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Review article

Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report

Asthma is the leading chronic disease among children in most industrialized countries. However, the evidence base on specific aspects of pediatric asthma, including therapeutic strategies, is limited and no recent international guidelines have focused exclusively on pediatric asthma. As a result, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology nominated expert teams to find a consensus to serve as a guideline for clinical practice in Europe as well as in North America. This consensus report recommends strategies that include pharmacological treatment, allergen and trigger avoidance and asthma education. The report is part of the PRACTALL initiative**, which is endorsed by both academies.

Abbreviations: ACT, Asthma Control Test; DPI, dry powder inhaler; eNO, exhaled nitric oxide; FEF, forced expiratory flow; FEV_1, forced expiratory volume; FVC, forced vital capacity; GP, general practitioners; HPA, hypothalamic–pituitary–adrenal; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β2 receptor agonist; LTRA, leukotriene receptor antagonist; MDI, metered dose inhaler; nNO, nasal nitric oxide; PEF, peak expiratory flow; SLIT, sublingual immunotherapy.

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Asthma is the most common chronic childhood disease in nearly all industrialized countries. It is more prevalent in children with a family history of atopy, and symptoms and exacerbations are frequently provoked by a wide range of triggers including viral infections, indoor and outdoor allergens, exercise, tobacco smoke and poor air quality. Many infants and preschool children experience recurrent episodes of bronchial symptoms, especially wheezing and cough, beginning at a few months of age, mainly during a lower respiratory tract infection, and since a clinical diagnosis of asthma usually can be made with certainty by age 5, the early diagnosis, monitoring and treatment of respiratory symptoms are essential.

At the time of this report, there are few national (1–4) and no up-to-date international guidelines (5) that focus exclusively on pediatric asthma, even though children have a higher overall prevalence of asthma compared to adults. Pharmacotherapy for childhood asthma has been described in general asthma guidelines, including the recently updated Global Initiative for Asthma (GINA) guidelines (6) and in some national guidelines. However, the information available on specific aspects of pediatric asthma, in particular in children under 5 years of age, is limited and does not include the opinion and contributions of the pediatric allergy and respiratory community (1, 7, 8). In contrast to adults, the evidence base for pharmacotherapy in children under 5 years of age is very sparse. The current British Thoracic Society Guideline (9) has been the most accessible source of information for treatment of pediatric asthma, with recommendations based on the available literature and where evidence is lacking on expert opinion.

In view of the limited data from randomized controlled trials in children and the difficulties in applying systematic review criteria to diagnosis, prognosis and nonpharmacological management, this report employed a consensus approach based on available published literature (until June 2007) and on best current clinical practice. The report reviews the natural history and pathophysiology of pediatric asthma and provides recommendations for diagnosis, practical management and monitoring. The recommendations are aimed at both pediatricians and general practitioners (GPs) working in hospitals, office or primary care settings.

Natural history

Asthma in children can be described as 'repeated attacks of airway obstruction and intermittent symptoms of increased airway responsiveness to triggering factors, such as exercise, allergen exposure and viral infections' (10). However, the definition becomes more difficult to apply confidently in infants and preschool age children who present with recurrent episodes of coughing and/or wheezing. Although these symptoms are common in the preschool years, they are frequently transient, and 60% of children with infantile wheeze will be healthy at school age (11). Physicians should manage and exclude diagnoses other than asthma, and be aware of the variable natural history patterns of recurrent wheezing in early childhood.

Three different patterns of recurrent wheeze in pediatric patients have been proposed (12), and a fourth was recently described (13). However, it should be noted that patterns 1 and 2 (listed below) can only be discriminated retrospectively and are not suitable for use when treating the child.

1. Transient wheezing: Children who wheeze during the first 2–3 years of life, but do not wheeze after the age of 3 years
2. Nonatopic wheezing: Mainly triggered by viral infection and tends to remit later in childhood
3. Persistent asthma: Wheezing associated with the following:
   - Clinical manifestations of atopy (eczema, allergic rhinitis and conjunctivitis, food allergy), blood eosinophilia, and/or elevated total immunoglobulin E (IgE)
   - Specific IgE-mediated sensitization to foods in infancy and early childhood, and subsequently to common inhaled allergens (14–18)
   - Inhalant allergen sensitization prior to 3 years of age, especially with sensitization and high levels of exposure to specific perennial allergens in the home (10)
   - A parental history of asthma (15)
4. Severe intermittent wheezing (13): Infrequent acute wheezing episodes associated with the following:
   - Minimal morbidity outside of time of respiratory tract illness
   - Atopic characteristics, including eczema, allergic sensitization and peripheral blood eosinophilia

The highest incidence of recurrent wheezing is found in the first year of life. According to long-term population-related prospective birth cohort studies, up to 50% of all infants and children below the age of 3 years will have at least one episode of wheezing (19). Infants with recurrent wheezing have a higher risk of developing persistent asthma by the time they reach adolescence, and atopic children in particular are more likely to continue wheezing (Fig. 1) (10). In addition, the severity of asthma symptoms during the first two years of life is strongly related to later prognosis (20). However, both the incidence and period prevalence of wheezing decrease significantly with increasing age (12).

Determinants

Genetic factors. Studies on mono- and dizygotic twins along with the association of asthma phenotype within first degree relatives suggest a genetic basis to asthma. More recently, genome wide screens followed by posi-

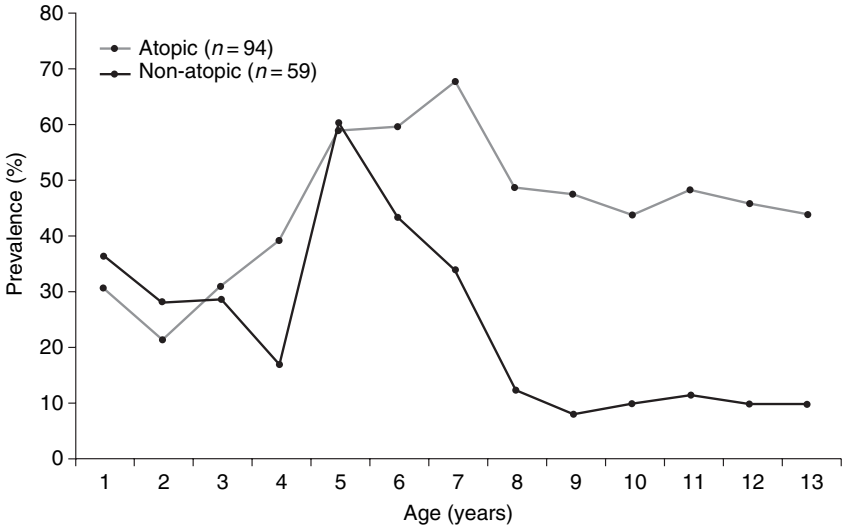


Figure 1. Prevalence of current wheeze from birth to age 13 years in children with any wheezing episode at school age (5–7 years), stratified for atopy at school age (10).

tional cloning and candidate gene association studies have identified genetic loci related to increased risk of asthma in certain populations (21). The effect of genetic variance on asthma and asthma-related phenotypes shows a great deal of heterogeneity, and may be strongly influenced by environmental factors (22–24). Accordingly, many children who develop asthma do not have parents with asthma, and many parents with asthma have children who do not develop asthma (10).

Most studies on the incidence and prevalence of asthma in childhood have indicated that the prevalence is higher in boys than in girls in the first decade of life (25, 26), although one serial cross-sectional study has suggested a recent narrowing of this gender gap (27). However, as children approach the teenage years, new-onset asthma becomes more common in girls than boys, especially in those with obesity and early-onset puberty (28). The reason for these gender differences is not well understood.

Environment and lifestyle as disease modifiers and triggers. *Allergens*: Exposure to outdoor and especially indoor allergens is a significant risk factor for allergic asthma (29–31). Exposure in infancy is related to early sensitization, and the combination of sensitization and exposure to higher levels of perennial allergens in the home is associated with asthma persistence and poor lung function in children (10). Clinical expression of the disease is variable, and depends on factors like the characteristics of the allergen, such as seasonality, regional specificity, and indoor or outdoor presence.

In infancy, food allergy with manifestations in the skin, the gastrointestinal tract or respiratory tract is more common than inhalant allergy (32). The presence of food allergy is a risk factor for the development of symptoms of asthma in children aged >4 years (15, 24). With increasing age, symptoms associated with inhaled allergens develop, particularly to indoor allergens, such as house-dust mites, pets, cockroaches and mold, and later to outdoor allergens, such as pollen or molds.

The classical allergic reaction involves binding of allergen-specific IgE antibodies to mast cells, and on re-exposure to the allergen, this may be followed by the early phase response associated with the release of mast cell mediators and presentation with typical allergic symptoms, followed by the late-phase response. Since repeated allergen exposure and allergic response may damage the tissues involved, the effect of allergy may persist even after removal of the allergen.

Infection. Some studies suggest that exposure to certain viruses (e.g. hepatitis A, measles), mycobacteria or parasites, may reduce the incidence of allergy and/or asthma (33–35), and that recurrent mild infections may protect against asthma (36, 37). Others suggest that microbes may initiate asthma (38–40). Currently there is insufficient evidence from intervention studies to clarify this relationship and particularly any potential clinical relevance.

Respiratory viral infections are the single most frequent asthma trigger in childhood (41, 42). They are the only trigger of wheeze and cough in many children and can exacerbate atopic asthma (43). Human rhinoviruses are responsible for the majority of asthma exacerbations (41, 42) and respiratory syncytial virus is a common cause of severe respiratory symptoms in infants (42, 44). Severe respiratory infections are associated with asthma persistence later in childhood (36), and recurrent respiratory infections may worsen asthma symptoms further. Infection can damage the airway epithelium, induce inflammation and stimulate both an immune reaction and airway hyperresponsiveness (45, 46). Once the infection resolves, hyperresponsiveness remains for a considerable

length of time (47). Infections remain an important trigger throughout childhood and into adulthood.

To date, there is no evidence that vaccinations given during the first years of life modify the risk of atopy or asthma (48). Exposure to antibiotics during infancy has been associated with an increased risk of asthma (49, 50). However, results from these studies remain inconclusive, and childhood vaccination guidelines and judicious antibiotic usage practices should remain unchanged.

Tobacco smoke: Passive exposure to tobacco smoke is one of the strongest domestic and environmental risk factors for developing recurrent coughing/wheezing or asthma symptoms at any age during childhood (19). Tobacco smoke increases oxidative stress and stimulates inflammation in both the lower and upper airways. In addition, maternal smoking during pregnancy results in impaired lung growth in the developing fetus, which may be associated with wheezing early in life (51). In existing asthma, smoking is associated with disease persistence (51, 52), and may impair the response to asthma treatment (53). Although tobacco smoke is harmful to everyone, its detrimental effects are relatively greater in younger children due to their smaller airway size. Avoiding tobacco smoke is therefore one of the most important factors in preventing asthma and other respiratory diseases (54).

Pollutants: The effect of air pollution caused by traffic or industry on pediatric asthma has been extensively studied (55–57). In addition to their direct toxicity on the lungs, pollutants induce oxidative stress, airway inflammation and may cause asthma in those who are genetically susceptible to oxidant stress exposures (58, 59). Although pollutants are typically considered to be an outdoor phenomenon, high concentrations of pollutants can be found indoors.

Nutrition: The value of breast feeding is clear and a recent systematic review suggests that it protects from the development of atopic disease, particularly in children with atopic heredity (60). Use of an extensively hydrolyzed infant formula does not appear to decrease the incidence of asthma (61). While strict avoidance of proteins, such as cows' milk or hens' eggs, reduces the incidence of atopic dermatitis in the first year of life, it does not prevent the development of asthma (62, 63).

Several studies have suggested that dietary factors, such as sodium content, lipid balance and level of antioxidants may also be associated with asthma activity, although such studies have been difficult to control, due to the complexity of diet (64). Studies on obesity and asthma offer general advice to avoid excess weight gain and maintain a lifestyle that includes a balanced diet (65).

Some studies show that supplementation with omega-3 polyunsaturated fatty acids may reduce symptoms of wheeze (66), and when combined with other protective measures, such as prevention of house-dust mite exposure, it may also reduce the likelihood of atopic sensitization (67). However, since the studies are inconclusive this regime should not be generally adopted.

Irritants: A number of different irritants have been associated with respiratory symptoms and asthma in children, including perfume, dust and chlorine. These triggers can become important in specific settings (e.g. swimming pools) (68). The mechanism may not be the same for all irritants and may include both neural and oxidative pathways. Avoidance of irritants is advisable. Chlorinated water can be an irritant; however this can be dealt with using a good ventilation system and should not be a reason to prevent children from swimming.

Exercise: Exercise will trigger asthma symptoms in the majority of children with asthma (69), and exercise-induced bronchospasm can also be a unique asthma phenotype. The mechanism may involve changes in airway osmolarity resulting from water loss and/or changes in airway temperature that lead to bronchoconstriction and bronchospasm (70). Regular aerobic exercise is crucial to healthy development, and therefore should not be avoided. In addition, there is evidence that low physical fitness in childhood is associated with the development of asthma in young adulthood (71). Consequently, airway inflammation and asthma should be kept under control to improve breathing and allow participation.

Weather: Different weather conditions, including extreme temperature and high humidity have been associated with asthma activity, including exacerbations (72). Since it is difficult to avoid weather entirely; for example, thunderstorms, parents should be aware of these potential triggers and may adjust the therapeutic strategies for the child accordingly.

Stress: Psychological factors, especially chronic stress, can also affect the activity of asthma (73), although this finding requires more study in children. Children's lung function and asthma activity may also be affected by parental stress levels (74). Stress can exacerbate asthma and there is a correlation between asthma and psychological disturbances (73). Avoidance of undue and unnecessary stress and/or training in stress management may, therefore, be beneficial.

Concurrent triggers: Simultaneous or subsequent exposure to different triggers may have additive or even synergistic effects on symptoms/exacerbations of asthma (43). Although in the majority of cases a particular trigger is prominent, interactions should be sought as they may influence the outcome.

Asthma phenotypes

In asthma, age and triggers can be used to define different phenotypes of disease. These phenotypes are likely to be useful because they recognize the heterogeneity of childhood asthma. They do not represent separate diseases,

but are part of the 'asthma syndrome'. Guidelines that recognize different phenotypes should provide better direction for prognosis and therapeutic strategies.

Phenotype-defining elements

Age

Age is one of the strongest determinants of asthma phenotype in childhood, and involves pathophysiological events, exposure and natural history determinants. Because of differences in disease presentation between the age groups, it is important to design diagnostic and management strategies based on age. Practical age groupings for these purposes are:

- Infants (0–2 years old)
- Preschool children (3–5 years old)
- School children (6–12 years old)
- Adolescents.

Infants (0–2 years old). In infants, persistence of symptoms is a major indicator of severity. Therefore, it should be established whether the child has wheezed on most days of the week during the last 3 months. If so, these children should be diagnosed with persistent infantile wheeze, after careful exclusion of other causes. Children with intermittent disease (recurrent episodes) can be classified as having either severe or mild disease, depending upon the need for medical resources (systemic steroids, hospitalization).

Preschool children (3–5 years old). In preschool children, the key differentiator of asthma phenotype is persistence during the last year (Fig. 2). If symptoms disappear completely between episodes, and usually follow a cold, viral-induced asthma is the most appropriate diagnosis. Viruses are the most common trigger in this age group. Exercise-induced asthma can also be a unique phenotype in this age group.

Skin prick tests or *in vitro* tests for the presence of specific IgE antibodies should be performed along with efforts to ascertain whether there is a clinically relevant association between exposure and symptom occurrence. If so, the phenotype is allergen-induced asthma. It should be emphasized that atopy is a risk factor for asthma persistence irrespective of whether or not allergens are obvious triggers of disease activity. If no specific allergic trigger can be identified, the phenotype can be characterized as nonallergic asthma with some caution. However, this may still mean that the specific allergic trigger was not detected.

School-age children (6–12 years old). The differentiators in school-age children are the same as those in preschool children (Fig. 2). However, allergen-induced cases are more common and visible and seasonality may become evident. Virus-induced asthma is still common in this age group. Severity may become an important issue in the treatment of allergen-induced asthma.

Adolescents. Atopic asthma can have its onset during adolescence and there are more new cases than remissions (75). Nonatopic asthma can also start during adolescence (28). There are additional problems associated with managing and classifying asthma in adolescent patients. Many adolescents are reluctant to use regular daily medications and do not like having any restrictions placed on their lives. Smoking may also become an issue. Also, there may be a difficult transition period when patients stop seeing a pediatrician and start seeing another physician.

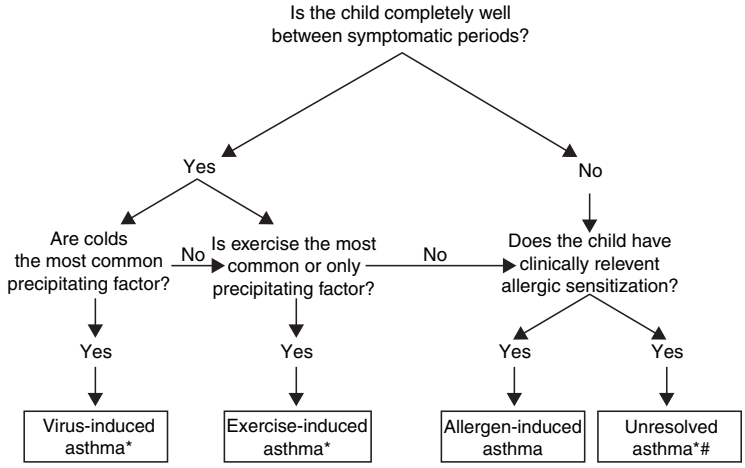


Figure 2. Asthma phenotypes in children aged >2 years of age. Note that phenotypes are a useful guide to the predominant problem and overlap between phenotypes is frequently present.

Severity

Pathologically, severe asthma in both adults (76) and children (77) has particular characteristics suggesting that it could be considered as a unique phenotype. Severity is associated with persistence and unresponsiveness to therapy. Although it can be useful as an additional parameter in defining phenotypes, severity levels tend to be arbitrary. Severity also depends on age. In infants, persistent disease should be considered severe; in older children, severe exacerbations are those with respiratory distress who require oxygen and hospitalization; these may occur independently of the usual measures of severity, i.e. frequency of symptoms, or lung function.

Recommendations

- Careful evaluation and recognition of asthma triggers is important in patient education, environmental control and prognosis
- Identification of asthma phenotype should be always attempted, including evaluation of atopic status
- Asthma symptoms between exacerbations (interval symptoms) are a major factor in phenotyping childhood asthma
- In infants particularly, a confident diagnosis of asthma is difficult to make
- In preschool and school-age children with recurrent viral exacerbations, the term 'virus-induced asthma' is preferable to terms that include 'wheeze'

Research recommendations

- Research on all aspects of childhood asthma should be encouraged as it is not as well understood as asthma in adults
- Special attention is required for infants and adolescents, due to the specific vulnerabilities and needs of these groups
- Study designs based on specific asthma phenotypes may improve understanding of natural history/medication effectiveness
- Mechanisms involved in the natural course of asthma should be studied in more detail to find ways of reducing the risk of disease persistence

Pathophysiology

Asthma symptoms most commonly occur in the setting of chronic and often systemic inflammation, which is probably present even when there is no evidence of clinical symptoms. Asthma is also characterized by considerable variability in activity since symptoms and exacerbations can be triggered by a number of different factors. In addition, repeated exacerbations may help perpetuate the disease. The relative contribution of each trigger to disease activity may change with the age of the child.

Asthma is particularly complex in children because several elements of the immune system including antigen presentation, T-cell function and antibody production are immature and thus facilitate atopic responses (78). Interactions between the rate of immune system maturation and lung growth and development during the first years of life seem to be crucial in the development of asthma (79). In addition, the airways of infants and children are more susceptible to obstruction due to their smaller size and the soft ribcage offers poor support for the underlying lung, which recoils to volumes more likely to cause airway closure (80). All of these phenomena are influenced by the child's genes (81) and by the interaction between genetic, developmental and environmental factors (82).

Immunological abnormalities

Immunological abnormalities associated with asthma have been extensively studied in murine models, *in vitro* and in adult asthma patients. Fewer studies have examined pediatric patients. Immune responses may vary among children whose asthma is associated with different triggers (e.g. allergen-induced *vs* virus-induced inflammation), but also in accordance with the developmental changes described above (83, 84). However, there is considerable overlap between phenotypes as well as between individuals (85, 86). The underlying disease in atopic (allergic) asthma is systemic, illustrated by the involvement of the bone marrow in effector cell mobilization (87) and imbalances in T-cell immunity are considered central in the majority of patients.

T-cell immunity. T cells play a prominent and complex role in the pathophysiology of asthma. Interleukin (IL)-4 and IL-13, which are crucial in IgE class switching, and IL-5, which drives eosinophilia, are the products of the Th2 subset of T-helper lymphocytes. A simple paradigm of imbalance between Th1 and Th2 cytokines has long been used to describe immunological abnormalities in asthma. However, it is becoming increasingly clear that interactions between T-cell subsets and related cytokines are more complex and differ depending on a number of factors including age and stimulus (88–91).

Evidence from animal models suggests that dendritic cells, which present antigen to T cells, are involved in driving the Th1/Th2 imbalance (92). Dendritic cell function is suboptimal in very young children since it does not mature until later in life. An important role also appears to be played by T-regulatory cells, which suppress immune responses by regulating inflammation via cell-to-cell contact and the release of suppressive cytokines (93).

Atopy. The majority of children with asthma are atopic, defined as the propensity to develop IgE antibodies and

related clinical syndromes (94). Although the atopic phenotype is frequently present in infancy, it becomes increasingly apparent in preschool and school-age children and remains associated with asthma at all ages (95). Atopic individuals tend to have elevated IgE antibody levels and a Th1/Th2 imbalance in response to mitogens, allergens and viruses (47, 89). The atopic environment promotes further allergen sensitization and aberrant responses to viral infections (96).

Structure–function interactions

In addition to inflammation, structural changes are also present in the airways of individuals with asthmatic symptoms. These changes can persist even in the absence of symptoms for more than 6 years and cessation of asthma therapy (97).

Airway remodeling. Airway remodeling is a general term describing chronic, possibly irreversible changes that occur in the airways of patients with asthma. These include smooth muscle hypertrophy, angiogenesis and increased vascularity, chronic inflammatory cell infiltration, goblet cell hyperplasia, collagen deposition, thickening of the basement membrane and reduced elasticity of the airway wall (98). Although such abnormalities have been described in both adults and children, they are less extensively characterized in pediatric patients (85, 99, 100). Evidence of remodeling has been described in children with postviral wheeze, but there is evidence that the changes do not begin until after infancy (101). Remodeling may be enhanced by elements of a Th2 immune response (102, 103). Early treatment (from 2 or 3 years of age) with inhaled corticosteroids (ICS) does not appear to alter the course of these changes (104).

Bronchial inflammation. Bronchial inflammation is a central characteristic of most patients who have asthma symptoms, and involves changes at the epithelial level, recruitment of inflammatory cells, and production of multiple mediators. It is closely associated with airway hyperresponsiveness. Cellularity and other characteristics of inflammation depend upon trigger and age and may differ between asthma phenotypes. Inflammation may persist to a varying extent during the intervals between exacerbations.

Nasal inflammation. In adult asthma, nasal inflammation is found even in the absence of symptoms and nasal allergen challenge results in increased bronchial inflammation and vice versa (105–107). Although this has not yet been shown in children, it appears to correlate with the clinical histories of many children with allergic asthma.

Role of epithelium. The bronchial epithelium plays a central role in asthma by reacting to external stimuli as well as regulating inflammatory and remodeling processes (108). Biopsy studies have shown that the epithelial barrier appears to be compromised in both adults and children with asthma (99).

Inflammatory cells and their recruitment. Eosinophils, neutrophils and T cells infiltrate the epithelium in childhood asthma and cause inflammation (85, 99, 100, 109). Neutrophilic inflammation is associated with both viral triggers and increased disease severity (86). Eosinophilic inflammation is associated with asthma and atopy and has also been associated with persistent symptoms (77, 100). Biopsy studies, bronchoalveolar lavage (86) and indirect measures of inflammation, such as exhaled nitric oxide (eNO) (110), all show that bronchial inflammation is present in young children with respiratory symptoms and asthma.

Airway obstruction. During asthma exacerbations, the airway is obstructed by a combination of edema, mucus hypersecretion and smooth muscle contraction. This occurs at all ages and in all asthma phenotypes and is a common endpoint induced by different triggers.

Airway hyperresponsiveness and neural control. Airway responsiveness to nonspecific stimuli is higher in normal infants and young children than in older children or adults (111). Airway hyperresponsiveness is a hallmark of asthma. It is also a feature of viral infection and can be present irrespective of asthma diagnosis or asthma symptoms. It is associated with inflammation and airway remodeling and is correlated with asthma severity.

Neural regulation of the airways consists of cholinergic excitatory, adrenergic inhibitory nerves and nonadrenergic, noncholinergic nerve pathways. Its role in the pathogenesis of asthma has been reviewed (112).

Research recommendations

- Additional studies are needed in order to understand remodeling in children, in particular the features, progression and responses to therapy
- Differentiating the patterns bronchial inflammation may prove useful in understanding the time course of different phenotypes
- Identification of noninvasive markers of different underlying pathophysiologies
- Studies of the relationship between upper and lower airways inflammation may help elucidate pathophysiology
- Further information on neural control of the airways in children

Diagnosis

There are no specific diagnostic tools or surrogate markers for detecting asthma in infancy. Therefore,

asthma should be suspected in any infant with recurrent wheezing and cough episodes. Frequently, diagnosis is possible only through long-term follow-up, consideration of the extensive differential diagnoses and by observing the child's response to bronchodilator and/or anti-inflammatory treatment.

Case history

A confident diagnosis of atopy can be difficult in young children (113). The individual case history should focus on the frequency and severity of symptoms including wheeze, nocturnal cough, exercise-induced symptoms, and persistence of cough with colds (114), atopic heredity and exposure to environmental factors including allergens and tobacco smoke. Symptom patterns in the last 3–4 months should be discussed, with a focus on details of the past 2 weeks. Wheezing should be confirmed by a physician due to possible misinterpretation of respiratory sounds by parents (115).

In all children, ask about:

- Wheezing, cough
- Specific triggers: e.g. passive smoke, pets, humidity, mold and dampness, respiratory infections, cold air exposure, exercise/activity, cough after laughing/crying
- Altered sleep patterns: awakening, night cough, sleep apnea
- Exacerbations in the past year
- Nasal symptoms: running, itching, sneezing, blocking

In infants (<2 years), ask about:

- Noisy breathing, vomiting associated with cough
- Retractions (sucking in of the chest)
- Difficulty with feeding (grunting sounds, poor sucking)
- Changes in respiratory rate

In children (>2 years), ask about:

- Shortness of breath (day or night)
- Fatigue (decrease in playing compared to peer group, increased irritability)
- Complaints about 'not feeling well'
- Poor school performance or school absence
- Reduced frequency or intensity of physical activity, e.g. in sports, gym classes
- Avoidance of other activities (e.g. sleepovers, visits to friends with pets)
- Specific triggers: sports, gym classes, exercise/activity

Adolescents should also be asked if they smoke.

Physical examination

A thorough physical examination should always be performed, which should include listening to forced expiration and nasal examination. In cases where nasal polyps are found, cystic fibrosis should be excluded. Key clinical signs suggesting an atopic phenotype include:

- Atopic eczema or dermatitis
- Dry skin
- Dark rings under the eyes (allergic shiners)
- Irritated conjunctivae
- Persistent edema of the nasal mucosa, nasal discharge, 'allergic salute' and 'allergic crease' on the bridge of the nose.

IgE-mediated allergy

Allergic sensitization is the major risk factor for the development of asthma and for its persistence and severity (10, 15, 18). In addition, the presence of atopic dermatitis and/or food-specific IgE increases the risk of sensitization to inhaled allergens and may be predictive of asthma development (116). Therefore, diagnostic evaluation should include allergy testing in all children (117). Allergy diagnosis is based on evaluation of symptoms, case histories and *in vivo* and *in vitro* testing.

In vivo testing for allergies

The skin prick test is simple, inexpensive and provides results quickly (118). Tests should be carried out using standardized methods and controls and standardized allergen extracts. The panel of allergens tested will depend on the age of the child and individual case history, and should vary depending on local environment-specific allergens. Optimally, testing should be carried out by qualified physicians or nurses with experience and training. Results from skin prick tests depend on a series of variables, including extract potency, recent H_1-antihistamine use by the child, skill of the operator and the device used to prick or puncture the skin. Interpretation of the results and assessment of their clinical significance should be performed by an experienced clinician.

There is no lower age limit for skin prick testing among children (119, 120). In high-risk, wheezing infants, skin prick testing revealed a high level of sensitization to foods and inhalant allergens, which is a major risk factor for asthma development at the population level (24). However, although a positive result to indoor allergens in young children is strongly associated with asthma (24), a negative result does not exclude the presence of asthma. Since new sensitivities can occur even during adolescence (75), consideration should be given to repeating skin prick tests at yearly intervals in wheezing children with negative tests who remain symptomatic. In infancy and early childhood, the size of skin test wheals is age-dependent (121).

In vitro testing for allergies

In vitro testing for allergen-specific IgE may be useful if skin prick testing cannot be performed because the child has severe atopic dermatitis/eczema, is unable to

discontinue antihistamine therapy, or has a potentially life-threatening reaction to a food or inhalant. Specific serum IgE measurement does not provide more accurate results than skin prick testing. Testing should be performed using a validated laboratory method, such as ImmunoCAP (Phadia AB, Uppsala, Sweden), should be related to the patient's clinical history, and should be used for the same indications as the skin prick test (117).

IgE panel tests, which measure IgE for a range of common allergens simultaneously, can be used to assess sensitization when determining asthma phenotype. They have been shown to have a high negative predictive value in excluding allergic sensitization among wheezing children (122).

Other tests. A chest x-ray can be performed at the first visit. Other tests available, such as eNO, exhaled breath condensates, eosinophil counting in induced sputum and peripheral blood, and basophil histamine release, may indicate the presence of allergic inflammation. However, in a population based study in school children, eNO levels correlated better than spirometric indices with reported asthma (123). Indirect measures of bronchial hyperresponsiveness, such as methacholine, histamine, mannitol, hypertonic saline, hyperventilation/cold air, exercise (preferably running) tests may also be useful in supporting a diagnosis of asthma.

Allergen inhalation challenge. In research settings allergen challenge tests of the bronchi, nose or eyes can be performed. However, a bronchial allergen challenge is generally not necessary in clinical practice and is not recommended.

Assessing lung function

The most widely used and accessible lung function measures are peak expiratory flow (PEF) and forced expiratory flow-volume loop (124). Mainly flow-volume loop is useful for identifying obstruction whether it is clinically relevant or not, and for classifying disease severity (125). Forced expiratory techniques can be reliably used in most children as young as 5–6 years of age, and in some children at the age of 3 years (126). MicroRint, the forced oscillation technique and other techniques can be used in preschool children, although information is of limited or no value for diagnosing asthma in this age group.

Bronchodilator response. β-agonist reversibility may provide information about the reversibility of airflow limitation (127). Using the percent change from baseline, an increase in forced expiratory volume (FEV_1) >12% suggests a significant bronchodilation. However, lack of response does not preclude a clinical response to bronchodilator therapy. Two recent studies have found a significant correlation between measures of airway inflammation (fraction of eNO and sputum eosinophils) with response to β2 agonists (128, 129). However, most children have FEV_1 values close to normal and reversibility tends to be smaller than that in adults (130–132).

Differential diagnosis and co-morbidities

In children with severe recurrent wheeze, or in infants with persistent nonresponsive wheeze, other diagnoses must be excluded as well as the presence of aggravating factors, such as gastroesophageal reflux, rhinitis, aspiration of a foreign body, cystic fibrosis, or structural abnormalities of the upper and lower airways. These cases may require fiber optic bronchoscopy with bronchoalveolar lavage, chest computed tomography scan, or esophageal pH probing (133). In addition, treatment response should be considered. If therapy with ICS, leukotriene receptor antagonists (LTRA) or bronchodilators fails, the asthma diagnosis should be reconsidered.

Recommendations

- Use of a standardized diagnostic questionnaire (Table 4) should be implemented along with spirometry in general practice

Research recommendations

- Improvements and new developments in lung function measurement for young children are needed
- Further standardization and demonstration of usefulness of indirect measures of bronchial inflammation (such as eNO, breath condensate and more)

Management

Management of asthma should include a comprehensive treatment plan that includes avoidance of airborne allergens and irritant triggers (where possible), appropriate pharmacotherapy and asthma education programs for patients, parents and caregivers. In selected patients, allergen-specific immunotherapy may be beneficial.

Avoidance measures

The effect of allergens on asthma is related to the frequency and level of exposure. Exposure leads to sensitization and the triggering of symptoms, and may also induce persistent bronchial inflammation, which predisposes individuals to other triggering factors. Studies suggest that avoidance of some allergens (e.g. cats, dogs, guinea pigs, horses) may reduce the incidence of symptoms and prevent sensitization.

Primary prevention has been defined as elimination of any risk or etiological factor before it causes sensitization, secondary prevention as the diagnosis and therapy at the earliest possible point in disease development, and tertiary prevention as the limitation of the disease effect (134). Studies of primary prevention of sensitization have reported conflicting results. Dust mite avoidance, for example, prevented sensitization in some studies (135), but not in others (136). Following implementation of more stringent, multifaceted avoidance programs, studies have reported reduced asthma prevalence and severity (137), reductions in the prevalence of wheezing (138), and improved lung function despite slightly increased sensitization to dust mites (139). More reliable results have been obtained from secondary (140) and tertiary prevention studies (140, 141).

The effort required by families to reduce exposure to ubiquitous airborne allergens can be difficult to achieve and sustain, and should be balanced against the ease or difficulty in controlling associated symptoms with pharmacotherapy.

Avoidable allergens. Table 1 lists common allergens and potential avoidance strategies (113, 142).

Pets: It will typically take up to 6 months after removal of the pet from the household for allergen levels to fall enough to reduce asthmatic reactions (143). However, there is very little evidence that not having a pet will decrease the risk of sensitization.

House-dust mites: Since house-dust mites are more common in humid rooms, humidity should be kept low using appropriate ventilation or a dehumidifier. Other measures to reduce exposure include use of mattress covers and regular washing of bedding and clothing in hot water (>56°C) (113).

Food allergens: In an infant or child with food allergy, ingestion of food may trigger a severe acute systemic reaction (anaphylaxis). In some reactions, upper airway obstruction, and lower airway obstruction manifest as asthma symptoms, and can be severe. If fatal anaphylaxis occurs, death usually results from upper and/or lower respiratory tract obstruction and respiratory failure, rather than from hypotension (144). Complete avoidance of the offending food(s) is recommended.

Table 1. Steps to avoid specific allergens in sensitized individuals

Allergen	Avoidance measure
Pets	Remove pet and clean home, especially carpets and upholstered surfaces
	Encourage schools to ban pets
Dust mites	Wash bedding and clothing in hot water every 1–2 weeks
	Freeze stuffed toys once per week
	Encase mattress, pillows and quilts in impermeable covers
	Use dehumidifying device
Cockroach	Clean home
	Use professional pest control
	Encase mattress and pillows in impermeable covers
Mold	Wash moldy surfaces with weak bleach solution
	Use dehumidifying equipment
	Fix leaks
	Remove carpets
	Use High Efficiency Particle Arrestor filtration

Avoidance of triggers. Avoidance of triggers should also be part of the general strategy for asthma management (see Pathophysiology, *triggers* and Asthma phenotypes section). Key avoidable triggers are tobacco smoke, other irritants, and some allergens; also, as far as possible, infections and stress should be avoided. Although exercise can be a trigger, it should not be avoided.

Avoidance of tobacco smoke. Tobacco smoke should be strictly eliminated from the environment of all children and particularly of children with history of wheezing. At every office visit, the smoking habits of the family should be assessed. Stopping smoking should be always discussed with parents who are smokers and counseling should be offered.

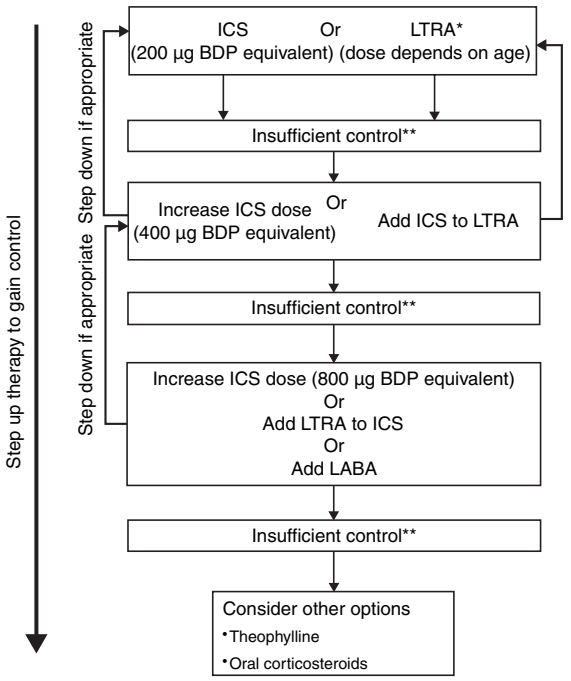
The home is one of the few places where parents can make free choices about their smoking. Given increasing official pressure to ban smoking in workplaces and public places, many smokers may smoke more at home. Thus, government programs aimed at reducing smoking in public may paradoxically place children at greater risk of exposure to the long-term effects of tobacco (145). This is an important issue, which requires further research.

Recommendations

- Allergen avoidance is recommended when there is sensitization and a clear association between allergen exposure and symptoms
- Only thorough allergen avoidance may have clinically relevant results
- Allergen testing (at all ages) to confirm the possible contribution of allergens to asthma exacerbations
- Avoidance of exposure to tobacco smoke is essential for children of all ages, as well as pregnant women
- A balanced diet and avoidance of obesity are favorable
- Exercise should not be avoided; asthmatic children should be encouraged to participate in sports, with efficient control of asthma inflammation and symptoms

Research recommendations

- Define the contribution of allergens to exacerbations and the role of allergen avoidance in disease modification



* LTRA may be particularly useful if the patient has concomitant rhinitis
** Check compliance, allergen avoidance and re-evaluate diagnosis
*** Check compliance and consider referring to specialist

Figure 3. Algorithm of preventive pharmacologic treatment for asthma in children >2 years of age.

Pharmacotherapy

The goal of pharmacotherapy is control of symptoms and prevention of exacerbations with a minimum of drug-related side-effects. Treatment should be given in a stepwise approach according to the persistence, severity, and/or frequency of symptoms and should take into account the presenting asthma phenotype (Fig. 3). It should be noted that some children will not respond to specific therapies. Children starting a new therapy should be monitored and changes made where appropriate.

Medications currently available for childhood asthma include:

Reliever medications

- Short-acting inhaled β2 agonists
- Other bronchodilators

Controller medications

- ICS
- LTRA
- Long-acting β2 receptor agonists (LABAs) (only in combination with ICS)
- Sustained-release theophylline
- Anti-IgE antibodies
- Cromolyn sodium
- Oral steroids

Reliever medications

Short-acting β2 agonists

- Treatment of choice for intermittent and acute asthma episodes in children, very young children and for preventing exercise-induced asthma. (The presence of exercise induced bronchospasm is, however, an indication to start regular preventive treatment with ICS or an LTRA).
- The safety margin for dose range is wide and determination of the optimal dose can be difficult. The lowest effective dose that provides adequate clinical control and minimizes side-effects, such as tachycardia, dizziness and jitteriness, is recommended.
- Salbutamol, the most commonly used drug, has a favorable safety and efficacy profile in patients aged 2–5 years (146).
- Terbutaline and formoterol also have safety and efficacy profiles comparable to that of salbutamol; directions for use are similar.

Ipratropium bromide

- The only other reliever of any relevance. In acute asthma its combined use with β2 agonists may result in favorable outcomes in children (147), although results were ambiguous in those less than 2 years of age (148).
- Side-effects are few and current evidence supports trial use when β2 agonists alone are not fully effective.

Regular controller therapy. The main goal of regular controller therapy should be to reduce bronchial inflammation.

ICS

- A first-line treatment for persistent asthma.
- Reduces the frequency and severity of exacerbations.
- Should be introduced as initial maintenance treatment (200 µg BDP equivalent) when the patient has inadequate asthma control.
- Atopy and poor lung function predict a favorable response to ICS (149).
- If control is inadequate on a low dose after 1–2 months, reasons for poor control should be identified. If indicated, an increased ICS dose or additional therapy with LTRAs or LABAs should be considered.
- It has been known for many years that the effect of ICS in older children begins to disappear as soon as treatment is discontinued (150).
- New evidence does not support a disease-modifying role after cessation of treatment with ICS in preschool children (104, 151, 152).

LTRA

- An alternative first-line treatment for persistent asthma.
- Evidence supports use of oral montelukast as an initial controller therapy for mild asthma in children (153), as it provides bronchoprotection (154), and

reduces airway inflammation as measured by nitric oxide levels in some preschool children with allergic asthma (155, 156).
- Younger age (< 10 years) and high levels of urinary leukotrienes predict a favorable response to LTRA (149).
- A therapy for patients who cannot or will not use ICS.
- Useful also as add-on therapy to ICS as their mechanisms of action are different and complementary (157).
- Suggested as treatment for viral-induced wheeze and to reduce the frequency of exacerbations in young children aged 2–5 years (158, 159).
- Benefit has been shown in children as young as 6 months of age (156, 160).

LABA

- Add-on controller therapy to ICS for partially controlled or uncontrolled asthma.
- Efficacy is not well documented in children in contrast to adults, and use should be evaluated carefully (161, 162).
- Safety concerns have been raised recently (163), suggesting that use should be restricted to add-on therapy to ICS when indicated.
- Combination products of LABA and ICS may be licensed for use in children over 4–5 years, however, the effect of LABAs or combination products has not yet been adequately studied in young children under 4 years.

Oral theophylline

- There is anecdotal evidence that low-dose theophylline may be of benefit in select groups of children who remain uncontrolled on ICS, LTRAs or LABAs.
- Theophylline is inexpensive, and in some countries, it is used for children whose families cannot afford ICS, LTRAs, or LABAs.
- Due to its narrow therapeutic index and variable metabolism rates between patients, blood levels must be monitored closely.

Cromolyn sodium (nedocromil)

- Cromolyn sodium can be prescribed for children as young as 2 years of age.
- Efficacy is in question (6), however, and it is less effective than ICS.
- Must be used frequently (four times per day), and may take up to 4 weeks to work (164).
- Free of side-effects.
- Available as oral or nasal inhalers, nebulizer solution, and eye drops.

Anti-IgE antibodies

- Patients aged ≥12 years may benefit if they have moderate-to-severe persistent atopic asthma that is inadequately controlled despite treatment with other therapies (165).
- Mode of application and cost will limit this intervention to patients who fail to respond to currently available therapies.
- The therapeutic index (benefit-to-risk ratio) of this relatively new agent is still being defined.

Risks and side-effects of pharmacotherapy. Awareness of potential side-effects of pharmacotherapy is mandatory. Precautions and considerations for each agent are listed below.

Short-acting β2 agonists: These agents are generally safe when used intermittently and earlier concerns about deaths when used for all age groups on a regular base have not been substantiated (166). However, the potential risk of tremor and hypokalemia must be taken into account.

ICS

At doses recommended for the majority of asthmatic children, a satisfactory safety profile has been established over 30 years of use. Although some concerns remain, both studies and experience show that serious steroid side-effects are unusual. Regular treatment for more than 4 years with budesonide once daily (200 or 400 μg) was safe and well tolerated in children from the age of ≥5 years with newly detected mild persistent asthma (167). Patients requiring higher doses, which are not licensed, should be referred to a specialist. This is particularly important in a minority of children whose parents may adjust doses upwards or remain highly compliant with treatment recommendations over long periods of time. Only 40–50% of patients are still taking the prescribed dose of ICS after 6 months of treatment (168), potentially biasing measures of their long-term effects (169). At high doses, oral candidiasis may arise (170) and ICS use has also been linked with effects on growth, hypothalamic–pituitary–adrenal (HPA) axis function and the eyes.

Growth. Well-designed, randomized, controlled trials demonstrate that steroid use may affect growth in children within the first few weeks or months of treatment, even at low doses (130, 171–177). This is a class effect that is influenced by delivery device, dose, and type of steroid used (178–183). Dry powder inhalers (DPIs) are associated with suppressive effects at lower doses than metered dose inhalers (MDIs) with a spacer. For example, budesonide may cause growth suppression at doses of 800 μg/day from an MDI with a spacer, and budenoside, fluticasone propionate and beclomethasone diprionate from a DPI may suppress growth at doses of 200–400 μg/day (175, 176, 178, 182). Randomized, double blind data have found that once-daily dosing in the morning may minimize growth suppressive effects (184). It should be noted that growth in asthmatic children may also be affected by a delay in puberty causing a physiological growth deceleration in prepubertal children (185, 186).

The deceleration, however, does not affect final height, which will be within the genetic target area. There are no randomized data to support occasional clinical observations that severe asthma in itself may suppress growth rate and long-term surveys have found final height to be normal regardless of asthma severity (187, 188).

Hypothalamic–pituitary–adrenal axis. Clinical trials demonstrate that ICS may cause suppression of the HPA axis (189–191) and adrenal suppression may occur with increasing doses (192). Even in children whose growth does not appear to have been affected, adrenal suppression cannot be ruled out (193, 194). Currently, no studies can provide a good basis for practice recommendations; however, HPA axis evaluation may be performed by specialists using measures of spontaneous cortisol secretion.

Bone. Clinical trial evidence in children receiving long-term low-dose ICS suggests no effect on bone density (130, 195, 196).

Ocular. Long-term, high-dose ICS exposure increases the risk for posterior subcapsular cataracts, and, to a much lesser degree, the risk for ocular hypertension and glaucoma (192).

LTRA. LTRAs are generally safe and well tolerated with an overall incidence of adverse events similar to placebo. Headache and gastrointestinal upset are the most commonly encountered side-effects, skin rashes or flu-like symptoms are much less common (153, 160).

LABA. Evidence of an increased risk of severe adverse events has led the US Food and Drug Administration to issue a public health advisory concerning LABAs (197). In particular, use of salmeterol has been linked to a small but statistically significant increase in deaths in patients >12 years of age if used regularly without ICS (198). At the time of this report, the European Medicines Evaluation Agency and other regulatory authorities were evaluating similar precautions. In addition, some studies suggest increases in asthma exacerbations and the risk of hospital admissions in children using LABAs regularly (199). LABAs should always be used in combination with ICS.

Theophylline. Chronic or acute overdoses can result in headaches, nausea, vomiting, seizures, hyperglycemia and gastroesophageal reflux. The most severe acute side-effect is convulsions. Attention deficit and deteriorating school performance have been observed in some cases (200).

Recommendations

- Height measurements should be performed by trained staff at every visit
- In children on high ICS doses (beclomethasone ≥800 μg, or equivalent) the possibility of HPA axis suppression should be considered
- Eye examinations should be considered for children on high ICS doses, or those receiving ICS through multiple routes (intranasally for allergic rhinitis, topically on skin for atopic dermatitis)
- LABAs should never be used regularly without concurrent ICS

Research recommendations

- In children not controlled by low-moderate dose of ICS the effect of combination therapy of ICS + LTRAs *vs* ICS + LABAs should be studied and parameters that predict better response to one or the other regimen should be identified

Treatment of severe asthma. In cases of inadequate asthma control, an increased ICS dose of up to 800 μg BDP equivalent (201) can be used at the discretion of the prescribing physician. Patients requiring higher doses should be referred to a specialist. The efficacy/safety ratio of routine oral steroids *vs* high-dose ICS generally favors ICS. Severe asthma may require regular treatment with an oral corticosteroid (i.e. daily or every other day). Prior to treatment, national guidelines on age-related indications should be reviewed.

Asthma control and maintenance therapy must be assessed regularly and specialist care should be sought when low-dose ICS plus add-on medication (or doubling of dose of standard ICS) are not adequate. Triple therapy with ICS, LTRAs and LABA can also be attempted before resorting to oral corticosteroids (202). If good control has been achieved and maintained, consideration should be given to gradually reducing maintenance therapy. Regular reassessments are necessary to ensure that adequate control is maintained and the minimum therapy needed to maintain acceptable asthma control is established. Severe asthma in children is uncommon and its presence should prompt careful consideration of the differential diagnostic possibilities as well as the potential for lack of adherence to prescribed treatment regimens.

Management of children aged 0–2 years. The 0–2 year age group is the most difficult to diagnose and treat because the evidence base in this age group is limited. (See Box 1 for stepwise treatment procedure in this age group). Persistent asthma begins in the preschool years and alterations in lung structure and function that are present at this time may determine asthma status and lung function throughout childhood and adolescence (11). It is not clear how frequent the child's obstructive episodes should be before continuous ICS or LTRA therapy is instituted according to the atopic or nonatopic phenotype. Although a Cochrane review reported no clear

Box 1. Asthma treatment in children aged 0–2 years

- Consider a diagnosis of asthma if >3 episodes of reversible bronchial obstruction have been documented within the previous 6 months
- Intermittent β2 agonists are first choice (inhaled, jet nebulizers in the US and oral in Europe) despite conflicting evidence
- LTRA daily controller therapy for viral wheezing (long- or short-term treatment)
- Nebulized or inhaled (metered-dose inhaler and spacer) corticosteroids as daily controller therapy for persistent asthma, especially if severe or requiring frequent oral corticosteroid therapy
- Evidence of atopy/allergy lowers the threshold for use of ICS and they may be used as first-line treatment in such cases
- Use oral corticosteroids (e.g. 1–2 mg/kg prednisone) for 3–5 days during acute and frequently recurrent obstructive episodes

Box 2. Asthma treatment in children aged 3–5 years

- ICS are the first choice, budesonide 100–200 μg × 2 or fluticasone 50–125 μg × 2 by MDI
- Short-acting β2 agonists, salbutamol 0.1 mg/dose or terbutaline 0.25 mg/dose 1–2 puffs at 4-h intervals as needed
- LTRA can be used as monotherapy instead of ICS if symptoms are intermittent or mild persistent
- If full control is not achieved with ICS, add LTRA montelukast 4 mg granules or 4 mg chewing tablet
- If control still not achieved consider the following (nonsequential) options:
  - Add LABA at least intermittently (although note lack of published evidence supporting use in this age group)
  - Increase ICS dose
  - Add theophylline

evidence of the benefit of β2-agonist therapy in the management of recurrent wheeze in this age group (203), the evidence is conflicting and some studies have reported benefit (204–206). LTRAs have reduced asthmatic episodes in children aged 2–5 years (158), and there is some evidence that they may be beneficial in the 0–2 age group (156). However, it is debatable whether a reduction from 2.34 to 1.60 episodes per year, as seen in this large study, justifies the use of LTRAs.

In smaller, double-blind, randomized controlled trials, infants characterized as having mild persistent (207) or severe (208) asthma and treated with nebulized corticosteroids (i.e. budesonide) had less day- and night-time asthma symptoms and fewer exacerbations. In a study of young children with severe, corticosteroid-dependent asthma, nebulized budesonide reduced day- and night-time asthma symptoms while concurrently reducing oral corticosteroid requirement (209). However, several studies have reported that use of inhaled corticosteroids in early infancy has no effect on the natural history of asthma or development of wheeze later in childhood (151, 152).

Management of children aged 3–5 years. First-line treatments in this group include ICS (210) and LTRA in children with intermittent (158) or persistent (153) disease. See Box 2 for stepwise treatment procedure in this age group (see also Fig. 2).

Management of acute asthma episodes. Steps for the management of acute asthma attacks are provided in Box 3. Note that airway obstruction in children with acute asthma improves faster on oral rather than ICS (211).*Management of exercise-induced asthma*. Exercise induced asthma is a common clinical presentation of asthma that occurs in 70–80% of children with asthma who do not receive anti-inflammatory treatment (69). Most children with exercise-induced asthma are allergic and allergen-specific treatment should be part of their management. Exercise-induced asthma without other manifestations of asthma can usually be controlled by short-acting inhaled β2 agonists taken 10–15 min before exercise (212, 213). When combined with other asthma symptoms, exercise-induced asthma is best controlled with ICS either alone or in combination with reliever treatment (214). Recent evidence suggests that LTRAs may be an alternative option to ICS in exercise induced asthma, since they have a quick, consistent, and long-lasting effect in preventing the fall in FEV_1 after exercise challenge (215). Regular use did not induce tolerance against their protective effects (216).

If full control is not achieved with ICS, add:
(a) inhaled short-acting β2 agonist before exercise,
(b) LTRA in addition to ICS,
(c) inhaled LABA in addition to ICS.

There is a possibility of developing tolerance to inhaled β2 agonists used on a regular basis (217). In some patients, the combination of ICS, LTRA and inhaled LABA may be needed to prevent exercise-related symptoms. Ipratropium bromide may be tried after individual assessment, but is usually added to other treatments. In certain circumstances (i.e. in asthmatic athletes with obvious exercise-induced asthma, but not satisfying the requirements set up by World Anti-Doping Agency and/or International Olympic Committee medical commission for using inhaled steroids) LTRA alone may be tried, but should be clearly followed up for assessment of treatment effect. Note that lack of response to treatment may

Box 3. Stepwise treatment for acute asthma episodes. Begin at first step available depending on whether patient is treated at home, in GP's office or in hospital

- Inhaled short-acting β2 agonists (spacer): Two to four puffs (200 μg salbutamol equivalent) every 10–20 min for up to 1 h. Children who have not improved should be referred to hospital
- Nebulized β2 agonists: 2.5–5 mg salbutamol equivalent can be repeated every 20–30 min
  - Ipratropium bromide: This should be mixed with the nebulized β2 agonist solution at 250 μg/dose and given every 20–30 min
- High-flow O_2 (if available) to ensure normal oxygenation
- Oral/i.v. steroids: Oral and i.v. glucocorticosteroids are of similar efficacy. Steroid tablets are preferable to inhaled steroids (a soluble preparation is also available for those unable to swallow tablets). A dose of 1–2 mg/kg prednisone or prednisolone should be given (higher doses may be used in hospital). Treatment for up to 3 day is usually sufficient
- Intravenous β2 agonists: The early addition of a bolus dose of i.v. salbutamol (15 μg/kg) can be an effective adjunct, followed by continuous infusion of 0.2 μg/kg/min
- High dependency unit: children should be transferred to a pediatric intensive care unit if there is a downhill trend and oxygenation cannot be maintained. Small children with limited ventilatory reserves are at particular risk of respiratory failure*

*Aminophylline can be used in the ICU setting for severe or life-threatening bronchospasm unresponsive to maximum doses of bronchodilators and steroid tablets. A dose of 6 mg/kg should be given over 20 min with ECG monitoring, followed by continuous i.v. dosing. Special caution is necessary when factors modifying aminophylline metabolism are present.

indicate misdiagnosis of exercise-induced asthma and patients may require reassessment.

Difficult asthma. Difficult (i.e. therapy-resistant) asthma – as indicated by frequent use of short-acting β2 agonists despite high dose ICS treatment – may present atypically, be infrequent and yet life-threatening and nonresponsive to treatment. Difficult asthma needs comprehensive assessment and meticulous exclusion of other causes of asthma-like symptoms (218–220). Lack of compliance and unrecognized adverse environmental influences should always be considered.

Use of inhalers. The preferred method of administration of ICS and β2 agonists is an MDI with a spacer or a DPI. However, there may be cases where a compressor-driven nebulizer is preferable due to lack of response, severity of attack, personal preference or convenience. Differences from adults are greatest for children under 4–5 years of age, who are unable to use DPIs or unassisted MDIs. Therefore, they must rely on nebulizers and MDIs with valved holding chambers for inhaled drug delivery (221).

Table 2. Age-dependent inhalant devices

Inhalation device	Age group	Inhalation technique
Nebulizer	All	Tidal breathing
Pressurized metered dose inhaler	0–2 years	5–10 tidal breaths through nonelectrostatic holding chamber (small volume) with attached face mask/activation
	3–7 years*	5–10 tidal breaths through nonelectrostatic holding chamber (small or large volume) with mouthpiece/activation
	>7 years	Maximal slow inhalation followed by 10 s breath hold through nonelectrostatic holding chamber (small or large volume) with mouthpiece/activation
Dry powder inhaler	>5 years	Deep and fast inhalation followed by a 10-s breath hold/activation

*Maximal slow inhalation should be attempted as early as possible since some young children can be compliant.

Table 2 shows the age-dependent outcomes of appropriate inhaler devices, MDIs and spacer products that are at least equivalent to nebulizer delivery of β2 agonists in acute asthma. Evidence is more reliable for children >5 years than for younger children (222–224). For maintenance therapy it is important to choose an age-appropriate device that requires the least cooperation, achieves the highest compliance and thus the greatest clinical efficacy and good cost–benefit ratio (225).

Other options. Omalizumab is a recently introduced monoclonal antibody that binds to IgE. It is licensed for children 12 years of age and older with severe, allergic asthma and proven IgE-mediated sensitivity to inhaled allergens. In such patients, omalizumab reduces the risk of severe exacerbations (165, 226). Omalizumab is administered via subcutaneous injection every 2–4 weeks, depending on patient weight and total serum IgE level.

Macrolide antibiotics have recognized anti-inflammatory properties in addition to their antimicrobial effects. Although some benefits have been reported in adults with chronic persistent asthma, a meta-analysis of seven randomized, controlled clinical trials involving both children and adult patients ($n = 416$) with chronic asthma and treated with macrolides or placebo for more than 4 weeks reported insufficient evidence to support or to refute their use in patients with chronic asthma (227).

Recommendations

- Treatment of airway inflammation leads to optimal asthma control
- Until further evidence of effectiveness and long-term safety are available LABAs should not be used without an appropriate ICS dose
- The choice of inhalation device is important. In general, select the device which is preferred by the patient, hence more likely to be used as directed, and is clinically efficacious

Research recommendations

- There is a clear need for additional clinical trials in children under 5 years of age
- More studies to establish which biomarkers accurately reflect disease control in order to rapidly identify responses to different treatments
- Establish the role of viral infections in precipitating obstructive airway symptoms and the role of antiviral agents as potential asthma medications
- The potential benefits of polytherapy *vs* monotherapy on both asthma control and the natural course of the disease
- Pharmacovigilance studies of long-term ICS prophylaxis to establish whether there are any significant long-term adverse effects, including on the eyes and on bone density

Immunotherapy

Allergen immunotherapy is the administration of increasing doses of specific allergen(s) over prolonged periods of time until a therapeutic level is reached that provides protection against allergic symptoms associated with natural exposure to the allergen. Such immune modulation is the only way of permanently redirecting the disease process of allergic (atopic) asthma (228).

Preventive effect. Specific immunotherapy can prevent sensitization to other allergens (229, 230). It can also improve asthma, prevent progression from allergic rhinitis to asthma (231, 232) and reduce the development of asthma in children with seasonal allergies (233, 234). The effect of immunotherapy appears to continue after treatment has stopped, resulting in prolonged clinical remission of allergic rhinitis symptoms (235).

Efficacy. Based on a meta-analysis of 75 studies, immunotherapy can be recommended for individuals with asthma who have proven sensitization to allergens (229). Efficacy of immunotherapy will depend on the quality of the extracts used.

Subcutaneous injection: Well-conducted studies show that injection immunotherapy reduces the use of asthma medications and consistently improves asthma symptoms, including bronchial hyperreactivity and bronchospasm (229). Significant clinical benefit has been reported 6 years (236), and even 12 years (237) after discontinuation of preseasonal grass pollen immunotherapy in childhood. There is also some evidence that injection immunotherapy is cost effective in patients 16 years of age and older (238).

Sublingual: Sublingual immunotherapy (SLIT) may be a safe and effective alternative to subcutaneous injections in children (239), although efficacy in young children under 5 years of age is less well documented (240). A systematic review concluded that SLIT has only low-to-moderate clinical efficacy in children with mild-to-moderate persistent asthma who are at least 4 years old and sensitized only to house-dust mites (241). The analysis failed to find evidence for use in seasonal allergic rhinitis, despite a prior recommendation for use in this indication from the ARIA Workshop Group (242). However, a recent meta-analysis shows that compared with placebo, SLIT with standardized extracts is effective in pediatric patients with allergic rhinitis (243).

The safety of SLIT has not been adequately addressed in severe asthma and anaphylaxis from SLIT has been reported (244). Recent data indicate superior efficacy of this form of immunotherapy for allergic rhinitis and conjunctivitis and thus potentially for grass pollen induced asthma in patients aged 18 years or more (245). Although there is some evidence that high doses may be effective, they are not licensed and need further study in children.

Injection vs SLIT: There are reports of severe and fatal anaphylaxis following subcutaneous injection immunotherapy (229, 246). Effective SLIT may, therefore, be an attractive alternative to injection for children, parents and physicians, although it is not entirely side-effect-free. Although some studies have compared injection and SLIT in children and reported similar efficacy (247, 248), definitive evidence of the efficacy of SLIT is lacking.

Patient selection. The treatment of allergic disease should be based on allergen avoidance, pharmacotherapy, allergen immunotherapy, and patient education. The combination of immunotherapy with other therapies allows a broad therapeutic approach that addresses the pathophysiological mechanism of allergy with the aim of making patients as symptom free as possible (242). Early institution of immunotherapy may be recommended not only as a therapeutic measure, but also as a prophylactic measure to prevent rather than reduce bronchial inflammation, particularly in children. Asthma without allergic sensitization is not an indication for immunotherapy.

Precautions. Injection immunotherapy should be performed only by trained personnel in the presence of a

physician who is experienced in its use. Although immunotherapy is usually safe, some precautions should be taken:

- Therapy should be carried out in an appropriate setting where emergency treatment, including adrenaline (epinephrine), oxygen, corticosteroids, and basic life support, is possible
- Patients should remain in the clinic for at least 30 min following injection to allow monitoring for adverse events
- If the patient develops side-effects while in the clinic, emergency treatment (e.g. intramuscular adrenaline for anaphylactic reaction, and oxygen) should be administered and the patient stabilized before transfer to hospital
- Patients should be adequately informed about possible side-effects of immunotherapy as well as the potential benefits

Recommendations

- Consider immunotherapy with appropriate allergens for allergic asthma and within the licensed indications only when the allergenic component is well documented and reliable allergen extracts are available
- Use immunotherapy in addition to appropriate environmental control and pharmacotherapy
- Immunotherapy is not recommended when asthma is unstable; on the day of treatment, patients should have few, if any, symptoms and pulmonary function (FEV_1) of at least 80% of the predicted value
- Sensitization to more than one allergen is not a contraindication for immunotherapy but can reduce its efficacy due to the need to limit the allergen dose when several allergens are being administered concurrently
- Age is not an absolute contraindication – such therapy can be used from 3 years of age, although with caution and only by well-trained staff in specialist centers as this is well below the current licensed age limit
- Patients should be able to comply with regular treatment

Research recommendations

- Large-scale clinical trials of SLIT with prolonged treatment periods, commercially available allergen extracts and well-standardized protocols are needed
- The role of allergen containing tablets in younger children and for a greater allergen spectrum needs to be explored

Education

A meta-analysis of 32 studies of self-management education programs for asthmatic children reported improvement in a range of asthma outcomes (249). Benefits have been reported for children under 5 years of age (250, 251) and in 7- to 14-year olds (252). School-based educational programs involving staff asthma training, advice on asthma policy, emergency β2-agonist inhaler, and classroom asthma workshops are also beneficial (253). Since education is an essential aspect of disease management, the level required should be determined at diagnosis and the course should begin as soon as possible. In addition, asthma updates should be included in continuing medical and professional education programs.

Planned educational strategies. Education should increase knowledge of the disease, allay fears about medication and increase communication between children, caregivers and healthcare providers. Parents should be made aware of the benefits as well as the potential risks of all therapies and reassured that side-effects may be minimized at the correct dose. Lack of adherence to treatment plans has been associated with poor outcomes (254, 255) and parents are frequently concerned about the need for 'lifelong' treatment. Hence, it needs to be pointed out that, for children with moderate–severe asthma, daily medication is much more effective than intermittent treatment. Long-term benefits may not be appreciated by young people, so the short-term benefits of regular prophylactic therapy should be emphasized. Patient self-confidence should also be built up, and the need for psychological support for some parents may be considered.

The minimum requirement in asthma education is face-to-face interaction and a review of individual treatment plans at every consultation. Ideally, a three-tier education program that considers disease severity, stage of development, and the need for information should be implemented.

The program includes:

1. Education following diagnosis – for the asthmatic child and (at least) one parent:

The level of education given should be based on the severity of disease and the age and developmental status of the child. Children under 5 years of age should receive practical instruction on inhaler use, while their parents should receive both practical training in the use of inhaler devices and strategies for managing episodes together with an outline of the underlying mechanisms of the disease. Children aged 5–13 years and their parents should be offered both practical and theoretical asthma education. Adolescents need to be directly engaged in all aspects of their disease management in order to ensure optimal management.

The program should use clear visual aids designed for nonprofessionals. Written materials should be presented

Table 3. Educational tools – to be adapted to the developmental status of the child

Target group	Essential requirements	Optional measures
Group 1: <6 years	Focus on parental education	Asthma videos/DVDs/games/interactive programs (250) Asthma picture books – simply illustrated and formatted to appeal to this developmental stage (250) Role of the day care centre
Group 2: 6–8 years	Colors and symbols to depict different types of medication, differentiating slow and fast-acting effects	Physical games illustrating the disease, e.g. narrowing tunnels and constricted airways DVDs, interactive programs, electronic games, internet searching, etc. Quizzes and challenges, e.g. parent *vs* child Role of the school in health education
Group 3: 9–12 years	Experience with exercise-induced bronchospasm	How to use peak flow Brochures and leaflets DVDs, interactive programs, electronic games internet searching, etc Quizzes and challenges, e.g. parent *vs* child Asthma/school nurse-led education in cooperation with teacher
Group 4: 13–18 years	Experience with exercise-induced bronchospasm	Peer-led initiatives/teaching within the peer group Communicating burden disease via novel methods, e.g. personal films, video diaries, song, art, etc. How to use peak flow Brochures and leaflets Internet/chat rooms Asthma camps (without parents, with parallel short parental education programs) Patient organizations/support groups Youth exchange programs
Group 5: Parents	'First information' courses – healthcare professional led presentation and discussions on asthma	Internet/chat rooms Patient organizations/support groups Leaflets and brochures
Group 6: Healthcare professionals (physicians, nurses and allied health professionals)	Continuing medical education/ continuing professional development	University and teaching hospital curricula Professional societies (national and local) Self education via internet, videos, journals, congresses, etc.

using simple words at the fifth grade reading level. The initial session should clearly explain that:

- Asthma is a chronic inflammatory disease
- Symptoms of asthma are not always obvious
- The causes and potential triggers of asthma include infections, rhinitis, allergens, exercise, cold air, and environmental factors (particularly tobacco smoke)
- In moderate–severe asthma, it is essential to take daily medication, even in the absence of symptoms.

2. Structured education – for the asthmatic child and parents:

Essential tools and methods for educating this group are described in Table 3. Structured and intensive education should be received by children with moderate persistent, or severe persistent asthma. Children who meet the following conditions may also be targeted:

- Acute severe asthma
- Problems with adherence
- Asthma-induced anxiety in the child or parents
- Bad experience with asthma, e.g. fatality in a close family member, severe adverse effects from oral corticosteroids in a close family member
- Poor perception of severe symptoms or poor perception by parents
- Poor adherence of the family and the patient
- Lack of peer support.

3. Education of other caregivers:

In addition to the children and their parents, all others involved in caring for children should be made aware of the child's asthma.

Education for healthcare professionals. *Primary care physicians*: Primary care physicians play a central role in the diagnosis and treatment of children with asthma. They should also be able to recognize and treat both asthma and acute asthma attacks in accordance with local guidelines. Physicians should also be aware of when patients should be referred to a specialist in pediatric asthma. Curricula in universities and teaching hospitals should include a focus on asthma diagnosis and treatment.

Nurses: Any member of this group who deals with asthmatic children must be trained to advise on asthma, according to national guidelines (6). Specialist asthma nurses should play a key role in educating other allied health professionals.

Pharmacists: Asthma specialists should have responsibility for organizing structured education on asthma for all pharmacists in their area.

Health education workers and patient support groups: These groups may participate in asthma education of

parents and other nonmedical workers and the general public provided that they follow national guidelines and ensure consistency of educational messages.

Education for health authorities and politicians. Health authority representatives and politicians need education on asthma to ensure prioritization of the disease and allow adequate organization and provision of care.

Recommendations

- Asthma education is an integral part of asthma management and must be offered to all parties involved

Research recommendations

- Long-term studies on cost–benefit of asthma education are needed in clearly defined age and disease-severity groups

Monitoring

The monitoring recommendations discussed below assume that the asthma diagnosis has been confirmed and that a treatment plan is in place. The recommendations emphasize practical procedures and assessments appropriate for routine clinical practice.

Signs and symptoms

Monitoring the signs and symptoms of asthma involves parents, children and physicians and should take place both in the clinic and at home.

History. A history should be taken as described in the Diagnosis section. In addition, the frequency, severity, and causes of asthma exacerbations should be ascertained. Worsening disease may be indicated by increased use of rescue medication and need for oral corticosteroids (256–258), unscheduled visits to health care providers, use of emergency care and hospitalizations.

Physical examination. Physical examination should include assessment of the child's height and weight, along with respiratory signs and symptoms (see Diagnosis section). Although physical examination alone is less reliable for assessing airway obstruction than lung function measurement (125, 259), signs of chest wall retraction and, rarely, chest wall deformity may provide evidence of obstruction in infants and young children. The nasal airway should also be assessed.

Defining and evaluating asthma control. Asthma control has become the main assessment focus of the new 2006 GINA asthma management guidelines (see Box 4) (6) and is proposed as a major assessment focus of the new NIH/NHLBI-sponsored National Asthma Education and Prevention Program Expert Panel Report 3 guidelines. However, it should be noted that the GINA definition of control refers primarily to adults. Children (particularly preschool children) may experience 1–2 exacerbations per year and their asthma can be considered controlled provided they have no symptoms outside the exacerbation.

Box 4. Well-controlled asthma in children according to 2006 GINA Global Strategy for Asthma Management (6) and the Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma (260)

- Asthma is well controlled when all of the following are achieved and maintained:
  - Daytime symptoms twice or less per week (not more than once on each day)
  - No limitations of activities due to asthma
  - Night-time symptoms 0–1 per month (0–2 per month if child is ≥12 years)
  - Reliever/rescue medication treatment twice or less per week
  - Normal lung function (if able to measure)
  - 0–1 exacerbations in the last year

Factors associated with poor asthma control include exposure to environmental tobacco smoke and poor parental perception of the psychosocial aspects of asthma (261). A number of tools that allow parents and children to record and describe symptoms have been shown to be helpful:

- The 'Asthma Quiz for Kidz' is a short questionnaire that can be used by children and parents of infants (262)
- The Asthma Control Test (ACT) (for children >12 years) and the Childhood ACT (for children 4–11 years), patient-based tools for identifying patients with inadequately controlled asthma (263–265)
- Patient diaries correlate with physiologic measures when used by older children (266), although their reliability has been questioned (267).

Adherence/compliance. Poor adherence to recommended therapy is common and studies in children report that 30–60% of patients do not use their medication regularly (254, 255). In clinical trial settings, adherence can be more rigorously monitored by methods, such as canister weighing, pill counting or the use of electronic recording devices embedded in inhaler devices (255). Less precise estimates can be made by comparing dispensed medica-

tion with expected use (268). In routine practice, evaluation can include asking parents/children a series of questions in a nonthreatening manner while acknowledging that most people forget to take their medicines at some time. Questions include:

- How many times did you forget to take your medication last week? …last month?
- Do you more often remember than forget to take your medication?
- When did you last take your medication? Which medication did you take?
- Are you taking your medication by yourself? (School-age children).

Pharmacotherapy. Success of pharmacotherapy will depend not only on adherence to the regimen, but on how well inhalers are used. Assessment of inhaler technique is particularly important if symptom control is poor (269). Regular and consistent follow-up is important in maintaining good asthma control, prescribing and adjusting therapy and encouraging compliance/adherence. Asthma symptoms can be characterized using a series of questions (Table 4).

Table 4. Follow-up visits: sample questions for routine clinical monitoring of asthma*

Signs and symptoms	Is your asthma better or worse since your last visit? In the past 2 weeks, how many days have you: Had coughing, wheezing, shortness of breath, or chest tightness? Awakened at night because of symptoms? Awakened in the morning with symptoms that did not improve within 15 min of using a short-acting inhaled β2 agonist? Had symptoms while exercising or playing? Had symptoms of allergic rhinitis?
Exacerbation history	Since your last visit, have you had any episodes/times when your asthma symptoms were a lot worse than usual? If yes: What do you think caused this? What actions did you take?
Environmental control	Have there been any changes in your home or work environment? Are there new pets or new contact with pets elsewhere? What is the current smoking status of the family? To adolescents: Do you have any significant contact with smokers (e.g. discos, etc.)? Do you smoke?
Pharmacotherapy	What medications are you taking? How often do you take each medication? How much do you take each time? Have you missed or stopped taking any regular doses for any reason? How many times have you forgotten your medication this week? …this month? Have you tried any other medicines or remedies?
Side-effects	Has your asthma medicine caused you any problems? For example: Shakiness, nervousness, bad taste, sore throat, cough, upset stomach, hoarseness, headache
Quality of life/functional status	Since your last visit, how many days has your asthma caused you to: Miss school? Reduce your activities? Change your routine because of your child's asthma? (Parents/caregivers)
Inhaler technique	Please show me how you use your inhaler Please show me how you measure your peak flow
Monitoring patient-provider communication and patient satisfaction	What did you do the last time you had an exacerbation of symptoms? Did you have any problem taking the medication? Let's review some important information: When should you increase your medications? Which medication(s)? When should you call me [your doctor or nurse practitioner]? Do you know the after-hours phone number? If you can't reach me, what emergency department would you go to?

*This questionnaire can be given by an asthma nurse to the parents, caregiver or patient prior to the visit.

Recommendations

Ask targeted, age-specific questions with respect to:

- Asthma symptoms
- Adherence (compliance)
- Asthma exacerbations

Lung function

PEF and FEV_1 are the most useful lung function tests (see Diagnosis section). There is evidence suggesting that lung function monitoring may improve asthma control as part of a written action self-management plan (6, 9), and that these tests may be useful in children with poor symptom perception (270). However, there is only one randomized, controlled trial examining routine use of PEF and FEV_1 measurement in the home setting, which concluded that PEF recording did not enhance asthma self-management (271). In addition, there is evidence of fabrication and erroneous reporting of peak flow data among children (272, 273).

FEV_1 is the standard reference measurement for assessing airway function in lung disease, but its utility in childhood asthma monitoring is less certain. FEV_1 is an independent predictor of asthma attacks in children (274) and it appears to identify changes with time, but values expressed as [FEV_1% predicted] poorly reflect the severity of symptoms and medication use (131, 132). Values of FEV_1/forced vital capacity (FVC) ratio and maximal mid-expiratory flow [forced expiratory flow

(FEF) 25–75%], or by inference FEF measured at 50% of expired vital capacity (FEF 50%), have been found to relate well to asthma severity as assessed by medication requirements, or a combination of symptom reports and medication requirements (132). No such relationship has been found for symptom reports alone, suggesting a disconnect between perception and degree of airflow obstruction.

Routine use of spirometry in pediatric clinics is now commonplace due in part to advances in the miniaturization of equipment. It should be performed at each patient visit to identify patients at risk for progressive loss of lung function. However, appropriate operator training and support is required to ensure reliable and reproducible results (275).

Exercise testing. Peak flow and/or spirometry can be evaluated during and after a free running test (6 min) (276, 277) or treadmill test (278). Heart rate should exceed 170 beats per minute during the test and evaluation should be performed during the test and at 5, 10 and 20 min after the exercise test. The test can be used when the patient has taken their usual medication to monitor correct dosing and evaluate the need for additional therapy.

Recommendations

- Long-term monitoring of PEF and FEV_1 at home are unlikely to contribute to asthma control unless part of written and mutually agreed asthma management plan
- In the clinic setting, spirometry – particularly FEV_1/FVC ratio and mid-expiratory flow – has a role in detecting unrecognized airflow obstruction
- Spirometry has a role in assessing asthma status and should be performed at least once a year in children with asthma
- Monitoring of PEF in severe asthma cases, or in poor symptom perceivers, may have a role in identifying early onset of exacerbations
- PEF variability may contribute to the assessment of exercise-induced bronchospasm and reinforce the need for appropriate therapy
- Consider exercise testing in patients with reported exercise-induced asthma and in patients who are regular participants in sporting activities

Exhaled nitric oxide. ENO is useful as an adjunct to routine clinical assessment in the management of asthma (279). It is a good marker of eosinophilic airway inflammation in both children (280) and adults (281) with asthma and since eNO levels are affected by steroid therapy, they can be used to assess whether airway eosinophilic inflammation is under control (128) or to predict benefit from ICS therapy (149, 282).

Measurement of eNO is a noninvasive procedure that is easily performed in children (283). In children with asthma, titration of ICS based on eNO measurement did not result in increased ICS doses and was associated with reduced airway hyperresponsiveness compared with titrating according to symptoms alone (284). In one high-quality study in adults, changes in therapy aimed at controlling eNO levels led to the use of a lower ICS dose to maintain the same degree of asthma control (285).

Monitoring eNO levels may also help in predicting asthma relapse in children after discontinuation of steroids (286). In addition, eNO levels may predict failure of ICS reduction attempts in children with good symptom control (287). Where available, nasal nitric oxide (nNO) may also provide useful information, since it is raised in the presence of nasal inflammation, but lowered when there is sinus obstruction or nasal polyps, and is particularly low in primary ciliary dyskinesia (288).

Guidelines for standardized eNO measurement have been developed (289, 290), and normal reference values with the recommended technique are available for children 4–17 years old (291).

Exhaled breath condensate. Collection of exhaled breath condensate is a new and promising method of collecting lung samples to measure a variety of variables, including isoprostanes, leukotrienes, pH and some cytokines. It can be used in children starting from the age of 4–5 years. However, this method has not yet been fully validated and cannot be recommended in routine clinical practice for assessing airway inflammation (292).

Recommendations

- eNO is a simple test that is helpful in evaluating eosinophilic airway inflammation in childhood asthma
- eNO may contribute to the optimization of ICS treatment
- eNO may be useful in identifying children in whom ICS can be safely reduced or withdrawn

Research recommendations

- Adequately powered, randomized, controlled trials of home monitoring of FEV_1/FVC ratio and mid-expiratory flows in the management of asthma is required
- Adequately powered, randomized, controlled trials of eNO in routine asthma management is required

- Validation of appropriate assessment techniques of airway function and airway inflammation in infants and young children is required
- Identification of the role of induced sputum and expired condensates in routine monitoring

Conflict of interest

L. B. Bacharier has served on the speakers bureau for AstraZeneca, Genentech, GSK, and Merck.

A. Boner has received research support from GSK and MSD and has participated once in a year to advisory board meeting for GSK and MSD.

K.-H. Carlsen has served on an international consultatory paediatric board for GSK, and given presentations for GSK, MSD, PolarMed and Schering Plough.

P. Eigenmann has received research grants and conference honoraria from Phadia, Milupa, UCB, Read Johnson, Fujisawa and Novartis Pharma.

T. Frischer has worked on a national advisory board for MSD since 2004.

M. Götz has served as a speaker and consultant on behalf of GSK, MSD, AstraZeneca and Novartis.

P. J. Helms has stated there is no conflict.

J. Hunt is a founder of Respiratory Research, Inc., and receives grant support from the US NIH, US Air Force, Pfizer, GSK. He has received honoraria from Merck and Galleon Pharmaceuticals.

A. H. Liu has served on advisory panels for GSK, Schering Plough and AstraZeneca, has received grant support from GSK, Novartis and Ross, and has received lecture honoraria from GSK, Merck, Schering Plough, AstraZeneca, and Aerocrine.

N. Papadopoulos has served on advisory boards and has delivered lectures for AstraZeneca, GSK, MSD, Novarits, SP and UCB.

T. Platts-Mills has stated there is no conflict.

P. Pohunek has received lecture honoraria from AstraZeneca, GSK, MSD, UCB Pharma and travel support for scientific meetings by AstraZeneca, GSK, MSD and Chiesi.

F. E. R. Simons has stated there is no conflict.

E. Valovirta has consultant agreements with MSD Finland, UCB Pharma Finland and ALK-Abello and has delivered lectures to MSD, UCB Pharma, ALK-Abello, GSK.

U. Wahn has received grants and lecture honoraria from Novartis, MSD, GSK, UCB-Pharma, ALK, and Stallergenes.

J. H. Wildhaber has served on national and international advisory boards of Nycomed and MSD and has received research grants from AstraZeneca, GSK and MSD.

References

1. Becker A, Berube D, Chad Z, Dolovich M, Ducharme F, D'Urzo T et al. Canadian Pediatric Asthma Consensus guidelines, 2003 (updated to December 2004): introduction. CMAJ 2005;**173**:S12–S14.
2. Busquets Monge RM, Sanchez SE, Pardos RL, Villa A Jr, Sanchez JJ, Ibero IM et al. [SENP-SEICAP (Spanish Society of Pediatric Pneunomology. Spanish Society of Pediatric Clinical Immunology and Allergology) consensus on asthma, pneumonology, and pediatric allergy (Draft)]. Allergol Immunopathol (Madr) 2004;**32**: 104–118.
3. Berdel D, Forster J, Gappa M, Kiosz D, Leupold W, Pfeiffer-Kascha D et al. Asthma bronchiale im Kindes - und Jugendalter. AWMF Leitlinien, AWMF-Leitlinien-Register Nr.026/010 2006. http://www.leitlinien.net; accessed 7 November 2007.
4. Duiverman EJ, Brackel HJ, Merkus PJ, Rottier BL, Brand PL. [Guideline 'Treating asthma in children' for pediatric pulmonologists (2nd revised edition). II. Medical treatment]. Ned Tijdschr Geneeskd 2003;**147**:1909–1913.
5. Warner JO, Naspitz CK. Third International Pediatric Consensus statement on the management of childhood asthma. International Pediatric Asthma Consensus Group. Pediatr Pulmonol 1998;**25**:1–17.
6. Global Strategy for Asthma Management and Prevention 2006. The Global Initiative for Asthma 2006. http://www.ginasthma.com/GuidelinesResources.asp; accessed 7 Novmber 2007.
7. National Asthma Education and Prevention Program. NAEPP expert panel report guidelines for the diagnosis and management of asthma – update on selected topics 2002. National Institutes for Health 2006: http://www.nhlbi.nih.gov/guidelines/archives/epr-2_upd/index.htm; accessed 7 November 2007.
8. Dahl R, Bjermer L. Nordic consensus report on asthma management. Nordic Asthma Consensus Group. Respir Med 2000;**94**:299–327.
9. British guideline on the management of asthma. Thorax 2003;**58** (Suppl. 1):i1–i94.
10. Illi S, von ME, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet 2006;**368**:763–770.
11. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med 2005;**172**:1253–1258.
12. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. J Allergy Clin Immunol 2003;**111**:661–675.
13. Bacharier LB, Phillips BR, Bloomberg GR, Zeiger RS, Paul IM, Krawiec M et al. Severe intermittent wheezing in preschool children: a distinct phenotype. J Allergy Clin Immunol 2007;**119**:604–610.
14. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. Am J Respir Crit Care Med 2002;**165**:176–180.
15. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;**162**:1403–1406.
16. de Marco R, Pattaro C, Locatelli F, Svanes C. Influence of early life exposures on incidence and remission of asthma throughout life. J Allergy Clin Immunol 2004;**113**:845–852.
17. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. J Allergy Clin Immunol 2002;**109**:189–194.

18. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;**349**:1414–1422.
19. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;**332**:133–138.
20. Devulapalli CS, Carlsen KC, Haland G, Munthe-Kaas MC, Pettersen M, Mowinckel P et al. Severity of obstructive airways disease by two years predicts asthma at 10 years of age. Thorax 2007;DOI: 10.1136/thx.2006.060616.
21. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun 2006;**7**:95–100.
22. Eder W, Klimecki W, Yu L, von ME, Riedler J, Braun-Fahrlander C et al. Opposite effects of CD 14/-260 on serum IgE levels in children raised in different environments. J Allergy Clin Immunol 2005;**116**:601–607.
23. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med 2002;**347**:869–877.
24. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004;**114**:1282–1287.
25. Gissler M, Jarvelin MR, Louhiala P, Hemminki E. Boys have more health problems in childhood than girls: follow-up of the 1987 Finnish birth cohort. Acta Paediatr 1999;**88**:310–314.
26. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992;**47**:537–542.
27. Osman M, Tagiyeva N, Wassall HJ, Ninan TK, Devenny AM, McNeill G et al. Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. Pediatr Pulmonol 2007;**42**:60–65.
28. de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. Am J Respir Crit Care Med 2000;**162**:68–74.
29. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von ME et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. Lancet 2000;**356**:1392–1397.
30. Plaschke P, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Association between atopic sensitization and asthma and bronchial hyperresponsiveness in swedish adults: pets, and not mites, are the most important allergens. J Allergy Clin Immunol 1999;**104**:58–65.
31. Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. Am J Respir Crit Care Med 2002;**166**:696–702.
32. Illi S, von ME, Lau S, Nickel R, Gruber C, Niggemann B et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004;**113**:925–931.
33. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. J Allergy Clin Immunol 2002;**110**:381–387.
34. Schaub B, Lauener R, von ME. The many faces of the hygiene hypothesis. J Allergy Clin Immunol 2006;**117**:969–977.
35. Ota MO, van der Sande MA, Walraven GE, Jeffries D, Nyan OA, Marchant A et al. Absence of association between delayed type hypersensitivity to tuberculin and atopy in children in The Gambia. Clin Exp Allergy 2003;**33**:731–736.
36. Illi S, von ME, Lau S, Bergmann R, Niggemann B, Sommerfeld C et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ 2001;**322**:390–395.
37. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med 2000;**343**:538–543.
38. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. Am J Respir Crit Care Med 2005;**171**:137–141.
39. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;**116**:571–577.
40. Nafstad P, Brunekreef B, Skrondal A, Nystad W. Early respiratory infections, asthma, and allergy: 10-year follow-up of the Oslo Birth Cohort. Pediatrics 2005;**116**:e255–e262.
41. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ 1995;**310**:1225–1229.
42. Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. J Allergy Clin Immunol 2004;**114**:239–247.
43. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax 2006;**61**:376–382.
44. Sigurs N. Clinical perspectives on the association between respiratory syncytial virus and reactive airway disease. Respir Res 2002;**3** (Suppl. 1): S8–S14.
45. Papadopoulos NG, Bates PJ, Bardin PG, Papi A, Leir SH, Fraenkel DJ et al. Rhinoviruses infect the lower airways. J Infect Dis 2000;**181**:1875–1884.
46. Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. A defective type 1 response to rhinovirus in atopic asthma. Thorax 2002;**57**:328–332.
47. Xepapadaki P, Papadopoulos NG, Bossios A, Manoussakis E, Manousakas T, Saxoni-Papageorgiou P. Duration of postviral airway hyperresponsiveness in children with asthma: effect of atopy. J Allergy Clin Immunol 2005;**116**:299–304.
48. Gruber C, Illi S, Lau S, Nickel R, Forster J, Kamin W et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. Pediatrics 2003;**111**:e282–e288.
49. Floistrup H, Swartz J, Bergstrom A, Alm JS, Scheynius A, van HM et al. Allergic disease and sensitization in Steiner school children. J Allergy Clin Immunol 2006;**117**:59–66.

50. Johnson CC, Ownby DR, Alford SH, Havstad SL, Williams LK, Zoratti EM et al. Antibiotic exposure in early infancy and risk for childhood atopy. J Allergy Clin Immunol 2005;**115**:1218–1224.
51. Moshammer H, Hoek G, Luttmann-Gibson H, Neuberger MA, Antova T, Gehring U et al. Parental smoking and lung function in children: an international study. Am J Respir Crit Care Med 2006;**173**:1255–1263.
52. Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. N Engl J Med 1987;**317**:1309–1314.
53. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 2002;**57**:226–230.
54. Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. Pediatr Allergy Immunol 2004;**15** (Suppl. 16):4–32.
55. Weiland SK, von ME, Hirsch T, Duhme H, Fritzsch C, Werner B et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. Eur Respir J 1999;**14**:862–870.
56. Hirsch T, Weiland SK, von ME, Safeca AF, Grafe H, Csaplovics E et al. Inner city air pollution and respiratory health and atopy in children. Eur Respir J 1999;**14**:669–677.
57. D'Amato G, Liccardi G, D'Amato M, Holgate S. Environmental risk factors and allergic bronchial asthma. Clin Exp Allergy 2005;**35**:1113–1124.
58. Gauderman WJ, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J et al. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology 2005;**16**:737–743.
59. Millstein J, Gilliland F, Berhane K, Gauderman WJ, McConnell R, Avol E et al. Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern California communities enrolled in The Children's Health Study. Arch Environ Health 2004;**59**:505–514.
60. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA et al. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003;**58**:833–843.
61. von Berg A, Koletzko S, Filipiak-Pittroff B, Laubereau B, Grubl A, Wichmann HE et al. Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. J Allergy Clin Immunol 2007;**119**:718–725.
62. von Berg A, Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;**111**:533–540.
63. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol 1989;**84**:72–89.
64. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 2005;**115**:1109–1117.
65. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. Arch Dis Child 2006;**91**:334–339.
66. Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 month of age. Pediatr Allergy Immunol 2004;**15**:517–522.
67. Peat JK, Mihrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K et al. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. J Allergy Clin Immunol 2004;**114**:807–813.
68. Bernard A, Carbonnelle S, Michel O, Higuet S, De BC, Buchet JP et al. Lung hyperpermeability and asthma prevalence in schoolchildren: unexpected associations with the attendance at indoor chlorinated swimming pools. Occup Environ Med 2003;**60**:385–394.
69. Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise induced asthma. Thorax 1985;**40**:481–487.
70. Parsons JP, Mastronarde JG. Exercise-induced bronchoconstriction in athletes. Chest 2005;**128**:3966–3974.
71. Rasmussen F, Lambrechtsen J, Siersted HC, Hansen HS, Hansen NC. Low physical fitness in childhood is associated with the development of asthma in young adulthood: the Odense schoolchild study. Eur Respir J 2000;**16**:866–870.
72. Villeneuve PJ, Leech J, Bourque D. Frequency of emergency room visits for childhood asthma in Ottawa, Canada: the role of weather. Int J Biometeorol 2005;**50**:48–56.
73. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. Thorax 1998;**53**:1066–1074.
74. Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. Am J Respir Crit Care Med 2002;**165**:358–365.
75. Xuan W, Marks GB, Toelle BG, Belousova E, Peat JK, Berry G et al. Risk factors for onset and remission of atopy, wheeze, and airway hyperresponsiveness. Thorax 2002;**57**:104–109.
76. Wenzel S. Physiologic and pathologic abnormalities in severe asthma. Clin Chest Med 2006;**27**:29–40.
77. de Blic J, Tillie-Leblond I, Tonnel AB, Jaubert F, Scheinmann P, Gosset P. Difficult asthma in children: an analysis of airway inflammation. J Allergy Clin Immunol 2004;**113**:94–100.
78. Martinez FD. Maturation of immune responses at the beginning of asthma. J Allergy Clin Immunol 1999;**103**:355–361.
79. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. J Allergy Clin Immunol 2005;**116**:16–24.
80. Chernick V, West J. The functional basis of respiratory disease. In: Chernick V, Boat T, Wilmott R, Bush A, editors. Kendig's disorders of the respiratory tract in children. Philadelphia, PA: Saunders, 2006:29–64.
81. Hoffjan S, Ostrovnaja I, Nicolae D, Newman DL, Nicolae R, Gangnon R et al. Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. J Allergy Clin Immunol 2004;**113**:511–518.
82. Meyers DA, Postma DS, Stine OC, Koppelman GH, Ampleford EJ, Jongepier H et al. Genome screen for asthma and bronchial hyperresponsiveness: interactions with passive smoke exposure. J Allergy Clin Immunol 2005;**115**:1169–1175.
83. Stevenson EC, Turner G, Heaney LG, Schock BC, Taylor R, Gallagher T et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. Clin Exp Allergy 1997;**27**:1027–1035.

84. Heaton T, Rowe J, Turner S, Aalberse RC, de KN, Suriyaarachchi D et al. An immunoepidemiological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children. Lancet 2005;**365**:142–149.
85. Pohunek P, Warner JO, Turzikova J, Kudrmann J, Roche WR. Markers of eosinophilic inflammation and tissue re-modelling in children before clinically diagnosed bronchial asthma. Pediatr Allergy Immunol 2005;**16**:43–51.
86. Marguet C, Jouen-Boedes F, Dean TP, Warner JO. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. Am J Respir Crit Care Med 1999;**159**:1533–1540.
87. Denburg JA, Sehmi R, Saito H, Pil-Seob J, Inman MD, O'Byrne PM. Systemic aspects of allergic disease: bone marrow responses. J Allergy Clin Immunol 2000;**106**:S242–S246.
88. Meiler F, Zimmermann M, Blaser K, Akdis CA, Akdis M. T-cell subsets in the pathogenesis of human asthma. Curr Allergy Asthma Rep 2006;**6**:91–96.
89. Smart JM, Kemp AS. Increased Th1 and Th2 allergen-induced cytokine responses in children with atopic disease. Clin Exp Allergy 2002;**32**:796–802.
90. Gern JE, Brooks GD, Meyer P, Chang A, Shen K, Evans MD et al. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. J Allergy Clin Immunol 2006;**117**:72–78.
91. Dahl ME, Dabbagh K, Liggitt D, Kim S, Lewis DB. Viral-induced T helper type 1 responses enhance allergic disease by effects on lung dendritic cells. Nat Immunol 2004;**5**:337–343.
92. Akbari O, DeKruyff RH, Umetsu DT. Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. Nat Immunol 2001;**2**:725–731.
93. Lewkowich IP, Herman NS, Schleifer KW, Dance MP, Chen BL, Dienger KM et al. CD4+ CD25+ T cells protect against experimentally induced asthma and alter pulmonary dendritic cell phenotype and function. J Exp Med 2005;**202**:1549–1561.
94. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;**113**:832–836.
95. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;**320**:271–277.
96. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005;**201**:937–947.
97. van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. Am J Respir Crit Care Med 2001;**164**:2107–2113.
98. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000;**161**:1720–1745.
99. Barbato A, Turato G, Baraldo S, Bazzan E, Calabrese F, Tura M et al. Airway inflammation in childhood asthma. Am J Respir Crit Care Med 2003;**168**:798–803.
100. Payne DN, Rogers AV, Adelroth E, Bandi V, Guntupalli KK, Bush A et al. Early thickening of the reticular basement membrane in children with difficult asthma. Am J Respir Crit Care Med 2003;**167**:78–82.
101. Saglani S, Malmstrom K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. Am J Respir Crit Care Med 2005;**171**:722–727.
102. Davies DE, Wicks J, Powell RM, Puddicombe SM, Holgate ST. Airway remodeling in asthma: new insights. J Allergy Clin Immunol 2003;**111**:215–225.
103. Vignola AM, Gagliardo R, Siena A, Chiappara G, Bonsignore MR, Bousquet J et al. Airway remodeling in the pathogenesis of asthma. Curr Allergy Asthma Rep 2001;**1**:108–115.
104. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006;**354**:1985–1997.
105. Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. Clin Exp Allergy 2000;**30**:663–669.
106. Braunstahl GJ, KleinJan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Respir Crit Care Med 2000;**161**:2051–2057.
107. Braunstahl GJ, Overbeek SE, KleinJan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001;**107**:469–476.
108. Holgate ST, Holloway J, Wilson S, Bucchieri F, Puddicombe S, Davies DE. Epithelial-mesenchymal communication in the pathogenesis of chronic asthma. Proc Am Thorac Soc 2004;**1**:93–98.
109. Cokugras H, Akcakaya N, Seckin, Camcioglu Y, Sarimurat N, Aksoy F. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. Thorax 2001;**56**:25–29.
110. Baraldi E, Dario C, Ongaro R, Scollo M, Azzolin NM, Panza N et al. Exhaled nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children. Am J Respir Crit Care Med 1999;**159**:1284–1288.
111. Montgomery GL, Tepper RS. Changes in airway reactivity with age in normal infants and young children. Am Rev Respir Dis 1990;**142**:1372–1376.
112. Joos GF. The role of neuroeffector mechanisms in the pathogenesis of asthma. Curr Allergy Asthma Rep 2001;**1**:134–143.
113. Gold MS, Kemp AS. Atopic disease in childhood. Med J Aust 2005;**182**:298–304.
114. Hall CB, Wakefield D, Rowe TM, Carlisle PS, Cloutier MM. Diagnosing pediatric asthma: validating the Easy Breathing Survey. J Pediatr 2001;**139**:267–272.
115. Elphick HE, Sherlock P, Foxall G, Simpson EJ, Shiell NA, Primhak RA et al. Survey of respiratory sounds in infants. Arch Dis Child 2001;**84**:35–39.
116. Nickel R, Kulig M, Forster J, Bergmann R, Bauer CP, Lau S et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. J Allergy Clin Immunol 1997;**99**:613–617.
117. Host A, Andrae S, Charkin S, az-Vazquez C, Dreborg S, Eigenmann PA et al. Allergy testing in children: why, who, when and how? Allergy 2003;**58**:559–569.

118. Wood RA. Skin testing: making the most of every prick. Ann Allergy Asthma Immunol 2002;**88**:347–349.
119. van Asperen PP, Kemp AS, Mellis CM. Skin test reactivity and clinical allergen sensitivity in infancy. J Allergy Clin Immunol 1984;**73**:381–386.
120. Menardo JL, Bousquet J, Rodiere M, Astruc J, Michel FB. Skin test reactivity in infancy. J Allergy Clin Immunol 1985;**75**:646–651.
121. Niemeijer NR, de Monchy JG. Age-dependency of sensitization to aero-allergens in asthmatics. Allergy 1992;**47**:431–435.
122. Fiocchi A, Besana R, Ryden AC, Terracciano L, Andreotti M, Arrigoni S et al. Differential diagnosis of IgE-mediated allergy in young children with wheezing or eczema symptoms using a single blood test. Ann Allergy Asthma Immunol 2004;**93**:328–333.
123. Nordvall SL, Janson C, Kalm-Stephens P, Foucard T, Toren K, Alving K. Exhaled nitric oxide in a population-based study of asthma and allergy in school-children. Allergy 2005;**60**:469–475.
124. Spahn JD, Chipps BE. Office-based objective measures in childhood asthma. J Pediatr 2006;**148**:11–15.
125. Nair SJ, Daigle KL, DeCuir P, Lapin CD, Schramm CM. The influence of pulmonary function testing on the management of asthma in children. J Pediatr 2005;**147**:797–801.
126. Zapletal A, Chalupova J. Forced expiratory parameters in healthy preschool children (3-6 years of age). Pediatr Pulmonol 2003;**35**:200–207.
127. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R et al. General considerations for lung function testing. Eur Respir J 2005;**26**:153–161.
128. Covar RA, Szefler SJ, Martin RJ, Sundstrom DA, Silkoff PE, Murphy J et al. Relations between exhaled nitric oxide and measures of disease activity among children with mild-to-moderate asthma. J Pediatr 2003;**142**:469–475.
129. Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J et al. Safety and application of induced sputum analysis in childhood asthma. J Allergy Clin Immunol 2004;**114**:575–582.
130. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 2000;**343**:1054–1063.
131. Paull K, Covar R, Jain N, Gelfand EW, Spahn JD. Do NHLBI lung function criteria apply to children?. A cross-sectional evaluation of childhood asthma at National Jewish Medical and Research Center, 1999–2002 Pediatr Pulmonol 2005;**39**:311–317.
132. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;**170**:426–432.
133. Saglani S, Nicholson AG, Scallan M, Balfour-Lynn I, Rosenthal M, Payne DN et al. Investigation of young children with severe recurrent wheeze: any clinical benefit? Eur Respir J 2006;**27**:29–35.
134. Gore C, Custovic A. Primary and secondary prevention of allergic airway disease. Paediatr Respir Rev 2003;**4**:213–224.
135. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. Thorax 2003;**58**:489–493.
136. Koopman LP, van Strien RT, Kerkhof M, Wijga A, Smit HA, de Jongste JC et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. Am J Respir Crit Care Med 2002;**166**:307–313.
137. Chan-Yeung M, Ferguson A, Watson W, mich-Ward H, Rousseau R, Lilley M et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. J Allergy Clin Immunol 2005;**116**:49–55.
138. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. Lancet 2001;**358**:188–193.
139. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. Am J Respir Crit Care Med 2004;**170**:433–439.
140. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R III et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;**351**:1068–1080.
141. Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. J Allergy Clin Immunol 1998;**101**:28–32.
142. O'Connor GT. Allergen avoidance in asthma: what do we do now? J Allergy Clin Immunol 2005;**116**:26–30.
143. Eggleston PA. Improving indoor environments: reducing allergen exposures. J Allergy Clin Immunol 2005;**116**:122–126.
144. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001;**107**:191–193.
145. El AW. Passive smoking and chronic illness in children: age and gender inequalities, and the fallacy of 'low-strength' cigarettes. Chronic Illn 2005;**1**:87–91.
146. Skoner DP, Greos LS, Kim KT, Roach JM, Parsey M, Baumgartner RA. Evaluation of the safety and efficacy of levalbuterol in 2-5-year-old patients with asthma. Pediatr Pulmonol 2005;**40**:477–486.
147. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax 2005;**60**:740–746.
148. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F, Mayowe V. Anticholinergic drugs for wheeze in children under the age of two years. Cochrane Database Syst Rev 2005;CD001279.
149. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005;**115**:233–242.
150. Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. N Engl J Med 1997;**337**:1659–1665.
151. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med 2006;**354**:1998–2005.
152. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study. Lancet 2006;**368**:754–762.

153. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001;**108**:E48.
154. Bisgaard H, Nielsen KG. Bronchoprotection with a leukotriene receptor antagonist in asthmatic preschool children. Am J Respir Crit Care Med 2000;**162**:187–190.
155. Straub DA, Minocchieri S, Moeller A, Hamacher J, Wildhaber JH. The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old. Chest 2005;**127**:509–514.
156. Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL et al. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. Eur Respir J 2005;**25**:289–294.
157. Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. J Pediatr 2001;**138**:694–698.
158. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005;**171**:315–322.
159. Bisgaard H. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. Am J Respir Crit Care Med 2003;**167**:379–383.
160. van Adelsberg J, Moy J, Wei LX, Tozzi CA, Knorr B, Reiss TF. Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. Curr Med Res Opin 2005;**21**:971–979.
161. Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. Am J Respir Crit Care Med 1998;**158**:213–219.
162. Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol 2007;**119**:64–72.
163. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med 2006;**144**:904–912.
164. Guevara JP, Ducharme FM, Keren R, Nihtianova S, Zorc J. Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. Cochrane Database Syst Rev 2006;CD003558.
165. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. Cochrane Database Syst Rev 2006;CD003559.
166. Walters EH, Walters J. Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Cochrane Database Syst Rev 2003;CD001285.
167. Sheffer AL, Silverman M, Woolcock AJ, Diaz PV, Lindberg B, Lindmark B. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. Ann Allergy Asthma Immunol 2005;**94**:48–54.
168. Jonasson G, Carlsen KH, Mowinckel P. Asthma drug adherence in a long term clinical trial. Arch Dis Child 2000;**83**:330–333.
169. Wolthers OD, Allen DB. Inhaled corticosteroids, growth, and compliance. N Engl J Med 2002;**347**:1210–1211.
170. Randell TL, Donaghue KC, Ambler GR, Cowell CT, Fitzgerald DA, van Asperen PP. Safety of the newer inhaled corticosteroids in childhood asthma. Paediatr Drugs 2003;**5**:481–504.
171. Sizonenko PC. Effects of inhaled or nasal glucocorticosteroids on adrenal function and growth. J Pediatr Endocrinol Metab 2002;**15**:5–26.
172. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;**361**:1071–1076.
173. Sharek PJ, Bergman DA. Beclomethasone for asthma in children: effects on linear growth. Cochrane Database Syst Rev 2000;CD001282.
174. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics 2000;**106**:E8.
175. Wolthers OD, Pedersen S. Growth of asthmatic children during treatment with budesonide: a double blind trial. BMJ 1991;**303**:163–165.
176. Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. Pediatrics 1992;**89**:839–842.
177. Wolthers OD, Heuck C. Assessment of the relation between short and intermediate term growth in children with asthma treated with inhaled glucocorticoids. Allergy 2004;**59**:1193–1197.
178. Wolthers OD, Pedersen S. Short-term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. Arch Dis Child 1993;**68**:673–676.
179. Heuck C, Wolthers OD, Hansen M, Kollerup G. Short-term growth and collagen turnover in asthmatic adolescents treated with the inhaled glucocorticoid budesonide. Steroids 1997;**62**:659–664.
180. Heuck C, Heickendorff L, Wolthers OD. A randomised controlled trial of short term growth and collagen turnover in asthmatics treated with inhaled formoterol and budesonide. Arch Dis Child 2000;**83**:334–339.
181. Schou AJ, Heuck C, Wolthers OD. Does vitamin D administered to children with asthma treated with inhaled glucocorticoids affect short-term growth or bone turnover? Pediatr Pulmonol 2003;**36**:399–404.
182. Schou AJ, Plomgaard AM, Thomsen K, Wolthers OD. Lower leg growth suppression caused by inhaled glucocorticoids is not accompanied by reduced thickness of the cutis or subcutis. Acta Paediatr 2004;**93**:623–627.
183. Wolthers OD. Short-term growth and adrenal function in children with asthma treated with inhaled beclomethasone dipropionate hydrofluoroalkane-134a. Pediatr Allergy Immunol 2006;**17**:613–619.
184. Heuck C, Wolthers OD, Kollerup G, Hansen M, Teisner B. Adverse effects of inhaled budesonide (800 micrograms) on growth and collagen turnover in children with asthma: a double-blind comparison of once-daily versus twice-daily administration. J Pediatr 1998;**133**:608–612.
185. Chang KC, Miklich DR, Barwise G, Chai H, Miles-Lawrence R. Linear growth of chronic asthmatic children: the effects of the disease and various forms of steroid therapy. Clin Allergy 1982;**12**:369–378.

186. Baum WF, Schneyer U, Lantzsch AM, Kloditz E. Delay of growth and development in children with bronchial asthma, atopic dermatitis and allergic rhinitis. Exp Clin Endocrinol Diabetes 2002;**110**:53–59.
187. Norjavaara E, Gerhardsson DV, Lindmark B. Reduced height in swedish men with asthma at the age of conscription for military service. J Pediatr 2000;**137**:25–29.
188. Shohat M, Shohat T, Kedem R, Mimouni M, Danon YL. Childhood asthma and growth outcome. Arch Dis Child 1987;**62**:63–65.
189. Sim D, Griffiths A, Armstrong D, Clarke C, Rodda C, Freezer N. Adrenal suppression from high-dose inhaled fluticasone propionate in children with asthma. Eur Respir J 2003;**21**:633–636.
190. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child 2002;**87**:457–461.
191. Gulliver T, Eid N. Effects of glucocorticoids on the hypothalamic-pituitary-adrenal axis in children and adults. Immunol Allergy Clin North Am 2005;**25**:541–555.
192. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999;**159**:941–955.
193. Dunlop KA, Carson DJ, Steen HJ, McGovern V, McNaboe J, Shields MD. Monitoring growth in asthmatic children treated with high dose inhaled glucocorticoids does not predict adrenal suppression. Arch Dis Child 2004;**89**:713–716.
194. Priftis KN, Papadimitriou A, Gatsopoulou E, Yiallouros PK, Fretzayas A, Nicolaidou P. The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children. Eur Respir J 2006;**27**:316–320.
195. Allen DB. Inhaled steroids for children: effects on growth, bone, and adrenal function. Endocrinol Metab Clin North Am 2005;**34**:555–564.
196. Roux C, Kolta S, Desfougeres JL, Minini P, Bidat E. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics 2003;**111**:e706–e713.
197. Martinez FD. Safety of long-acting beta-agonists – an urgent need to clear the air. N Engl J Med 2005;**353**:2637–2639.
198. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;**129**:15–26.
199. Bisgaard H, Szefler S. Long-acting beta2 agonists and paediatric asthma. Lancet 2006;**367**:286–288.
200. Ellis EF. Theophylline toxicity. J Allergy Clin Immunol 1985;**76**:297–301.
201. Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database Syst Rev 2005;CD005533.
202. Rabinovitch N, Zhang L, Gelfand EW. Urine leukotriene E4 levels are associated with decreased pulmonary function in children with persistent airway obstruction. J Allergy Clin Immunol 2006;**118**:635–640.
203. Chavasse R, Seddon P, Bara A, McKean M. Short acting beta agonists for recurrent wheeze in children under 2 years of age. Cochrane Database Syst Rev 2002;CD002873.
204. Hofhuis W, van der Wiel EC, Tiddens HA, Brinkhorst G, Holland WP, de Jongste JC et al. Bronchodilation in infants with malacia or recurrent wheeze. Arch Dis Child 2003;**88**:246–249.
205. Conner WT, Dolovich MB, Frame RA, Newhouse MT. Reliable salbutamol administration in 6- to 36-month-old children by means of a metered dose inhaler and Aerochamber with mask. Pediatr Pulmonol 1989;**6**:263–267.
206. Kraemer R, Frey U, Sommer CW, Russi E. Short-term effect of albuterol, delivered via a new auxiliary device, in wheezy infants. Am Rev Respir Dis 1991;**144**:347–351.
207. Zielen S, Rose MA, Bez C, Jarisch A, Reichenbach J, Hofmann D. Effectiveness of budesonide nebulising suspension compared to disodium cromoglycate in early childhood asthma. Curr Med Res Opin 2006;**22**:367–373.
208. de Blic J, Delacourt C, Le BM, Mahut B, Ostinelli J, Caswell C et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. J Allergy Clin Immunol 1996;**98**:14–20.
209. Ilangovan P, Pedersen S, Godfrey S, Nikander K, Noviski N, Warner JO. Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. Arch Dis Child 1993;**68**:356–359.
210. Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol 1997;**100**:452–457.
211. Schuh S, Dick PT, Stephens D, Hartley M, Khaikin S, Rodrigues L et al. High-dose inhaled fluticasone does not replace oral prednisolone in children with mild to moderate acute asthma. Pediatrics 2006;**118**:644–650.
212. Boner AL, Spezia E, Piovesan P, Chiocca E, Maiocchi G. Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children. Am J Respir Crit Care Med 1994;**149**:935–939.
213. Carlsen KH, Roksund O, Olsholt K, Nja F, Leegaard J, Bratten G. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. Eur Respir J 1995;**8**:1852–1855.
214. Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children with exercise-induced asthma. Am Rev Respir Dis 1983;**128**:993–997.
215. Pearlman DS, van AJ, Philip G, Tilles SA, Busse W, Hendeles L et al. Onset and duration of protection against exercise-induced bronchoconstriction by a single oral dose of montelukast. Ann Allergy Asthma Immunol 2006;**97**:98–104.
216. De Benedictis FM, del Giudice MM, Forenza N, Decimo F, de BD, Capristo A. Lack of tolerance to the protective effect of montelukast in exercise-induced bronchoconstriction in children. Eur Respir J 2006;**28**:291–295.
217. Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment 4. Pediatrics 1997;**99**:655–659.
218. Balfour-Lynn I. Difficult asthma: beyond the guidelines. Arch Dis Child 1999;**80**:201–206.
219. Payne DN, Balfour-Lynn IM. Children with difficult asthma: a practical approach. J Asthma 2001;**38**:189–203.
220. Payne D, Bush A. Phenotype-specific treatment of difficult asthma in children. Paediatr Respir Rev 2004;**5**:116–123.

221. Ahrens RC. The role of the MDI and DPI in pediatric patients: 'Children are not just miniature adults'. Respir Care 2005;**50**:1323–1328.
222. Cates CJ, Bestall J, Adams N. Holding chambers versus nebulisers for inhaled steroids in chronic asthma. Cochrane Database Syst Rev 2006;CD001491.
223. Boyd R, Stuart P. Pressurised metered dose inhalers with spacers versus nebulisers for beta-agonist delivery in acute asthma in children in the emergency department. Emerg Med J 2005;**22**:641–642.
224. Rubilar L, Castro-Rodriguez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. Pediatr Pulmonol 2000;**29**:264–269.
225. De Benedictis FM, Selvaggio D. Use of inhaler devices in pediatric asthma. Paediatr Drugs 2003;**5**:629–638.
226. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001;**108**:E36.
227. Richeldi L, Ferrara G, Fabbri LM, Lasserson TJ, Gibson PG. Macrolides for chronic asthma. Cochrane Database Syst Rev 2005;CD002997.
228. Pajno GB. Allergen immunotherapy in early childhood: between Scylla and Charybdis!. Clin Exp Allergy 2005;**35**:551–553.
229. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. Cochrane Database Syst Rev 2003;CD001186.
230. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;**99**:450–453.
231. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000;**162**:2048–2052.
232. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006;**61**:855–859.
233. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De ME et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;**114**:851–857.
234. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;**109**:251–256.
235. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;**341**:468–475.
236. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002;**57**:306–312.
237. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;**61**:198–201.
238. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. Allergol Immunopathol (Madr) 2005;**33**:296–302.
239. Olaguibel JM, varez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. J Investig Allergol Clin Immunol 2005;**15**:9–16.
240. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy 2003;**33**:206–210.
241. Sopo SM, Macchiaiolo M, Zorzi G, Tripodi S. Sublingual immunotherapy in asthma and rhinoconjunctivitis; systematic review of paediatric literature. Arch Dis Child 2004;**89**:620–624.
242. Bousquet J, Van CP, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;**108**:S147–S334.
243. Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol 2006;**97**:141–148.
244. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy 2007;**62**:567–568.
245. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;**117**:802–809.
246. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;**113**:1129–1136.
247. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. Allergy 2004;**59**:45–53.
248. Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma – a placebo controlled study. Ann Allergy Asthma Immunol 1999;**82**:485–490.
249. Wolf FM, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children. Cochrane Database Syst Rev 2003;CD000326.
250. Holzheimer L, Mohay H, Masters IB. Educating young children about asthma: comparing the effectiveness of a developmentally appropriate asthma education video tape and picture book. Child Care Health Dev 1998;**24**:85–99.
251. Ward A, Willey C, Andrade S. Patient education provided to asthmatic children: a historical cohort study of the implementation of NIH recommendations. J Asthma 2001;**38**:141–147.
252. Gebert N, Hummelink R, Konning J, Staab D, Schmidt S, Szczepanski R et al. Efficacy of a self-management program for childhood asthma – a prospective controlled study. Patient Educ Couns 1998;**35**:213–220.
253. McCann DC, McWhirter J, Coleman H, Calvert M, Warner JO. A controlled trial of a school-based intervention to improve asthma management. Eur Respir J 2006;**27**:921–928.
254. Dekker FW, Dieleman FE, Kaptein AA, Mulder JD. Compliance with pulmonary medication in general practice. Eur Respir J 1993;**6**:886–890.
255. Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled asthma medication in preschool children. Thorax 1995;**50**:1274–1279.

256. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. Pediatrics 1990;**86**:350–356.
257. Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. Am J Emerg Med 1992;**10**:301–310.
258. Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. Cochrane Database Syst Rev 2003;CD002886.
259. Shim CS, Williams MH Jr. Relationship of wheezing to the severity of obstruction in asthma. Arch Intern Med 1983;**143**:890–892.
260. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. National Heart Lung and Blood Institute 2007. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm; accessed 7 November 2007.
261. McGhan SL, MacDonald C, James DE, Naidu P, Wong E, Sharpe H et al. Factors associated with poor asthma control in children aged five to 13 years. Can Respir J 2006;**13**:23–29.
262. Ducharme FM, Davis GM, Noya F, Rich H, Ernst P. The Asthma Quiz for Kidz: a validated tool to appreciate the level of asthma control in children. Can Respir J 2004;**11**:541–546.
263. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;**113**:59–65.
264. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;**117**:549–556.
265. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;**119**:817–825.
266. Guyatt GH, Juniper EF, Griffith LE, Feeny DH, Ferrie PJ. Children and adult perceptions of childhood asthma. Pediatrics 1997;**99**:165–168.
267. Hyland ME, Kenyon CA, Allen R, Howarth P. Diary keeping in asthma: comparison of written and electronic methods. BMJ 1993;**306**:487–489.
268. Jones C, Santanello NC, Boccuzzi SJ, Wogen J, Strub P, Nelsen LM. Adherence to prescribed treatment for asthma: evidence from pharmacy benefits data. J Asthma 2003;**40**:93–101.
269. Burkhart PV, Rayens MK, Bowman RK. An evaluation of children's metered-dose inhaler technique for asthma medications. Nurs Clin North Am 2005;**40**:167–182.
270. Lloyd BW, Ali MH. How useful do parents find home peak flow monitoring for children with asthma? BMJ 1992;**305**:1128–1129.
271. Wensley D, Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. Am J Respir Crit Care Med 2004;**170**:606–612.
272. Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. Thorax 2001;**56**:180–182.
273. Sly PD, Flack F. Is home monitoring of lung function worthwhile for children with asthma? Thorax 2001;**56**:164–165.
274. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. J Allergy Clin Immunol 2001;**107**:61–67.
275. Zanconato S, Meneghelli G, Braga R, Zacchello F, Baraldi E. Office spirometry in primary care pediatrics: a pilot study. Pediatrics 2005;**116**:e792–e797.
276. Randolph C, Fraser B, Matasavage C. The free running athletic screening test as a screening test for exercise-induced asthma in high school. Allergy Asthma Proc 1997;**18**:93–98.
277. Williams D, Bruton J, Wilson I. Screening a state middle school for asthma using the free running asthma screening test. Arch Dis Child 1993;**69**:667–669.
278. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000;**161**:309–329.
279. Taylor DR, Pijnenburg MW, Smith AD, de Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. Thorax 2006;**61**:817–827.
280. Strunk RC, Szefler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol 2003;**112**:883–892.
281. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. Clin Exp Allergy 2005;**35**:1175–1179.
282. Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol 2006;**117**:45–52.
283. de Jongste JC. Yes to NO: the first studies on exhaled nitric oxide-driven asthma treatment. Eur Respir J 2005;**26**:379–381.
284. Pijnenburg MW, Bakker EM, Hop WC, de Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. Am J Respir Crit Care Med 2005;**172**:831–836.
285. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;**352**:2163–2173.
286. Pijnenburg MW, Hofhuis W, Hop WC, de Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. Thorax 2005;**60**:215–218.
287. Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. Am J Respir Crit Care Med 2005;**171**:1077–1082.
288. Scadding G. Nitric oxide in the airways. Curr Opin Otolaryngol Head Neck Surg 2007;**15**:258–263.
289. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. Am J Respir Crit Care Med 2005;**171**:912–930.
290. Baraldi E, de Jongste JC. Measurement of exhaled nitric oxide in children, 2001. Eur Respir J 2002;**20**:223–237.
291. Buchvald F, Baraldi E, Carraro S, Gaston B, De JJ, Pijnenburg MW et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;**115**:1130–1136.
292. Horvath I, Hunt J, Barnes PJ, Alving K, Antczak A, Baraldi E et al. Exhaled breath condensate: methodological recommendations and unresolved questions. Eur Respir J 2005;**26**:523–548.