

Will Symptom-Based Therapy Be Effective for Treating Asthma in Children?

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Abstract Traditionally, symptoms are important patient-oriented outcomes in asthma treatment, and assessment of symptoms is an essential component of assessing asthma control. However, variable airways obstruction, airways hyperresponsiveness and chronic inflammation are key components of the asthma syndrome, and correlations among these hallmarks and symptoms are weak or even absent. Therefore, it might be questioned if symptom-based therapy is effective for treating asthma in (all) children. To date, there is no firm indication that monitoring asthma based on repetitive lung function measurement or markers of airway inflammation is superior to monitoring based on symptoms only. In the majority of patients, symptom-based asthma management may well be sufficient, and in preschool children, symptoms are presently the only feasible outcome. Nevertheless, there is some evidence that selected groups might benefit from an approach that takes into account individual phenotypic characteristics. In patients with poor perception, those with a discordant phenotype and those with persistent severe asthma, considering lung function, airways hyperresponsiveness and inflammatory markers in treatment decisions might improve outcomes.

Keywords Asthma · Children · Symptoms · Asthma control · Asthma control questionnaire · Asthma control test · Childhood asthma control test · Lung function · Airways · Symptom-based therapy · Hyperresponsiveness ·

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Exacerbations · Sputum eosinophils · Exhaled nitric oxide ·
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Introduction

Asthma is the most prevalent chronic disorder in the Western world affecting 5–8 % of school-aged children (www.euro.who). The present guidelines stress that the goal of asthma treatment is to achieve clinical control and to reduce future risks to the child with asthma [1–5]. Treatment aims at reducing daytime symptoms, awakenings at night, the use of rescue bronchodilators and limitations to activity including sports. Second, future risk to the patient, including exacerbations, accelerated decline in lung function and side effects of treatment, should be avoided. However, despite effective anti-inflammatory medication, many children with asthma still have uncontrolled or partly controlled disease with high proportions of children reporting limitation of activities (47 %), waking up due to asthma (5–34 %) and school absenteeism in the past year (23–51 %) [6, 7].

Traditionally, asthma treatment has been individualized using symptoms as the main read-out. Symptoms of wheezing, cough, chest tightness and dyspnoea are used to diagnose asthma and monitor the response to treatment, and assessment of symptoms is an essential component of assessing asthma control [1, 2]. Symptoms and derivatives as symptom-free days or asthma control days are important patient-oriented outcomes, strongly correlate with (asthma-related) quality of life, and are highly relevant endpoints in clinical asthma studies [8•]. Symptom monitoring is easy, cheap, feasible in patients of all ages and in all populations, and requires only limited resources. Some disadvantages of symptom assessment are recall bias and poor perception of symptoms in selected children [9, 10].

However, the question remains whether symptom-based treatment is indeed effective enough in paediatric asthma

management, given the high proportion of children with partly or uncontrolled asthma.

Asthma is a chronic disorder with variable and reversible airways obstruction, airways hyperresponsiveness, and chronic, mostly eosinophilic, inflammation as hallmarks. Several studies show poor or absent correlation between current or recent symptoms and lung function or markers of airway inflammation, including airway hyperresponsiveness (AHR) to methacholine, fractional concentration of nitric oxide in exhaled air (FENO), induced sputum eosinophils and inflammatory cells in bronchial biopsies [11–13]. On the one hand, patients without any evidence of eosinophilic inflammation, either in sputum or in bronchial biopsies, may be highly symptomatic [14]. On the other hand, asymptomatic adolescents in clinical remission of asthma may show increased AHR, ongoing eosinophilic inflammation and airway remodelling in bronchial biopsies [15].

Obviously, the relationship between inflammation and symptoms, asthma control and asthma severity is complex. The discrepancy between symptoms, lung function and airway inflammation implies that decisions on anti-inflammatory treatment based on symptoms only might well be inappropriate. This review tries to answer the question whether symptom-based therapy is effective for treating asthma in children.

What is the Problem with Symptoms?

Although symptoms are of great importance to the patient, and are a prominent feature of asthma management plans, they are only part of the asthma syndrome and certainly the most subjective part. It has been demonstrated that asthmatic children who have moderate or severe asthma symptoms commonly believe that their asthma is well controlled, and thus overestimate their own level of control and asthma severity [9, 16]. This discrepancy between perceived asthma control and reported symptom severity suggests that patients seem to accept quite severe symptoms and adapt their lifestyle accordingly. Bad perception of bronchoconstriction is a major pitfall in symptom-based asthma management. In a Dutch study, more than one-third of asthmatic children had poor perception, about one in five over-reported symptoms and one in four showed a complete dissociation between symptoms and lung function [17]. Patients who suffer frequent exacerbations, those with severe asthma and those with more severe AHR are at increased risk of poor perception of bronchoconstriction [18].

An extra challenge in the treatment of asthmatic children is symptom communication. It is usually the parents that provide paediatricians with information about their children's asthma. Treatment decisions, nevertheless, should also be based on the child's own perception of symptoms,

next to accurate interpretation and evaluation of signs by the parents, and be established through effective communication with the physician, and followed by appropriate action by the physician [10, 19]. However, up to 78 % of parents underestimate the severity of their child's asthma and report good control, while the child does not meet the criteria for good control [10, 20]. Low socioeconomic status and parental smoking were shown to be risk factors for parental underestimation [21].

When relying on symptoms, physicians should be aware of the great variability of perception of bronchoconstriction, between patients and within a patient over time.

Measuring Symptoms

Vague, nonspecific questions on asthma control are more likely to lead to incomplete information and misinterpretation than more specific questions on symptoms [21]. To overcome this, specific short questionnaires have been developed and validated that assess symptoms and asthma control in a standardized way. Standardized questionnaires are attractive as they are cheap, easy to use and give a quick impression on asthma control. They provide a reproducible, objective measure that may be repeated over time and may improve communication between patient/parent and physician. However, validation studies are only conducted in a limited number of patient populations, and actually no studies are available on the potential of such questionnaires to improve asthma outcomes in children.

Three asthma questionnaires have been validated for use in children: the Asthma Control Test (ACT) or Childhood Asthma Control Test (C-ACT), the Asthma Control Questionnaire (ACQ), and the Asthma Therapy Assessment Questionnaire (ATAQ).

The ACQ is a 5- to 7-item questionnaire recalling the previous 7 days, with 5 items on symptoms and 2 optional items on use of rescue medication and FEV1 [22]. Each item scores from 0 (well controlled) to 6 (poorly controlled) and the mean score is used as an endpoint, with optimal cut-points of 0.75 or less for 'well controlled' asthma and 1.5 or greater for 'not well controlled'. [23]. The ACQ is validated for children 6–10 years of age, in whom a trained interviewer administers the questionnaire to children and for self completion by children aged 11 years or older [24]. Changes of 0.5 are considered clinically relevant.

The asthma control test (ACT) is a questionnaire designed to detect uncontrolled asthma and is available for children >11 years (ACT) and 4–11 years old (C-ACT) [25, 26]. Maximum scores range from 25 (ACT) to 27 (C-ACT) and a score of 19 or less corresponds with poorly controlled asthma, with sensitivities ranging from 71 to 74 % and specificities between 68 and 71 % [25]. The ACT asks back for 4 weeks on 5 items including symptoms, rescue bronchodilator use, and patient

rating of asthma control. The 7-item C-ACT comprises 4 questions which have to be filled in by the child with the help of a visual scale; 3 more questions are answered by the parents. The minimal clinically significant difference for (C-) ACT in children is 2 points (unpublished data).

The 20-item, parent-completed ATAQ has been validated for children 5 years and older and covers issues related to asthma control, patient–provider communication, attitudes and behaviours and self-efficacy with regard to medication-taking [27]. There are no data on the minimal clinically important difference of the ATAQ.

Symptom Diaries

Patient-reported daily diaries provide the opportunity to collect real-time information on asthma symptoms, medication use and other information. If diaries are completed on a daily base, incomplete recall or recall bias may be avoided. Daily diaries may be more sensitive than retrospective questionnaires [28]. However, paper diaries are susceptible to data fabrication, in particular if they are not completed in real time. Electronic diaries may overcome this problem as they have the possibility of time and date stamping, of sending reminders, and of restricted data entry times. Disadvantages of electronic diaries are the costs and the need for adequate technical support [29]. Routine use of diaries, either paper- or web-based, introduces a certain level of burden to the children and their parents. Most diaries used in clinical trials are not validated and a minimal clinically important difference in change in symptoms is not known.

Exacerbations

Prevention of asthma exacerbations is one of the most important goals of asthma treatment, as patients consider exacerbations as the most frightening aspect of their asthma, and exacerbations pose a substantial risk to the patient and are related to considerable costs. Therefore, the severity and frequency of exacerbations should be part of routine monitoring in all children with asthma. Yet, clinical criteria for asthma exacerbations in children are not very clear and more work is needed to define which changes in symptoms, use of beta-2-agonists and lung function are relevant in individual children and should be treated as an exacerbation [4]. In this respect, electronic diaries may be helpful.

Asthma Treatment Based on Lung Function, Airways Hyperresponsiveness or Inflammatory Markers

Lung function

Asthma is characterized by variable airways obstruction, and one of the goals of asthma management is to obtain optimal

lung function. Peak Expiratory Flow (PEF) and Forced Expiratory Volume in 1 second (FEV1) are frequently used in the assessment of asthma control and severity [1, 2, 5]. GINA guidelines use FEV1 or PEF to adjust treatment if less than 80 % predicted or less than 80 % of the personal best value [1]. Somewhat surprisingly, there is no evidence that regular monitoring of lung function improves asthma control in children. Changes in PEF poorly reflect changes in asthma activity [30]. PEF records are unreliable, and self-management plans that take PEF into account are no more effective than plans based on symptom monitoring alone [31, 32]. An open, randomized, parallel-group controlled study including 90 children showed no benefit of peak-flow guided treatment over symptom-based treatment [33]. In individual, motivated children when symptomatic or children with poor perception PEF monitoring in addition to symptom monitoring might have additional value in guiding treatment.

To date, there are no studies comparing symptom-based treatment versus treatment on symptoms plus FEV1, although, without lung function, physicians might overestimate the level of asthma control [34].

The presence and degree of airways obstruction has short- and long-term prognostic value for asthmatic children and is an independent predictor of future risk [35, 36]. This legitimates its use in asthma monitoring.

Airways Hyperresponsiveness

AHR is in a sense the first biomarker explored as a tool in an individualized asthma management plan to guide inhaled corticosteroid treatment. Benefits of AHR-driven asthma management have been shown in adults with asthma, and resulted in improved lung function and a significant reduction in the number of asthma exacerbations, at the cost of higher doses of inhaled steroids [37]. In a pediatric study, preservation of lung function was shown as a result of an AHR- based treatment strategy, with the greatest benefit in children with low symptom scores despite AHR [38]. This emphasises that there is room for improvement of strategies based on symptoms alone, and that phenotyping, in this case by measuring AHR, can improve the effect of treatment.

Airways Inflammation

Eosinophils in sputum and exhaled nitric oxide (FENO) have been shown reliable biomarkers of eosinophilic airway inflammation [39]. Sputum eosinophils may predict the response to ICS, predict exacerbations, and are predictive of successful steroid reduction [40–42]. Up-titrating of ICS in order to control sputum eosinophilia resulted in a markedly reduced exacerbation rate in adults [43]. As could be expected, treatment strategies based on findings in sputum were of particular benefit for patients with eosinophilic airway inflammation and

few symptoms. Only a single RCT in children has assessed the usefulness of 3-monthly measurement of sputum eosinophils [44•]. Contrary to findings in adults, this strategy did not significantly reduce overall exacerbations or improve asthma control in these children. This discrepancy could be due to patient selection, as these children were from a tertiary care centre and were treated for severe problematic asthma. Second, sputum eosinophils were only measured once every 3 months, which might not have been frequent enough.

Moderate feasibility for repeated sputum induction procedures, the risk of bronchoconstriction, high technical demands and costs of sputum induction and analysis limit the use of sputum samples in clinical practice.

The most easy-to-measure, feasible and accessible biomarker of eosinophilic airway inflammation is FENO, and FENO seems a promising marker to titrate the dose of ICS in asthma, thus tailoring the treatment to those patients who actually have chronic eosinophilic airway inflammation [45•, 46]. A limited number of studies in adults and children has explored the effect of such FENO-driven asthma treatment in a randomized controlled way [47–52]. The results were inconsistent, with marked benefits in certain populations and no benefits in others. Two Cochrane reviews concluded that there was insufficient evidence that tailoring of asthma treatment based on FENO monitoring improved asthma outcome in children [53]. However, these reviews were compromised by inconsistency between studies with respect to differences in populations, treatment algorithms, and definitions of outcomes.

Alternatively, airways inflammation may be assessed by analysis of exhaled breath condensate (EBC) or volatile organic substances (VOC) in exhaled breath, which contain an almost infinite number of substances [54•, 55•]. New approaches like ‘metabolomics’ make use of spectrometry techniques to detect thousands of components. Analysis of EBC or VOC may generate hypotheses on the pathogenesis of airways diseases, and offers huge opportunities to diagnose and monitor lung diseases. However, despite the growing number of studies in this area, these techniques are not yet in current use due to methodological problems and are restricted to research purposes.

Phenotype-based Management

In randomised controlled trials, treatment effects in groups of patients are compared, while the response of individual patients may differ considerably. In this respect, it might be interesting to study which patients might actually benefit from adjusting treatment to inflammatory markers. Obviously, in patients with a ‘concordant’ phenotype, in whom symptoms, FENO and sputum eosinophils correlate positively, the use of inflammatory markers is unlikely to influence decision making

based on symptoms [56]. However, in patients who are discordant for symptoms and markers of airway inflammation, incorporating such markers in treatment decisions might produce a better outcome. Hence, studies are needed that take these considerations into account, by stratifying the treatment strategy for concordance of symptoms and inflammation markers.

Likewise, it is important to identify patient groups like obese patients, pregnant women or highly allergic patients, who might benefit from specific monitoring strategies [52, 57].

One of the problems with treatment driven by inflammatory markers is the fact that inflammatory phenotypes (e.g. eosinophilic vs. neutrophilic asthma) are not stable in children with asthma, which may complicate a management strategy based on FENO or sputum eosinophils and might urge for frequent assessment of the inflammatory phenotype [58].

How can we Improve Symptom-based Management in Children?

At the moment, there is no firm indication that monitoring asthma based on repetitive lung function measurement or markers of airway inflammation is superior to monitoring based only on symptoms, although there is some evidence that selected groups might benefit from a symptoms ‘plus’ approach. Identification of these selected groups of children is a major challenge.

Still, many children with asthma are not well controlled. Poor adherence to treatment is most likely one of the major reasons for this. However, if we were able to improve symptom monitoring, a substantial proportion of children might benefit and show better asthma outcomes. Standardized asthma questionnaires and diaries may be helpful to improve symptom monitoring, yet validation of questionnaires and diaries in different populations is a major issue, and determining minimal clinically important differences should be a focus of research before we can use these in clinical practice [8]. Thus, standardization of (electronic) questionnaires and diaries is urgently needed to be able to compare studies and to study the results.

Conclusions

Symptoms and symptom-related parameters are important patient-reported outcomes of asthma, and should remain a core outcome in clinical care and research. Symptom diaries and asthma control questionnaires are increasingly used, but it is not clear if their use indeed improves asthma outcomes in children. Also, more research is needed to compare the value of measuring symptoms alone to symptoms as part of a

composite index including lung function parameters or inflammatory markers.

In a substantial proportion of patients, symptom-based asthma management may well be sufficient, and in pre-school children, symptoms are presently the only feasible outcome. However, further improvement of asthma monitoring may well be possible by taking individual phenotypic characteristics into account, and adapting the treatment accordingly. In patients with poor perception, those with a discordant phenotype, and those with persistent severe asthma, considering lung function, airways hyperresponsiveness and inflammatory markers in treatment decisions might improve outcomes. It is a challenge to identify those patients who might benefit from an alternative approach, and randomised controlled trials are urgently needed in specific patient categories for which this is likely to be the case.

Compliance with Ethics Guidelines

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Marianne Nuijsink and Johan C. De Jongste declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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