Monitoring asthma in children

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ABSTRACT   The goal of asthma treatment is to obtain clinical control and reduce future risks to the patient. To reach this goal in children with asthma, ongoing monitoring is essential. While all components of asthma, such as symptoms, lung function, bronchial hyperresponsiveness and inflammation, may exist in various combinations in different individuals, to date there is limited evidence on how to integrate these for optimal monitoring of children with asthma. The aims of this ERS Task Force were to describe the current practise and give an overview of the best available evidence on how to monitor children with asthma.

22 clinical and research experts reviewed the literature. A modified Delphi method and four Task Force meetings were used to reach a consensus.

This statement summarises the literature on monitoring children with asthma. Available tools for monitoring children with asthma, such as clinical tools, lung function, bronchial responsiveness and inflammatory markers, are described as are the ways in which they may be used in children with asthma. Management-related issues, comorbidities and environmental factors are summarised.

Despite considerable interest in monitoring asthma in children, for many aspects of monitoring asthma in children there is a substantial lack of evidence.

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Introduction

Asthma is a chronic, heterogeneous disease with symptoms and features that include wheeze, cough (particularly at night and during exertion), dyspnoea and chest tightness, variable airways obstruction and bronchial hyperresponsiveness (BHR). The underlying chronic inflammation is often characterised by eosinophilic activity and allergic inflammation, and airways remodelling is a frequent feature of asthma, even in young children, although not in the very early stages [1–3].

The ultimate goals of asthma treatment are to achieve and maintain clinical control, reduce future risks to the patient and enable the patient to lead a life without restrictions due to the disease [1, 4–7]. The concept of asthma control is central to all asthma guidelines and the level of control is defined as the extent to which features of asthma are controlled by daily therapy, for example exertional symptoms, night awakening, the use of reliever medication and the ability to carry out daily activities. The longer-term risks for the patient with poor control include asthma attacks, impaired development or accelerated decline in lung function, and side-effects of treatment. Despite the availability of effective medication, many children do not have adequately controlled asthma [8, 9]. This has implications for quality of life (QoL) and daily physical activity, and clearly increases the burden of disease in terms of costs to the family and society. Children with asthma frequently report limitations in activities and sports (reported in ⩽47% of children with asthma), nocturnal awakening due to asthma (⩽34%) and absence from school (⩽51%) [8, 9].

Asthma management should be adjusted in a continuous cycle with ongoing assessment of disease control in order to obtain and maintain asthma control and a life with no or very minimal impairment. Therefore, ongoing monitoring is essential in children with asthma and ideally provides optimal asthma control at the lowest step and dose of treatment to minimise costs and reduce possible side-effects of medication [7]. Asthma control can be assessed using many indices, including symptoms, medication use or activity limitations, and more objective surrogate measures, such as lung function or inflammatory markers reflecting the underlying pathophysiologic and immunologic mechanisms involved in the disease. Aspects of the disease that are treatment responsive should receive particularly close attention.

All components relevant to the assessment of asthma control, such as frequency and severity of symptoms, changes in lung function and level of BHR and inflammation, may exist in various combinations in different individuals; however, to date there is limited evidence on how to integrate these characteristics in the optimal monitoring of children with asthma. The definition of control based on measures of inflammation (such as sputum eosinophils and the exhaled nitric oxide fraction (F_{eNO})) is likely to differ from control based on clinical measures (like symptoms), lung function or BHR. Moreover, information regarding the occurrence of recent exacerbations and oral corticosteroid use is important and should be included in the assessment of control and future risks, although it is often unrelated to disease severity [10].

The variable and fluctuating course of asthma symptoms and objective findings throughout childhood introduce specific challenges in terms of deciding what, when, how, how often, by whom and in whom different assessment of asthma should be performed. Variability in asthma severity, clinical presentation, exacerbations, comorbidities, age, socioeconomic status, psychosocial factors and environmental exposures may influence monitoring strategies.

Ideally, monitoring asthma in children should take into account all these aspects, but there are no clear guidelines on how to integrate these in the overall assessment of an individual patient. Therefore, in 2011 the European Respiratory Society (ERS) established a Task Force with the aim of describing current practises and giving an overview of the best available evidence on how to monitor children with asthma at various ages and, ultimately, reach better asthma control in children.

This Task Force targets children with asthma treated in primary, secondary and tertiary care.

Methods

For many aspects of monitoring asthma in children there is a paucity of data. This Statement summarises the available evidence and current practises of monitoring asthma in children. It is based on a review of the literature and the clinical expertise of the Task Force members. As no formal grading of the evidence was conducted, this statement does not contain recommendations for clinical practise.

The multinational Task Force was composed of 22 clinical and research experts, and members were vetted for potential conflicts of interest according to ERS procedures. Three working groups reviewed the literature on monitoring: symptoms, exacerbations and QoL (Chair P.L.P Brand); lung function, bronchial responsiveness and airways inflammation (Chair A. Moeller); and management-related issues, comorbidities and environment (Chair B.L. Rottier). This was done through identification of systematic reviews of randomised trials, published until May 2013, *via* Medline/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and supplementing this with studies that added to the evidence based on monitoring asthma in children. The Task Force members selected the relevant papers themselves, irrespective of the study designs used. A modified Delphi method with two rounds and four Task Force meetings were used to reach consensus. The Chairs (M.W. Pijnenburg and K.C. Lødrup Carlsen) composed the final document, which was reviewed and approved by all co-authors.

The summary of this Task Force's work is presented in the current paper. Four separate papers that are to be published in the *European Respiratory Review* (*ERR*) will provide detailed information on the methods available for monitoring disease, factors that should be considered when deciding on their use and management-related issues, and will also describe knowledge gaps [11–14].

Limitations of this Task Force

The present Task Force did not address the diagnosis and treatment of childhood asthma, nor did it consider monitoring of acute asthma exacerbations. The Task Force exclusively considered paediatric studies.

The availability, cost and reimbursement of the costs of different monitoring tools differ substantially throughout and between countries and influence what tools can and may be used in individual patients. The cost-effectiveness of the different monitoring tools was initially considered to be part of the task, but this was soon found to be impossible due to variability within and across countries as well as the common lack of literature to support such estimates.

Recommendations on monitoring in asthma guidelines

Over the years, the treatment goal has changed from reducing disease severity and improving long-term prognosis [15] to achieving asthma control and reducing the burden of asthma and future risks to the patient [1, 4–7]. Asthma control has been defined by the National Asthma Education and Prevention Program (NAEPP) as: "the degree to which the manifestations of asthma are minimized by therapeutic intervention and the goals of therapy are met" [1]. The Global Initiative for Asthma (GINA) distinguishes between controlled, partly controlled and poorly controlled asthma (table 1) [7].

Asthma control as a pivotal concept in asthma monitoring is included in several guidelines, whereas recommendations on monitoring are largely lacking. The GINA guidelines state that monitoring is essential "to maintain control and establish the lowest step and dose of treatment to minimize cost and maximize safety" [7]. Preferably, asthma should be monitored by the healthcare physician as well as by the patient and parents themselves using simple schemes (as seen in table 1) or composite asthma scores [7]. The British Thoracic Society (BTS) guidelines recommend the assessment of asthma control through: questions on symptoms, exacerbations and school absence; checks for adherence, inhaler technique, exposures and availability of self-management plans; and measurement of height and weight annually [6].

The American NAEPP guidelines advise that patients should be instructed to monitor their asthma control in an ongoing manner, either by monitoring symptoms or peak expiratory flow (PEF), whereas healthcare providers should assess asthma control, medication technique, the written asthma action plan, adherence, and patient concerns at every patient visit as well as spirometry at least once every 1–2 years [1].

TABLE 1 Levels of asthma symptom control according to the Global Initiative for Asthma (GINA) in patients >5 years of age

In the past 4 weeks has the patient had	Well controlled	Partly controlled	Uncontrolled
Daytime symptoms >2 per week? Yes/No Any night waking due to asthma? Yes/No Reliever needed[#] >2 per week? Yes/No Any activity limitation due to asthma? Yes/No	None of these	1–2 of these	3–4 of these

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Factors to consider when choosing monitoring tools
Frequency of follow-up visits

Asthma is a highly variable disease and periodic adjustment of treatment is recommended by all guidelines. However, the frequency of follow-up visits is considered a matter of clinical judgement. Most Task Force members consider that the frequency of follow-up visits depends on initial evaluation of clinical severity, with the frequency increasing in proportion to asthma severity, and may be adjusted depending on response to and intensity of treatment. The consideration of the patients' and parents' training and confidence in playing a role in the monitoring of the child's asthma also determines the frequency of follow-up visits [16]. Adequate provision of self-management education might be achieved in two or more educational and instructional sessions, followed by reviews every 3–6 months thereafter. Self-management mostly consists of symptom monitoring. The evidence indicates that peak flow monitoring, home spirometry and/or monitoring F_{eNO} at home do not improve asthma outcomes compared with symptom monitoring [17–19].

Most Task Force members would schedule a follow-up visit 3–6 months after any substantial change in treatment, to discuss the degree of asthma control and to evaluate whether maintenance treatment should be modified [20]. To account for seasonal influences, one might consider scheduling follow-up visits at least every 3 months, particularly in preschool children. In children with problematic severe asthma (PSA), more frequent follow-up visits (e.g. every 1–3 months) may be warranted.

Age

Obviously, age is one of the limiting factors of the tools that may be used in monitoring asthma. In infants and toddlers, the variability and severity of asthma symptoms may prompt more frequent monitoring. In children <4–6 years of age, objective measurements of asthma control, such as lung function and inflammatory markers, are more challenging and are not feasible in all countries in routine clinical care outside specialist centres. However, electronic monitoring tools that use the internet or apps may fit the interests of adolescents in particular, although documentation for their long-term effectiveness and cost-effectiveness is currently lacking [21]. Table 2 summarises the available tools for monitoring asthma based on age.

Asthma severity

Although severity may be difficult to define, in general asthma severity is defined as the difficulty in controlling asthma with treatment and the treatment step that is necessary to achieve asthma control [4]. Children with persistent symptoms and/or severe exacerbations despite high-dose treatment, especially inhaled corticosteroids (ICS), are diagnosed with PSA and may represent ∼5% of children with asthma and 0.5% in a general population-based cohort [22, 23]. Clinically, it is essential to distinguish between children with PSA who present with truly severe therapy-resistant disease and those with difficult-to-treat asthma because of underlying modifiable factors such as ongoing allergen exposure, poor adherence to treatment, poor inhaler technique, smoking and comorbidities [22]. Although clear recommendations and flow charts for the assessment of PSA have been published [24], data on and guidelines for the monitoring of PSA in children are lacking. Used in isolation, monitoring with home spirometry or with sputum eosinophils did not improve asthma outcomes in children with severe asthma [18, 25].

In general, children with severe therapy-resistant asthma are treated and monitored in tertiary care centres. In children with PSA, an increase in the frequency (e.g. every 1–3 months) and intensity of monitoring is justifiable in order to achieve asthma control and prevent side-effects of high-dose ICS treatment or treatment with oral corticosteroids.

Asthma phenotypes

As the clinical presentation of asthma varies considerably through childhood, a great deal of effort has been put into trying to identify new asthma phenotypes [26, 27] or endotypes [28] for more individually targeted management. Several phenotypes of asthma have been described, based upon the time of presentation of first wheeze, the presence of allergic sensitisation, eosinophilic or non-eosinophilic inflammation [29, 30], response to treatment [31, 32], asthma severity [33] and allergic comorbidities. At present there is a lack of data to support the use of different monitoring strategies directed by asthma phenotypes. The Task Force therefore did not consider the usefulness of particular monitoring tailored to phenotypic presentations.

Risk factors

Several risk factors have been identified that predict impaired lung function development or accelerated lung function decline, exacerbations, hospital admissions or fatal or near-fatal asthma, and might warrant a more frequent or more extensive monitoring scheme (table 3) [10, 34–40].

TABLE 2 Monitoring tools for asthma in children

	Age years			
	0–2	2–4	4–6	>6
Clinical tools				
Symptoms	x	x	x	x
C-ACT/ACT	-	-	x	x
ACQ	-	-	-	x
Exacerbations	x	x	x	x
QoLQ	-	-	-	x
Lung function				
Flow–volume curves/BDR	(Tidal)	(Tidal)	(x)	x
PEF	-	-	(x)	x
R_{int}-IOS-FOT	-	x	x	x
LCI	x	x	x	x
ILF	x	-	-	-
BHR				
Direct (methacholine/histamine)	-	-	(x)	x
Indirect (exercise, mannitol)			x[#]	x
Inflammatory markers				
F_{eNO}	x	x	x	x
Induced sputum (eosinophils, LTE$_4$, EPX)	-	-	-	x
Exhaled breath condensate	-	-	(x)	x

C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; QoLQ: quality of life questionnaire; BDR: bronchodilator response; PEF: peak expiratory flow; R_{int}; interrupter resistance; IOS: impulse oscillometry; FOT: forced oscillation technique; LCI: lung clearance index; ILF: infant lung function; BHR: bronchial hyperresponsiveness; F_{eNO}: fraction of exhaled nitric oxide; LTE$_4$: leukotriene E$_4$; EPX: eosinophil peroxidase. x: can be used in this age category; (x): might be possible to use in this age group in specialised centres. [#]: modified exercise challenge possible at preschool age.

Allergy is associated with worsening asthma, and allergen exposure is associated with a higher risk of exacerbation. It is therefore important to establish whether the patient is exposed to relevant allergens, whether new allergic sensitisations are developing, or whether any relevant changes in clinical allergic diseases occur [41, 42]. Questions on aeroallergens or food allergies deserve attention, especially where control is suboptimal, and before any changes in treatment are considered.

Most Task Force members assess risk factors during the first visit; during follow-up visits, Task Force members will usually ask for exacerbations and asthma control in the period between two visits, and will assess other risk factors only in uncontrolled patients.

In children with uncontrolled, PSA who are exposed to relevant allergens, home visits by specialised asthma nurses may provide useful information [24, 43].

Exposure to outdoor and indoor air pollution, tobacco smoke (including maternal smoking during pregnancy) and viral infections also increase the risk of exacerbations and impairment of lung function,

TABLE 3 Risk factors for exacerbations/poor control

Emergency visit, admission, oral steroid course during previous year
Low FEV$_1$
ACT score <19
Low socioeconomic status, low income
Comorbidities (rhinitis, sinusitis, food allergy, reflux)
Severe asthma, high-dose medications
Smoking or exhaled smoke exposure
Reduced symptom perception
Reduced adherence
Persistent eosinophilic airways inflammation

Data from [10, 34–40]. FEV$_1$: forced expiratory volume in 1 s; ACT: Asthma Control Test.

which might suggest that a more intense monitoring programme is justified [44–56]. Although unfavourable socioeconomic conditions and psychosocial factors may increase the risk of uncontrolled disease, there is a current lack of literature that supports the possible ways of monitoring these factors during childhood. However, such factors are likely to become apparent during follow-up visits.

Levels of care and implementing monitoring schemes

Monitoring schemes and available tools will differ between levels of care (primary, secondary and tertiary), and optimal monitoring schemes for individual patients through the various healthcare levels are largely unavailable. Therefore, it appears to be impossible to define the minimum, ideal and optimum monitoring schemes for the various healthcare sectors.

In Finland and some other countries, a strategic approach to asthma management as well as education of healthcare professionals at all levels appears to have been effective in reducing the burden of asthma in children [57–59].

In many countries, children who are not controlled on step 2 treatment are referred to specialist care and children with unstable disease on step 4 treatment or higher are treated in specialised tertiary care centres, with or without shared care facilities. Admission to hospital for acute asthma represents a failure of control and should trigger a review of maintenance therapy by an asthma specialist.

Since asthma is difficult to diagnose in preschool children and the response to treatment varies considerably in these children, a low threshold for referring young children for further appraisal and possibly follow-up in specialist care is necessary.

Available monitoring tools in primary and secondary care may differ considerably between countries. For most general practitioners, spirometry and basic allergy diagnostics for inhalant allergies are available, whether in their office or in collaboration with diagnostic centres or hospitals. Allergic sensitisation to food allergens may need further evaluation in specialist care.

In general, secondary care centres at least have spirometry and allergy testing facilities. In most countries, tertiary care centres are fully equipped to conduct complex pulmonary diagnoses and are multidisciplinary in nature, combining the expertise of pulmonologists, allergists and immunologists. Task Force members indicate that access to psychosocial support (for complex behavioural issues) and lung function measurements are generally available for preschool children in tertiary care centres.

Monitoring tools

Tools for monitoring asthma have to a large extent focused around the measures outlined in table 2. However, as will be evident from the four papers in the *ERR*, documentation of the efficacy of these measures in monitoring is generally scarce or lacking.

Traditionally, subjective parameters like daily and nocturnal symptoms and more objective measures such as spirometry, PEF and BHR have been used to assess asthma control. Subsequently, the level of asthma control guides treatment adjustments.

More recently, questionnaires have been developed to assess asthma control in a standardised way, in addition to or including lung function tests (to be reviewed later). In the last 10 years, much attention has been given to markers of inflammation, like F_{eNO} and eosinophils in induced sputum, as objective tests to monitor asthmatic patients.

Clinical tools: symptoms, exacerbations and QoL

Symptoms and rescue medication use are the easiest clinical tools to apply, are available for all ages and form a distinct domain in the clinical expression of asthma, independent from exacerbations, lung function and inflammation [16]. One should be aware that the use of rescue bronchodilators varies considerably between children and depends highly on the subjective perception of the degree of airway narrowing, or symptoms observed by caregivers in the case of young children. Such symptom-based tools may therefore be an unreliable marker of asthma control in some children [60]. For patients, exacerbations and the limitations that asthma imposes on their daily activities, including sports and play, are the most bothersome and are important aspects to be questioned at every visit [61]. Table 4 summarises the symptoms and consequences of asthma disease activity that most Task Force members discuss at every visit.

There is no evidence supporting the use of diaries to monitor asthma symptoms in clinical practise [62]. However, it cannot be excluded that some individual patients may benefit from daily symptom monitoring in a diary.

TABLE 4 Symptoms and consequences of asthma disease activity
Type of symptoms
Wheeze
Shortness of breath
Chest tightness
Cough
Use of rescue medication
Use of daily controller medication
Pattern of symptoms
Daytime symptoms
Symptoms related to exercise
Night-time symptoms
Seasonality
Impact of symptoms
Limitations in sports, play and daily activities
Absent from school
Parent absent from work
Impact on sleep

Composite asthma control scores

Paediatric composite asthma control scores are increasingly being used in asthma management [63]. The Childhood Asthma Control Test (C-ACT), the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ) are instruments that have been studied and validated most extensively [64, 65]. Although a single numerical value to express asthma control is highly attractive, C-ACT, ACT and ACQ do not include exacerbations and future risks, such as lung function decline [66–69]. Therefore, these composite scores appear to underestimate the level of asthma control as defined by GINA [70]. Recently, two composite asthma control scores have been developed that include exacerbations: the Test for Respiratory and Asthma Control in Kids (TRACK) and the Composite Asthma Severity Index (CASI) [71, 72].

Poor asthma control is associated with reduced lung function, increased risk of exacerbations and elevated F_{eNO} [64, 65, 73–77]. Changes in composite measures of asthma control reflect changes in the overall clinical assessment of asthma control by healthcare providers, changes in QoL, and the need to step up or step down therapy, suggesting that these composite measures have criteria validity [78, 79].

All Task Force members assess clinical asthma control with an interview, and the use of composite asthma control scores has so far not been shown to improve symptoms or impact on daily life.

E-health and telemonitoring

Mobile phones and web-based applications offer new possibilities for guided self-management. 21 studies in adults and children were summarised in a Cochrane meta-analysis, which concluded that e-health initiatives did not improve patient QoL or reduce exacerbations and hospital admissions in children [80].

Therefore, to date e-health initiatives have no place in routine clinical care of children with asthma.

Exacerbations

Asthma exacerbations constitute one of the most troublesome and frightening aspects of asthma to patients and carers [81]. The risk of exacerbations is increased in children with inadequate adherence to controller therapy, poor asthma control, frequent prior exacerbations and elevated F_{eNO} levels, but none of these factors reliably predict exacerbations [82–85]. Obviously, severity, frequency and management of exacerbations outlined in an asthma action plan should be reviewed at each consultation.

All Task Force members ask for exacerbations that have occurred between clinic visits.

QoL

QoL instruments provide independent additional information on asthma status, complementary to symptoms and lung function, and are a potentially useful additional outcome parameter to assess response to longer-term treatment trials [6, 86]. However, no study has assessed whether asthma management based on usual care plus QoL monitoring is superior to routine asthma management in improving asthma outcomes.

At present, paediatric asthma QoL questionnaires are too time-consuming and lack documentation of improved clinical outcomes to be part of routine clinical care, and are primarily developed for research purposes [87].

Lung function

Pulmonary function, and particularly forced expiratory volume in 1 s (FEV1), is an important component of assessment of asthma control and predictor of future risk to the patient, as reduced lung function is associated with poorer asthma outcomes [88, 89].

Significant bronchial obstruction may be present in asymptomatic asthmatic children. In general, children with chronic airway obstruction are less likely to experience dyspnoea compared with children with acute obstruction [90, 91]. In contrast, some children may experience dyspnoea without any bronchial obstruction, suggesting that their symptoms are not due to asthma. Therefore, in some but not all guidelines, periodic assessment of maximal flow–volume curves is recommended in asthmatic children aged 5–6 years to optimise asthma management and to ensure therapeutic goals are met [1, 6, 7]. In younger children, lung function may be monitored by other measures, such as impulse oscillometry (IOS) and the forced oscillation technique (FOT), but these are not available outside tertiary care centres in many countries.

Maximal flow–volume curves, peak flow and bronchodilator response

The measurement of maximal expiratory flow–volume curve parameters is considered the gold standard for the assessment of lung function in children with asthma, and reversibility of airway obstruction is a key feature of asthma. Spirometry every 1–2 years has been recommended by the NAEPP guidelines for children $\geqslant$5 years of age with asthma, but the BTS and GINA do not provide clear recommendations on monitoring FEV1 in children [1, 6, 7]. There are several arguments for regular monitoring of FEV1 in asthmatic children. Epidemiological studies have consistently tracked FEV1 and the FEV1/forced vital capacity (FVC) ratio from childhood to adulthood [88, 89]. FEV1 and persistent bronchodilator response (BDR) might help identify children at risk of developing a progressive decline in lung function [92]. High BDR has been associated with poor asthma control and clinical outcome, increased airway inflammation, BHR and a good response to ICS [93, 94]. In addition, in the short term, FEV1 measurements may predict exacerbations [36] and FEV1 is considered important in defining asthma severity [36, 95]. While measurement of peripheral airflow obstruction, *i.e.* forced expiratory flow at 50% FVC (FEF50%) and/or FEF from 25 to 75% FVC (FEF25–75%), may be more sensitive for the pathophysiological changes in asthma, the value of these measurements in asthma monitoring needs to be established [96].

In children <5 years of age, reproducible maximal flow–volume curves are difficult to achieve. In addition, FEV1 may not be sensitive enough and may have a different physiological meaning in comparison to older children [97].

For the reasons mentioned above, office-based spirometry is useful for monitoring asthma in children $\geqslant$5 years of age when performed at least annually. For children <5 years of age, a specialty setting and training may be required.

More frequent spirometry is sometimes indicated depending on the clinical course (*e.g.* in children with poor perception, recent admission, risk factors of decline, low FEV1). Home spirometry using electronic devices can be performed in selected cases, when symptom-guided treatment is difficult. However, this is not feasible or necessary in most children [18, 98].

In asthmatic children with reduced FEV1 and reduced post-BDR FEV1, it is useful to consider further investigations and follow-up in specialist care [99].

All Task Force members assess spirometry to monitor asthma in children $\geqslant$5 years of age at least annually, and more frequently in patients with reduced lung function or poor asthma control. The evidence indicates that PEF measurements are not useful in monitoring asthma in children. Two randomised controlled trials failed to show a benefit of PEF-guided treatment in comparison to management based on symptoms alone, and the addition of PEF did not enhance self-management even during acute exacerbations [19, 94]. Peak flow diaries are also unreliable and are poorly accepted by patients [100, 101].

Methods used in children <5 years of age

Interrupter resistance (R_{int}), IOS and FOT measure respiratory resistance as a proxy of airway obstruction and as such, may be used in the diagnosis and in the assessment of treatment response in wheezing children [102–107]. Moreover, tidal flow–volume loops may reflect abnormal breathing patterns and bronchial obstruction. As only limited cooperation is required, these tests are suitable for preschool children [103–105, 108–110].

Although R_{int}, IOS and FOT measurements have some potential as monitoring tools, longitudinal studies confirming their usefulness in the monitoring of wheezing in preschool children are lacking and at present there is insufficient evidence for routine monitoring with R_{int}, IOS, FOT or tidal flow–volume loops of all (preschool) children with wheezing.

Body plethysmography

In general, body plethysmographic measurements of lung volumes are restricted to tertiary (or specialised) clinics and have no place in the routine monitoring of asthma in children. In selected cases, body plethysmography may be of help, particularly in the management of difficult and severe asthma [111]. In obese asthmatic children, measurements of specific airway resistance and lung volumes *via* body plethysmography may differentiate lung function changes due to asthma (elevated specific airway resistance and elevated total lung capacity) from those due to obesity (normal specific airway resistance) [112].

Multiple breath gas washout techniques (lung clearance index)

The lung clearance index is a measure of ventilation inhomogeneity and is derived from multiple breath washout tests. The lung clearance index is considered to be more sensitive than conventional lung function tests in detecting early airway disease in children with asthma but particularly in children with cystic fibrosis [113]. However, due to the lack of appropriate studies, to date there is no role for multiple breath washout techniques in the routine monitoring of asthma in children.

Infant lung function

In infants with wheeze, lung function may be assessed with several techniques, such as the analysis of tidal flow–volume breathing loops [114–116], forced expirations (rapid thoracic compression technique or raised volume rapid thoracic compression technique) [115, 117–121] or body plethysmography [122]. Infant lung function testing has been used to define phenotypes in infants with wheeze and to predict treatment effects and prognosis [120, 121, 123–125]; several studies have tracked lung function from infancy to school age [115–117, 119, 126–131]. However, at present there is no data to support the clinical use of infant lung function tests for monitoring wheezing infants.

Bronchial hyperresponsiveness

One hallmark of asthma is variable airflow obstruction (*i.e.* the variability in bronchial tone in response to a variety of different stimuli), and BHR can be assessed using bronchial provocation tests. Bronchial provocation tests may be performed with different chemical substances, such as histamine or methacholine which are both considered as nonspecific direct bronchoprovocation tests [132, 133], or by inhaling allergens (specific direct bronchoprovocation tests) [134]. Several other stimuli can also be used, such as physical exercise [135], inhaled cold air [136] and hyperventilation with dry air [137], all of which are indirect bronchial provocation tests. Assessment of BHR using indirect bronchial provocation tests is rapidly influenced by treatment with ICS [138], compared with direct bronchial provocation tests where several months of treatment is required to show an effect [139]. This is of importance when considering bronchial provocation tests as a monitoring tool. One randomised controlled trial in children showed that routine assessment of BHR using methacholine bronchoprovocation is not useful in monitoring asthma in children [140].

Although routine monitoring of BHR is not useful, BHR assessment *via* methacholine or exercise tests may be of use in children with exercise limitation, poor symptom perception, or those who do not respond to their current treatment or with atypical asthma symptoms. It may also play a moderate role in predicting future asthma [141].

Markers of inflammation

Chronic airways inflammation is one of the hallmarks of asthma. The following sections focus on the role of noninvasive biomarkers in monitoring asthma and guiding therapy in routine clinical practise.

F_{eNO}

The most extensively studied biomarker is F_{eNO}, which has been reported to reflect both airway and tissue eosinophilia [142–144]. F_{eNO} can be measured in a noninvasive standardised way and is an attractive technique for use in children, usually from school age onwards [144–146].

Studies incorporating F_{eNO} into management algorithms have used many different protocols, not only in terms of the frequency of measurements but also in the inclusion of other indices of asthma control. The results are variable, with only some showing significant effects such as reduced BHR and higher maximal expiratory flow at 25% of FVC, and the outcome measures are not consistent across studies [17, 147–150]. There is a view that the potential of this technique has not been fully evaluated and more work is required that evaluates F_{eNO}-based management in appropriate patients and clinical settings.

In preschool children, there is no published data that considers the utility of F_{eNO} in monitoring asthma control, adjusting therapy or predicting exacerbations. However, some studies imply that elevated F_{eNO} in preschool children is associated with a risk of future wheezing or later asthma, and predicts a decline in lung function in infants with recurrent wheeze [151–154]. F_{eNO} measurements in preschool children have not been standardised and there is insufficient evidence to support the use of such measurements when monitoring preschool children.

A Cochrane review concluded that based on current evidence, F_{eNO} cannot be recommended for routine monitoring of asthma in children [155]. Most Task Force members support this recommendation; however, in children with difficult or uncontrolled asthma, F_{eNO} is sometimes used for monitoring disease in specialist centres. Persistently high F_{eNO} should alert the physician of reduced adherence to treatment, a faulty inhalation technique, ongoing allergen exposure or severe airways inflammation [146].

Sputum analysis
Induced sputum cytology analysis is recognised as a noninvasive tool that allows the assessment of inflammatory cells, such as eosinophils and neutrophils, as well as the investigation of a variety of fluid phase mediators in supernatants.

Sputum induction is feasible and safe in asthmatic children, and the technique of sputum induction and processing has been standardised for schoolchildren [25, 156–158]. Percentage of eosinophils is the marker used most frequently in clinical studies. Elevated sputum eosinophils were reported to be predictive of failed ICS reduction and asthma exacerbations in mild-to-moderate asthma, but incorporating the control of sputum eosinophils into the management algorithm did not significantly reduce overall exacerbations or improve asthma control in severe asthma [25, 159, 160]. This may be due to the observation that sputum inflammatory phenotypes are not stable over time [161].

Therefore, there is no evidence that induced sputum cytology is useful for monitoring asthma. None of the Task Force members uses this technique in routine clinical practise. However, for specific patients in specialised tertiary centres, this method may be justified when treatment decisions are difficult to make.

Exhaled breath condensate
The analysis of exhaled breath condensate (EBC) has been increasingly used as a research tool and many different components of EBC have been assessed. This is a simple, well-tolerated and safe method, even in children with severe asthma [162]. However, even though a joint American Thoracic Society (ATS)/ERS Task Force document was published on the methodology of EBC, technical issues and a lack of standardisation remain major issues that prevent the use of EBC in clinical practise [163]. To date, EBC does not play a role in monitoring asthma in children.

Management-related issues, comorbidities and the environment
In this section, we discuss aspects of treatment that may be checked to monitor asthma routinely (adherence to treatment, inhalation technique, side-effects of treatment) or as clinically indicated, particularly in the case of poorly controlled asthma (e.g. persisting exposures to tobacco smoke or allergens). Conditions that may aggravate asthma (e.g. allergic rhinitis, environmental irritant exposure) or may become apparent during follow-up (e.g. allergic rhinitis or obesity) are also discussed here.

Adherence to treatment
Adherence to treatment is defined as the extent to which the patient continues the agreed-upon treatment under limited supervision. More recently, the term "concordance" has been used to express the collaborative relationship between care-taker and care-provider on the basis of equality. The Task Force members chose to use "adherence" in the present paper as in general this is the more commonly used term.

Adherence to ICS is strongly influenced by the patients' and parents' illness and medication beliefs [145, 164–166]. Repeated tailored education, agreement on treatment goals and how to reach these, and addressing patients' and parents' beliefs and concerns therefore help to improve adherence to treatment and hence asthma control [164, 167–171]. Risk factors for decreased adherence include growing up in a single-parent family or replacement of the caregiver, and being prescribed more than two puffs a day [168, 172, 173].

There is no gold standard for the measurement of adherence to treatment. Self-reporting by the patient or caregiver, and pharmacy refill rates tend to overestimate adherence [174]. Electronic data recording could be superior; however, this should be balanced against extra costs [175]. Face-to-face interviews are more effective in reporting adherence than computer-assisted or pencil and paper interviews; however, all three

methods considerably overestimate adherence in comparison with electronic measurement [175]. Motivational interviews are a patient-centred approach used to discuss behavioural changes and a considerable body of evidence suggests that adherence can be improved by applying specific communicative consultation skills [176].

Several members of the Task Force routinely discuss adherence to treatment in a non-confrontational way as part of every asthma review. In children with severe, uncontrolled asthma, there are several ways of assessing adherence: electronic measurement and directly observed therapy are the most reliable, and if these are unavailable prescription records or refill rates could provide useful information. In some cases, home visits may be useful [43].

Inhaler technique

Correct inhaler technique is one of the prerequisites of successful asthma treatment. In children, this might be challenging as less than one-third of asthmatic children using a dry powder inhaler and two-thirds of children using a pressurised metered-dose inhaler/spacer combination perform all essential steps correctly [177]. The evidence suggests that inhalation technique should be taught, taught back and checked at least twice when new drugs or devices are prescribed, when asthma control deteriorates or at least annually [178, 179]. In addition, in young children, parents are usually asked to demonstrate inhaler technique at each visit and advice may be given about correct administration. In agreement with the ERS/International Society of Aerosols in Medicine (ISAM) consensus paper on inhalation, all Task Force members check the technique for each type of inhaler device according to the device-specific recommendations [180].

Side-effects of drug treatment

The risk of systemic side-effects during long-term use of low-to-moderate doses of ICS (beclometasone 200–400 $\mu g \cdot day^{-1}$ or equivalent) is considered rare [181, 182]. Height growth may be reduced by ∼0.5–2 cm during the first 1–2 years of treatment; whether or not this persists over time is under debate but cannot be excluded [183–185]. Adrenal suppression is more frequently seen during treatment with high-dose ICS; however, the frequency and severity of hypothalamic-pituitary-adrenal axis suppression is highly dependent on the tests used to assess this axis, and one should be aware that adrenal insufficiency may occur at low-to-moderate doses of ICS [186, 187]. More research is needed to define which tests for adrenal suppression are useful in which children. Nasal and dermal corticosteroids have to be considered in assessing total corticosteroid dose.

Local side-effects, such as thrush and hoarseness, are rare and are in general easily managed by teeth brushing or mouth rinsing after administration of ICS [188].

Side-effects of other medications given to control asthma, such as β_2-agonists and leukotriene antagonists, are also considered during monitoring by the Task Force members. However, there is limited evidence to support the need for specific investigations that monitor drugs other than corticosteroids.

In children using ICS, all Task Force members measure height and weight at least annually, but preferably at every visit. Children using high doses of ICS deserve special attention and monitoring for possible adrenal suppression.

Monitoring diseases that may aggravate asthma

Rhinitis, food allergy, gastro-oesophageal reflux (GOR) and obesity are conditions that may aggravate or mimic asthma; however, there is currently no evidence that treatment of these conditions improves asthma control [189]. There is no role for routine monitoring of these diseases in children with asthma; however, appropriate diagnostics might be considered for these diseases in children with uncontrolled asthma.

Asthmatic children with rhinitis, compared to those without, have poorer asthma control, reduced QoL, an increased risk of emergency visits or hospitalisations, and higher healthcare costs [41, 190–192]. Therefore, signs and symptoms suggestive of rhinitis and rhinosinusitis are often discussed and although treatment for rhinitis has not been proven to improve asthma control, it is considered good practise to ensure that rhinitis symptoms are managed appropriately in children with asthma.

Food allergy is commonly considered to be a risk factor for poor asthma control, and it may cause severe and even fatal asthma exacerbations, although food allergy in most studies has not been diagnosed with a double-blind-placebo-controlled food challenge [86, 193]. However, it appears that not the food allergy *per se* but sensitisation to multiple foods and aeroallergens is a risk factor associated with poor asthma control or severe exacerbations [194–196]. After appropriate counselling, children with comorbid food anaphylaxis might be considered for receiving an adrenaline auto-injector and appropriate training in its use [197].

GOR has been suggested as a cause of poor asthma control in children but treatment with lansoprazole in children with poorly controlled asthma, without symptoms of GOR, improves neither symptoms nor lung function [198–201]. There is no role for the routine assessment of GOR or swallowing abnormalities in children with asthma.

The relationship between obesity and asthma is complex and as yet not completely understood [202–206]. All Task Force members measure height and weight during routine clinical monitoring, with calculation of body mass index or percentile estimates of weight and height based on a relevant population.

Environmental factors

Multiple indoor and outdoor environmental stimuli are known to worsen asthma symptoms. The most common stimuli are discussed here; these include exposure to tobacco smoke, combustion-derived air pollutants, house dust mites, fungal spores, pollens and pet dander.

Tobacco smoke

There is good evidence that second-hand tobacco smoke exposure causes asthma, more severe asthma symptoms, BHR, airways inflammation and adverse effects on respiratory health in children [207–210]. There can be no doubt that smoking in the parents or caregivers should be strongly discouraged [44, 207–209, 211]. Success rates in asthma education, including second-hand smoke harm awareness, are low but in children who live in households where tobacco smoke exposure was successfully reduced, hospital admissions were halved over the following year [212]. A better understanding of how to motivate parents of children with asthma to change their smoking habits is urgently needed [213, 214].

Several methods are used to objectively measure children's second hand smoke exposure (cotinine, hair or nail nicotine, exhaled carbon monoxide, airborne nicotine) but a gold standard is lacking and currently there is no single recommended method for monitoring such exposure in children with asthma or for monitoring maternal smoking during pregnancy.

Air pollution

Children are more vulnerable to the health effects of outdoor and indoor air pollution than adults as their lungs are still developing, they have a higher minute ventilation, and they have higher levels of physical activity outdoors [215–218]. There is a positive association between exposure to traffic-related air pollution and exacerbation of asthma symptoms in children and reduced growth in lung function [47, 52, 54, 219, 220]. However, the measurement of outdoor pollutants is mainly performed for regulatory purposes and is not currently used to monitor asthma in children.

Indoor pollutants are mainly derived from incomplete combustion of biomass and solid fuels (*e.g.* dung, wood, agricultural residues, charcoal, coal, kerosene, candles, incense and mosquito coils) [50, 51, 55, 56]. Children seem to be more vulnerable to the effects of indoor pollution, and chronic exposure to indoor pollutants is associated with persistent wheeze, current asthma and use of asthma medication in children [45, 46, 49, 51]. Indoor dampness is another important factor that imposes a higher risk of asthma [48, 53].

Home visits by an asthma nurse are often conducted in patients with severe uncontrolled asthma to check for aggravating factors in the home.

Environmental allergen load

House dust mites, pollens, pet allergens and fungal spores are amongst the most common allergens in the indoor and outdoor environment. Single measures to reduce indoor allergen loads are likely to be of little benefit; individualised intervention programmes may reduce exposure to indoor allergens and result in decreased asthma morbidity, but a recent meta-analysis showed that measures to reduce house dust mite exposure were not helpful [221–223]. Specific questions about environmental exposures that are likely to increase the risk of asthma or to trigger asthma exacerbations are generally included in the assessment of all asthmatic children (table 5). Local air quality websites may be checked for warnings of high levels of air pollution and pollen loads, and precautions may be taken accordingly.

Monitoring through home visits to specifically assess the environmental allergen load could assist in the management of children with difficult-to-treat asthma before any changes to treatment regimens are considered [43].

Knowledge gaps and research needs in monitoring childhood asthma

Several research gaps were identified by this Task Force.

It is obvious that symptom control, prevention of exacerbations or lung function decline, and lack of lung growth represent three different clinical outcomes that may require different monitoring strategies. In

TABLE 5 List of possible pollutants/sources to be discussed with parents and children in the clinic or during a home visit
Exhaled tobacco smoke exposure
Traffic density near home/school
Industries near home/school
Cooking: use of wood/gas
Type of heating: any use of biomass
Pets: dogs/cats
House dust mite
Mould
Chemicals used at home for cleaning
Use of incense sticks/candles

addition, several studies demonstrate a number of parameters that can be used to assess asthma control in children through a single examination, but follow-up studies assessing the usefulness of these parameters in monitoring asthma are lacking. The variability of the pathophysiology in asthma is not in parallel, *e.g.* inflammation and bronchial obstruction may independently vary in time, underpinning the need for the availability of several tools for longitudinal monitoring. There is therefore an urgent need for studies that consider more targeted monitoring strategies in specific populations. Personalised medicine asks for personalised monitoring, which is not possible yet.

To date, phenotypic description of asthma has not been helpful in choosing monitoring schemes, and studies are needed not only to assess the effectiveness of asthma phenotypes *per se* but also take complex allergic diseases into consideration, regardless of whether they constitute certain phenotypes.

Studies that assess the usefulness of composite asthma control scores and longitudinal QoL measures in improving asthma control in primary and secondary care are needed.

Clinical trials that assess the utility of F_{ENO} in adjusting treatment or in predicting exacerbations in specific phenotypes, such as obese children, children with severe persistent asthma or preschool children, have not been performed. In addition, the meaning of significant changes in F_{ENO} in a longitudinal setting is still unclear and needs further attention. The use of "personal best" cut-off points in F_{ENO} algorithms requires further investigation.

In the same way, the feasibility and utility of induced sputum cytology to guide treatment in schoolchildren with mild-to-moderate asthma and preschool children with wheezing has yet to be investigated.

The use of lung function testing and noninvasive markers in preschool children is of particular interest and although their role in monitoring may be limited, their role in predicting the development of asthma and showing those who might benefit from ICS is a real challenge.

There is a general lack of monitoring schemes that are optimal for different healthcare settings, disease severities and ages. Data on optimal frequency of follow-up, tools to be used at each level and health cost–benefit are lacking. All these issues warrant further study.

Conclusion

Monitoring asthma in children requires careful review of the impact of asthma on the child's daily life, including sports and play. Adherence to maintenance therapy, inhaler technique and the patients' (and parents') views and beliefs on the goals of treatment are essential in monitoring children with asthma. The use of composite asthma control scores has not been shown to improve asthma outcome and QoL measures, and though potentially useful in research, they have limited value in clinical practise. Spirometry with BDR is of value and should be performed at least annually and more frequently in risk groups. There is no evidence that measurements of bronchial responsiveness and markers of inflammation are useful in the routine monitoring of children with asthma.

In children with poor asthma control, it is necessary to screen for allergic or non-allergic rhinitis/rhino-sinusitis and other comorbidities, and for exposure to indoor pollutants like tobacco smoke and allergens.

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