Monitoring asthma in childhood

Karin C. Lødrup Carlsen[1,2] and Mariëlle W. Pijnenburg[3] on behalf of the ERS Task Force Monitoring Asthma in Children[4]

Affiliations: [1]Dept of Paediatrics, Oslo University Hospital, Oslo, Norway. [2]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [3]Dept of Paediatric/Paediatric Respiratory Medicine, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands. [4]A full list of the ERS Task Force Monitoring Asthma in Children members and their affiliations can be found in the acknowledgements section.

Correspondence: Karin C. Lødrup Carlsen, Dept of Paediatrics, Oslo University Hospital, NO-0407 Oslo, Norway. E-mail: k.c.l.carlsen@medisin.uio.no

ABSTRACT The goal of asthma treatment is to obtain clinical control and reduce future risks to the patient. However, to date there is limited evidence on how to monitor patients with asthma. Childhood asthma introduces specific challenges in terms of deciding what, when, how often, by whom and in whom different assessments of asthma should be performed. The age of the child, the fluctuating course of asthma severity, variability in clinical presentation, exacerbations, comorbidities, socioeconomic and psychosocial factors, and environmental exposures may all influence disease activity and, hence, monitoring strategies. These factors will be addressed in herein.

We identified large knowledge gaps in the effects of different monitoring strategies in children with asthma. Studies into monitoring strategies are urgently needed, preferably in collaborative paediatric studies across countries and healthcare systems.

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Monitoring asthma in children is essential for disease control and should reflect age, triggers and disease activity http://ow.ly/J0k7f

Introduction

Asthma is a life-long disease that varies over time, frequently presents in early childhood and is the leading chronic disease in children in the western world, affecting 5–20% of school-aged children in Europe [1]. In contrast to other common diseases that more often present later in life, such as cancer, cardiovascular disease and diabetes, for the majority of cases asthma represents a life-long disease [2]. Childhood asthma presents a substantial burden to the patient, their family and society. High frequencies of sleep disturbances due to asthma (up to 34%), absence from school (23–51%) and limitation of activities (47%) have been reported [3–5]. In many countries obstructive airways disease and asthma are the leading causes of paediatric hospital admissions, and in the USA asthma is the leading cause of school absenteeism due to chronic disease among children (www.aafa.org). Although severe asthma affects only a minority (4–5%) of children with asthma, the prevalence of severe asthma symptoms is highly variable, from 0.1% in Pune, India, to 20% in Costa Rica [5–7].

Asthma is associated with reduced growth of lung function, and impaired lung function at a young age is a determinant of lung function in adult life, with an increased risk of chronic obstructive pulmonary disease [8–11].

Evidence of the socioeconomic burden of childhood asthma is largely lacking for most countries, including direct costs such as medication and healthcare utilisation, as well as indirect costs including absenteeism from work and school, and loss of productivity due to asthma [12]. In the USA the annual total cost of

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asthma in children and adults is estimated to be nearly $18 billion (www.cdc.gov/VitalSigns/asthma/). However, it has been estimated that improved national focus on diagnosis, disease control and education within healthcare may reduce the costs of asthma, as has been suggested in Finland [13]. Thus, improving asthma control is beneficial not only for the child and their family, but appears to be highly relevant in reducing the societal burden of childhood asthma [12, 13].

Monitoring disease activity is an important part of follow-up of any chronic disease. Current monitoring of childhood asthma focuses on the level of asthma control or reduction of future risk to the patient but should ideally encompass both aspects. Still, clear recommendations on the best strategy to monitor asthma in children are missing. Therefore, in 2011 a European Respiratory Society (ERS) Task Force was initiated to identify what is documented, frequently performed or recommended for monitoring asthma in children [14].

Asthma pathology

In order to understand the background for various potential measures used in monitoring childhood asthma, herein we briefly summarise the important features of asthma.

Asthma is a chronic inflammatory airways disease characterised by reversible airways obstruction and bronchial hyperresponsiveness (BHR). Classical symptoms of asthma are wheeze, cough (particularly at night or during exertion), dyspnoea and chest tightness. However, there is no current consensus on the underlying pathophysiology of asthma throughout childhood.

This said, the underlying chronic inflammation is often characterised by eosinophilic activity and allergic inflammation, but non-allergic asthma is not uncommon in childhood [15]. Although the underlying mechanisms of asthma are poorly understood, there is accumulating evidence that the interaction between respiratory viral infections and allergic sensitisation is crucial in the cause and pathogenesis of atopic asthma, whereas the link to common allergic type comorbidities is still not clear [16, 17]. With the varying clinical presentation of asthma through childhood there is increasing focus on trying to identify new types of asthma phenotypes or endotypes for future individual targeted management [18–20]. Several phenotypes of asthma have been described and identified, which are commonly based on the time of presentation of "wheeze" within the first part of childhood [21]. In addition, phenotypes based on the presence or absence of allergic sensitisation, eosinophilic or noneosinophilic inflammation, response to treatment, asthma severity or allergic disease comorbidities are recognised [22–26]. However, at present we are still struggling with untangling the optimal management and follow-up strategies, including monitoring, particularly among the youngest children with asthma-like disease (often referred to as "wheezy" disorders in the first few years of life) and among children with difficult to treat asthma.

No universally accepted definition of asthma exists that includes children from infancy to post puberty. Particularly in childhood, reversible bronchial obstruction may be a final common feature of a number of different diseases with distinct aetiologies and different environmental and genetic features. With this background, various definitions are used, and common to them all are reversible airways obstruction and chronic airways inflammation. Thus, a descriptive and pragmatic approach is necessary in the clinic, since the diagnosis will elicit targeted treatment.

Briefly, the underlying pathophysiology of asthma involves bronchial obstruction, impaired lung function, BHR, remodelling of the airways and airways inflammation, with their respective features partly reflecting chronic state and exacerbations.

Bronchial obstruction is a result of bronchial muscle constriction, acting through the β-receptors, as well as mucosal oedema and increased airways secretions resulting from airways inflammation, all of which contribute to reduce airway flow. The obstruction to airway flow is reflected in reduced lung function and classical symptoms such as wheezing, dyspnoea and coughing. Reversibility of the bronchial obstruction may occur spontaneously or through the use of bronchodilators (particularly β_2-agonists), whereas anti-inflammatory medications, such as inhaled corticosteroids are used to reduce the underlying pathophysiological causes of bronchoconstriction.

The role of impaired lung function in the development of asthma in contrast to lung function decline with chronic asthma is not entirely clear. Asthma is clearly associated with reduced lung function, as well as a more rapid decline in lung function compared to healthy individuals, although impairments in lung function appear more modest among children than adults [8–11]. But even in children and adolescents with mild-to-moderate asthma with adequate anti-inflammatory treatment, lung function following maximal bronchodilation is still somewhat reduced compared to healthy children, suggesting that airway remodelling affects lung function even in well-controlled paediatric asthma [27]. In a few birth cohorts, reduced lung function has been found to precede asthma in some, but not all children with asthma [28–30].

Airway remodelling is a common feature in adult asthma, but its role in childhood asthma is less clear, particularly as to when it starts and what elicits the process [31]. Nevertheless, lung function reductions in older children are likely to reflect structural changes in the airways, such as sub-epithelial reticular basement layer thickening, epithelial cell disruption, and imbalance of proteases and antiprotease, as well as neoangiogenesis (remodelling) [31].

BHR is a common, but not obligate, feature of childhood asthma, representing a general liability to develop symptoms by exposure to various physiological or environmental stimuli, with exercise being a classical trigger of childhood asthma symptoms. The underlying mechanisms for BHR development are not clear, but may involve barrier dysfunction as well as possibly neural parasympathetic mechanisms involving heat and fluid exchange over the epithelium [32]. Although BHR is a modest predictor for later asthma it tends to decrease throughout childhood [29, 33–35].

The underlying airways inflammation in asthma is generally considered to be an eosinophilic inflammation although the strength of the association between allergic sensitisation and asthma varies, with the majority of atopic subjects (*i.e.* those producing IgE antibodies to common inhalants and food allergens) not having asthma [36]. In some patients, allergen exposure may lead to a break in natural tolerance, triggering allergic inflammation and an allergen-specific immune response involving T- and B-lymphocytes. This allergic inflammation involves the production of specific IgE antibodies against allergens (allergic sensitisation) by local and systemic immune cells and biomarkers of the innate and adaptive immune system.

Asthma exacerbations are commonly triggered by viral infections in childhood, whereas at a later age many children with "viral wheeze" may not have asthma. Triggers of asthma development are likely to differ from triggers of exacerbations. Recent studies suggest that respiratory viruses, possibly (sub-types of) human rhinovirus in particular, may play a role in triggering the immune system, particularly in children who are already sensitised to allergens [37]. The mechanisms are currently not known but allergic sensitisation appears to be an important underlying feature of triggering disease development; although several hypotheses exist, including an immune circle in asthma development in which repeated airborne irritant stimuli (such as allergens or viruses) evoke cycles of inflammation giving intermittent inflammation resulting in episodic symptoms at first, later turning into more persistent inflammation and disease expression [16].

Chronic underlying inflammation with a variable course of asthma throughout childhood requires a decision to be made on the purpose of monitoring, *i.e.* symptom control, lung function, inflammation or treatment adherence, as well as considering age, severity, comorbidity, technical ability, impact of standardised test conditions and effort/cost/utility.

Guidelines: change from disease severity to asthma control and lack of monitoring knowledge

Over the years, the treatment target has changed from reducing disease severity in the undocumented hope of improving long-term prognosis to achieving asthma control and thereby reducing the burden of asthma [38–40]. Thus, the ultimate goal of current asthma treatment is to achieve and maintain clinical control and reduce future risks to the patient [41–45]. The future risk to the patient includes loss of asthma control, exacerbations, accelerated decline in lung function and side-effects of treatment.

Asthma control

All current asthma guidelines emphasise the importance of asthma control [42–44]. The 2007 National Asthma Education and Prevention Programme (NAEPP) guidelines define asthma control as the degree to which the manifestations of asthma are minimised by therapeutic intervention and the goals of therapy are met [44].

The Global Initiative for Asthma (GINA) proposes to distinguish between controlled, partly controlled and poorly controlled asthma [43]. Asthma is well controlled if: daytime symptoms occur ≤2 times per week; there are no limitations of activities due to asthma; there are no night-time symptoms; rescue medication is needed ≤2 times per week; and lung function is normal. Nonetheless, this working scheme (as proposed by GINA) is based on current opinion, is not validated and primarily refers to adults.

Asthma treatment should be adjusted in a continuous cycle driven by the patient's control status.

Aims of the ERS Task Force

Monitoring disease activity is an important part of follow-up of any chronic disease. Monitoring asthma is a tool or set of tools used by healthcare professionals in collaboration with the patient to obtain control of their asthma. To date, there is no clearly identified ideal way to monitor childhood asthma. However, a recent review paper outlines the current knowledge of the usefulness of various measures of asthma control, from peak flow measurements to composite measures for use in clinical trials [45]. Furthermore, spirometry, exhaled nitric oxide, BHR and genotype (β-receptor gene) had limited predictive value to

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identify differential response to step-up treatment in children with asthma, whereas the asthma control test appeared to have some benefit over the other measures in predicting treatment response [46]. However, no one measurement could predict treatment response to various medications [46]. Nevertheless, monitoring is essential to obtain and maintain control and establish the lowest step and dose of treatment in order to minimise cost and maximise safety [43].

Childhood asthma introduces specific challenges in terms of deciding what, when, how often, how, by whom and in whom different assessments of asthma should be performed. The fluctuating course of asthma severity, variability in clinical presentation, disease exacerbations, comorbidities, age of the subject, socioeconomic and psychosocial factors, and environmental exposures may all influence disease activity and monitoring strategies. Thus, any monitoring scheme should be adjusted to several of these factors. The availability, costs and reimbursement of different monitoring tools differ substantially throughout and between countries and influence what tools can and may be used in individual patients.

Therefore, the aims of the present task force are to: 1) define outcomes of asthma control that are useful in the context of monitoring; 2) define which tools are available for monitoring children of various ages with asthma; 3) define which tools are useful in the monitoring of asthma; and 4) review the evidence of different strategies for monitoring children with asthma.

Limitations of the ERS Task Force

This task force does not address the diagnosis or treatment of asthma in children. Monitoring of acute asthma attacks is not within the scope of this task force, and the task force have exclusively considered paediatric studies.

In this issue of the *European Respiratory Review* three reviews describe the available methods for monitoring disease, the factors that usually influence the decision to use these methods (*e.g.* age and risk factors), and describe the knowledge gaps in terms of documenting the effect of the measurements [47–49].

During the task force work it became evident that for most aspects of monitoring asthma in childhood there was a substantial lack of documentation with respect to levels of evidence, paediatric studies, cost-effectiveness or lack of data in general. Areas with limited documentation will be addressed here. As cost-effectiveness data on the use of several monitoring strategies are scarce and may differ substantially between countries, cost-effectiveness will not be discussed.

All strategies described in the reviews in this issue are based on a modified Delphi process, as well as on what the task force members do in clinical practice and, where possible, are supported by evidence [47–49].

Most task force members include all measurements that will be used for monitoring in a baseline assessment according to disease level, age or other factors, for use in follow-up assessments.

In the present issue of *European Respiratory Review* the first review focuses on symptoms, exacerbations and quality of life [47], the second review focuses on management-related issues, including comorbidities and environmental factors [48], and the third focuses on lung function, bronchial hyperresponsiveness and inflammation [49].

Common factors to consider when choosing monitoring tools

Frequency

As asthma is a highly variable disease, all guidelines recommend adjusting treatment periodically. However, the frequency of monitoring is considered a matter of clinical judgement [44]. GINA guidelines are the most specific and state that asthma control should be monitored by the healthcare professional and preferably also by the patient at regular intervals [43]. The frequency of healthcare visits depends on the initial clinical severity and the patient's training and confidence in playing a role in monitoring their asthma. Most task force members schedule a clinic visit 1–3 months after the initial visit and every 3–6 months thereafter in order to assess asthma control, adherence to treatment and evaluate whether treatment changes are needed, based upon available literature combined with clinical experience [50]. Visits every 3 months may allow seasonal influences to be accounted for. In controlled patients on stable doses of maintenance treatment, visits every 6 months may be sufficient, in particular in patients with adequate self-management skills. Factors that may suggest more frequent visits or more intense monitoring schemes are outlined in table 1.

In general, self-management is based on symptom monitoring and there is no evidence that home monitoring of peak flow, spirometry or exhaled nitric oxide fraction improves asthma outcomes [51–53].

Age and predicting prognosis

Ideally we should be able to identify children at risk of uncontrolled or severe asthma as soon as possible after the presentation of the disease. This way, monitoring schedules could be targeted to different ages

TABLE 1 Factors that should prompt consideration of more intense monitoring schemes

Emergency visits, admission or oral steroids for <1 year
Low FEV_1
ACT score <19
Low socioeconomic state or low income
Comorbidities: rhinitis, sinusitis and reflux
Severe asthma
Smoking or environmental smoke exposure
Reduced symptom perception
Reduced adherence

FEV_1: forced expiratory volume in 1 s; ACT: asthma control test.

depending on individual risk. However, at present this is not an option. Asthma in childhood is difficult to predict from early asthma-like symptoms and the younger the child the more difficult it is to ascertain a diagnosis of asthma [19, 54, 55]. Recurrent wheeze in children <3 years of age is commonly associated with viral respiratory infection, whereas the prognosis of these children may be less favourable than previously reported as only one-third of children with recurrent bronchial obstruction in a birth cohort study were symptom free or medication free for asthma or BHR at 16 years of age [56–61]. However, several scores have been tested for their ability to predict persistence of asthma, such as the asthma predictive index and the Oslo severity score, with varying clinical value in individual patients [62, 63].

The second step is to identify scores that may adequately predict the risk of exacerbations, which may identify children with a short-term need of increased care. Thus, we lack a significantly specific and sensitive tool to predict which young children are likely to go on to have persistent or relapsing asthma through childhood, which are those who should be most closely monitored.

Obviously, age is one of the limiting factors for tools that may be used in monitoring asthma. In particular, in infants and pre-school children objective measurements of asthma control (*e.g.* lung function and inflammatory markers) are scarce and, in general, are not feasible in routine clinical care in most countries. Alternatively, in adolescents, electronic monitoring tools using the Internet or apps might be of benefit. Table 2 summarises the available tools for monitoring childhood asthma based on age.

Risk factors of exacerbations or lack of asthma control

It is important to ascertain what the risk factors in fact predict; is it development of diseases, lung function decline, exacerbations, hospital admissions or death? Herein we address risk factors that warrant a more frequent or more extensive monitoring scheme (table 1).

TABLE 2 Available tools for monitoring childhood asthma based on age

	0–2 years	2–4 years	4–6 years	>6 years
Symptoms	✓	✓	✓	✓
C-ACT/ACT	–	–	✓	✓
ACQ	–	–	–	✓
Exacerbations	✓	✓	✓	✓
Flow volume curves/BDR	–	–	(✓)	✓
PEF	–	–	(✓)	✓
R_{int}-IOS-FOT	–	✓	✓	✓
LCI	✓	✓	✓	✓
ILF	✓	–	–	–
AHR	–	–	(✓)	✓
F_{eNO}	✓	✓	✓	✓
Induced sputum	–	–	–	✓
EBC	–	–	(✓)	✓

Tick marks indicate relevant/available tools, while tick marks in parenthesis indicates partly relevant/available tools. C-ACT: childhood asthma control test; ACT: asthma control test; BDR: bronchodilator response; PEF: peak expiratory flow; R_{int}-IOS-FOT: interrupter resistance–impulse oscillometry–forced oscillation technique; LCI: lung clearance index; ILF: infant lung function; AHR: airway hyperresponsiveness; F_{eNO}: exhaled nitric oxide fraction; EBC: exhaled breath condensate.

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In children younger than school age allergic sensitisation increases the likelihood of recurrent bronchial obstruction reflecting asthma, particularly in boys [64–67]. However, it appears that around 30–40% of pubertal children are sensitised to at least one allergen, and many of these children will not have asthma [58].

Since allergy is associated with worsening of asthma, it is important to establish whether new allergies are developing or there are any relevant changes in allergic diseases. Thus, questions on allergies to inhalants or food allergens are usually routinely performed at the annual visits, but sometimes more often in the case of a changing clinical presentation, followed by relevant investigations (skin prick test and/or specific IgE), regardless of age. Whether children with allergies should be monitored more frequently than children without allergies is still a matter of debate. However, children with multiple allergies are at risk of poorer asthma control, suggesting that they might probably benefit from closer monitoring [68–72].

Exposures

Allergen exposure in atopic children increases the risk of exacerbations, as does second-hand tobacco smoke exposure, outdoor air pollution and viral infections, which might suggest why more intense monitoring programmes are required when exposures are unavoidable [73–76]. Thus, most task force members ask about allergen exposure, tobacco smoke, water-damaged housing, air pollution and other relevant exposures at the annual visits or in cases of unexplained loss of asthma control. In every allergic asthmatic child exposed to relevant allergens, particularly in patients with uncontrolled symptoms, most task force members consider home visits by specialised asthma nurses and allergen reduction measures [77].

Levels of care and implementing monitoring schemes

To date there has been little discussion on what monitoring tool(s) should be used in primary *versus* secondary care, and documentation of optimal schedules for individual patient flow through the various levels of healthcare is largely unavailable. Such discussions are on-going in many countries, where there is an increasing demand to reduce the costs at a societal level and reduce individual burden of disease.

However, in Finland and some other countries a strategic approach to diagnosis and management, as well as education of healthcare personnel at all levels, appears to be effective in reducing the burden of asthma in children [78].

The present task force found an overwhelming lack of documentation on: the effect of monitoring at different levels of healthcare; what type of testing should be optimally and minimally performed at different levels of healthcare; and how often monitoring should be performed. In view of the differences in health politics and national healthcare systems, and the lack of documentation, it was found that any recommendations were outside the scope of the present task force.

Conclusion

The task force found that the large knowledge gaps in the effects of different monitoring strategies in terms of what tools to use, how often, in whom and at what healthcare level precluded any firm recommendations on monitoring childhood asthma. However, despite the lack of documentation on the efficacy of monitoring schemes, the task force members have outlined their interpretation of the available documentation and leave the decision on how to monitor childhood asthma to the reader. The task force has clearly shown that studies into these matters are urgently needed, preferably collaborative paediatric studies across countries and healthcare systems.

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The Task Force members and their affiliations are as follows. Karin C. Lødrup Carlsen: Dept of Paediatrics, Oslo University Hospital, and Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; Mariëlle W. Pijnenburg: Dept of Paediatric/Paediatric Respiratory Medicine, Erasmus MC — Sophia Children's Hospital, Rotterdam, The Netherlands; Eugenio Baraldi: Women's and Children's Health Dept, Unit of Respiratory Medicine and Allergy, University of Padova, Padova, Italy; Paul L.P. Brand: Dept of Paediatrics/Princess Amalia Children's Centre, Isala Hospital, Zwolle, and UMCG Postgraduate School of Medicine, University Medical Centre and University of Groningen, Groningen, The Netherlands; Kai-Hakon Carlsen: Dept of Paediatrics, Oslo University Hospital, and Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, and Norwegian School of Sports Sciences, Oslo, Norway; Ernst Eber: Respiratory and Allergic Disease Division, Dept of Paediatrics and Adolescence Medicine, Medical University of Graz, Graz, Austria; Thomas Frischer: Dept of Paediatrics and Paediatric Surgery, Wilhelminenspital, Vienna, Austria; Gunilla Hedlin: Dept of Women's and Children's Health and Centre for Allergy Research, Karolinska Institutet and Astrid Lindgren Children's Hospital, Stockholm, Sweden; Neeta Kulkarni: Leicestershire Partnership Trust and Dept of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK; Christiane Lex: Dept of Paediatric Cardiology and Intensive Care Medicine, Division of Paediatric Respiratory Medicine, University Hospital Goettingen, Goettingen, Germany; Mika J. Mäkelä: Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland; Eva Mantzourani: Dept of Paediatrics, University Hospital of Heraklion, University of Crete, Heraklion, Greece; Alexander Moeller: Division of Respiratory Medicine, University Children's Hospital Zurich, Zurich, Switzerland; Ian Pavord: Dept of Respiratory Medicine, University of Oxford, Oxford, UK; Giorgio Piacentini: Paediatric Section, Dept of Life and Reproduction Sciences, University of Verona, Verona, Italy;

David Price: Dept of Primary Care Respiratory Medicine, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK; Bart L. Rottier: Dept of Pediatric Pulmonology and Allergology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Sejal Saglani: Leukocyte Biology and Respiratory Paediatrics, National Heart and Lung Institute, Imperial College London, London, UK; Peter D. Sly: Queensland Children's Medical Research Institute, The University of Queensland, Brisbane, Australia; Stanley J. Szefler: Children's Hospital Colorado and University of Colorado Denver School of Medicine, Denver, CO, USA; Steve Turner: Dept of Paediatrics, University of Aberdeen, Aberdeen, UK; Edwina Wooler: Royal Alexandra Children's Hospital, Brighton, UK.

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