-school age, exercise-induced asthma can be a manifestation of problematic severe asthma.

In the early school-age years (6–12 yrs of age), measurement of lung function, as well as other investigations, is possible. Allergies are an increasing factor, and compliance with management should still largely depend upon carers.

Adolescence is associated with increased asthma and asthma severity among females [43]. Furthermore, psychosocial factors become increasingly important associations of severe disease [44–46].

PROGNOSIS OF PROBLEMATIC SEVERE ASTHMA IN CHILDHOOD

Longitudinal studies of problematic severe asthma in childhood *per se* are lacking. However, some information can be obtained from the long-term studies of childhood asthma (table 2).

In the Melbourne Asthma Study, 83 subjects with severe asthma were followed from the age of 10 yrs to 42 yrs [48]. At 42 yrs of age, 90% of the original severe asthma group continued to have symptoms, and 45% had persistent asthma [48]. The risk of more severe asthma in adult life was increased by the presence of severe asthma and atopy in childhood (table 2) [47, 48, 51]. In the New South Wales Belmont cohort study, the subjects were recruited in 1982 at the age of 8–10 yrs and reassessed 15–17 yrs later [50]. The strongest predictors of troublesome asthma in adulthood were obstructive spirometry and atopy in childhood (table 2). Male sex was the strongest independent predictor for the absence of troublesome asthma in adult life.

It should be noted that the Melbourne study was started at a time at which inhaled corticosteroids were hardly available. It is possible that the long-term outcome would be different for children receiving modern treatment.

TABLE 2 Prognostic factors for more severe or troublesome persistent asthma in adulthood in children with severe asthma

Cohort	First author [Ref.]	Birth year	Inclusion		Assessment		Prognostic factors
			Age yrs	Year	Age yrs	Year	
Melbourne, AU	WOLFE [47]	1957	10	1967	35	1992	Atopic condition in childhood (hay fever, eczema, skin test reactivity)
	PHELAN [48]	1957	10	1967	42	1999	Frequent or persistent asthma symptoms
Dunedin, NZ	SEARS [49]	1972–1973	9	1981–1982	26	1998–1999	Airway hyperresponsiveness, sensitisation to house dust mite, female sex, early age at onset
Belmont, AU	TOELLE [50]	1972–1974	8–10	1982	23–27	1997–1999	Obstructive spirometry, allergic sensitisation, female sex, hay fever

AU: Australia; NZ: New Zealand.

GENETICS AND ASTHMA SEVERITY

There are few genetic studies on different phenotypes of asthma severity, as opposed to asthma presence. The genes encoding IL-4 receptor (*IL4R*), tumour necrosis factor (*TNF*), PHD finger protein 11 (*PHF11*) and cortactin (*CTTN*) are examples of genes that have been associated with severe asthma [52–55]. There is a clear need for further studies to better characterise the role of genetic factors in problematic severe childhood asthma.

CONCLUSION

The present review highlights the fact that problematic severe asthma in children may present itself in many different symptom patterns, ranging from a few acute really severe attacks in between excellent asthma control to chronic severe daily symptoms and impairment. There is a clear need for a common international approach, since there is currently no uniform agreement as to how best to approach children with problematic severe asthma. Many children with problematic severe asthma do not require molecular-based therapies, but rather proper attention to basic care. This is an essential first step, before genetics studies or trials of interventions should be initiated. Failure to consider where the child lies in the spectrum of problematic severe asthma diminishes the power of such studies and prejudices the results.

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STATEMENT OF INTEREST

Statements of interest for F.M. de Benedictis, A. Bush, K-H. Carlsen and G. Wennergren can be found at www.erj.ersjournals.com/misc/statements.dtl

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