

Asthma between 2 and 5 years: a key period

Asthme de deux à cinq ans : une période clé

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Abstract

The preschool asthmatic child is at the crossroads between virus induced airway obstruction and allergy-based asthma. There are no diagnostic tests other than a careful history and if possible prospective observation. Allergy tests are helpful and may guide the required treatment. Pharmacotherapy is the mainstay but may be supplemented by allergen-specific immunotherapy. Unfortunately inhaled corticosteroids (ICS) do not seem to lead to improved symptom-free periods once this treatment is stopped. In the allergy-driven asthmatic long-term treatment strategies must be envisaged.

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Résumé

L'enfant asthmatique d'âge pré-scolaire est à un carrefour entre l'obstruction des voies aériennes induites par les virus et l'asthme allergique. Il n'y a pas d'autres tests diagnostiques que ceux donnés par un recueil précis de l'histoire de la maladie et si possible un suivi prospectif. Les tests allergiques sont utiles et peuvent guider les traitements nécessaires. La pharmacothérapie est primordiale mais on peut y adjoindre une immunothérapie spécifique. Malheureusement, les bénéfices thérapeutiques des corticoïdes inhalés disparaissent à l'arrêt du traitement. Chez l'enfant allergique asthmatique, ce sont les stratégies thérapeutiques à long terme qui doivent être envisagées.

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1. Introduction. Is it asthma?

Most asthmatic children develop symptoms before 5 years of age. However, ascertaining a diagnosis of asthma in children between the ages 2 and 5, i.e. in many countries the preschool period, may be a tiresome and tense experience both for parents, caregivers, the pediatrician or GP and, last not least, for the child. The major reason for this is the uncertainty whether or not asthma is present, what this implies for the future of the child in case of a positive answer and the question of the treatment and perspective in case of an alternative diagnosis. The preschool period in particular is one where major changes are

not uncommon and the possible burden of a disease may influence decisions regarding schooling and education and even the lifestyle of whole families.

A diagnosis of early childhood asthma defined as recurrent episodes of wheezing, breathlessness, chest tightness and coughing may be difficult to apply confidently in young children with such symptoms. Wheezing in infancy and early childhood is a common manifestation of diseases other than asthma. The level of bronchial hyperresponsiveness assessed by methacholine challenge in wheezing infants is not predictive of the persistence of asthma 4 years later [13]. Both the incidence and period prevalence of wheezing decrease significantly with increasing age [41].

The physical investigation may be unrewarding in this age as major changes such as rib flaring or chest wall deformities would rarely be encountered. Auscultation between asthmatic

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episodes may be normal and the wellbeing of a child wheezing only intermittently may not be affected to any major extent.

Major information towards establishing a diagnosis of asthma is derived from evidence of allergy or atopy. Allergy tests may be useful in seeking causal factors. The presence of allergy is not essential for the diagnosis of asthma but if absent in a school child with symptoms suggestive of asthma alternative diagnoses should also be considered. Children most likely to develop persistent symptoms are those:

- with a positive history of asthma in first degree relatives;
- with other clinical manifestations of atopy (such as eczema), eosinophilia, and (perhaps) elevated total immunoglobulin E (IgE);
- with specific IgE-mediated sensitization, to foods in infancy and early childhood and subsequently to common inhaled allergens [8,11,34].

A relatively large number of differential diagnoses have to be taken into account the most common being upper respiratory virus infection-induced airway obstruction. Whether or not this very common condition should be termed early childhood asthma remains a matter of debate. Other conditions mimicking preschool asthma are anatomic abnormalities, cystic fibrosis, defective immunity, ciliary defects and a number of other, rarer, conditions.

The natural history of asthma is determined by a number of factors relevant for the 2–5 years age group.

2. Genetics

There is a significant genetic element to asthma. More recently, genome wide genetic screens followed by position cloning and candidate gene association studies have identified genetic loci that increase the risk of asthma in certain populations [24]. Unfortunately, to date there is no reliable genetic information available to establish or even only support the diagnosis.

3. Allergy and allergen exposure

In infants and children, the airways are more susceptible to obstruction due to their smaller size. In the preschool child asthma is the result of the interplay of maturation of the immune system, lung growth and development, the child's genes and by the interaction between genetic and environmental factors. A large proportion of children with asthma have atopy, defined as the propensity to develop IgE antibodies and related clinical syndromes. Although the atopic phenotype is frequently present in infancy, it becomes more clearly apparent in preschool and school-age children and remains associated with asthma at all ages. Atopic individuals tend to have elevated IgE antibody levels and a Th1/Th2 imbalance in response to mitogens, allergens and viruses. The atopic environment promotes further allergen sensitization and aberrant responses to viral infections [46].

Exposure to indoor allergens might be a significant risk factor for allergic asthma [19,28]. Data from observational birth cohort studies suggests that indoor allergen exposure in infancy is related to early sensitization, but that this cannot be considered as the primary cause for asthma [18].

4. Pollutants

Passive tobacco smoke exposure is the strongest domestic and environmental risk factor. Maternal smoking during pregnancy results in impaired lung growth in the child, which may be associated with wheezing early in life [23]. Similarly, environmental tobacco smoke exposure has been shown to be a risk factor for early transient wheezing [20]. In existing asthma, smoking is known to be associated with disease persistence [23]. With increasing years tobacco smoke exposure appears to be less relevant but remains an important irritant.

5. Early nutrition

Although the value of breast feeding is clear, it does not appear to prevent the development of asthma [33]. Intervention studies have indicated that using an extensively hydrolyzed infant formula also fails to affect asthma incidence. By the age of 5 years nutrition plays a minor role in provoking or maintaining asthma.

6. Infections

Exposure to viruses (e.g. hepatitis A, measles), mycobacteria or parasites, may have protective potential [22,36].

Results are difficult to reproduce and there is insufficient evidence from intervention studies to clarify this relationship. To date, there is no evidence that vaccinations given during the first years of life increase the risk of atopy or asthma.

7. Airway remodeling

The bronchial epithelium plays a central role in asthma by reacting to external stimuli as well as regulating inflammatory and remodeling processes. Biopsy studies have shown that the epithelial barrier appears to be compromised in both adults and children with asthma [3]. These structural changes are less well characterized in pediatric patients [3,25,29]. Evidence of remodeling has been described in children with postviral wheeze, but there is evidence that the changes do not begin until after infancy [31]. In addition to biopsy studies, bronchoalveolar lavage and indirect measures of inflammation, such as exhaled nitric oxide [2] also show that bronchial inflammation is present in young children with symptoms of asthma.

8. Asthma provoking triggers

Common preschool triggers are infections, allergens, exercise, tobacco smoke, pollutants, irritants such as vapors, dusts, chemicals such as chlorine or volatile organic compounds. A careful assessment of indoor and outdoor conditions and expo-

sure should be attempted. Weather, emotion, diet should also be investigated and can, in rare cases, be of importance for the preschooler. Trigger-based phenotyping is likely to be useful because it recognizes the heterogeneity of childhood asthma. Phenotype-based guidelines should, therefore, provide better guidance for prognosis and therapeutic strategies, particularly for so-called difficult asthmatics [26].

9. Age

Age is one of the strongest determinants of asthma phenotypes in childhood, induced by pathophysiological events, exposure and natural history determinants. The most practical age groups are:

- infants (0–2 years old);
- preschool children (2–5 years old);
- school children (6–12 years old);
- adolescents.

In preschool children aged 2–5 years the key differentiator of phenotype is persistence during the last year. If symptoms disappear completely between episodes, and usually follow a cold, the child likely has viral-induced asthma. Viruses are the most common trigger in this age group and it is possible that particularly in the winter months some children will have infections that are so frequent that there is no symptomless period.

The presence of specific IgE antibodies should be tested to ascertain whether there is clinically relevant positivity. If so, allergens are the phenotype-defining trigger. If not, the child has persistent, episodic asthma.

10. Making a diagnosis of preschool asthma

There are no specific diagnostic tools or surrogate markers for detecting asthma in infancy or the preschool period. Therefore, asthma should be suspected in any child with recurrent wheezing and cough episodes. Frequently, diagnosis is possible only through long-term follow-up and by observing the individual's response to anti-inflammatory or bronchodilator treatment.

Allergy should always be assessed and may greatly influence the prognosis [16]. Allergy testing may also help establish the best course of treatment for asthma. There is no lower age limit for skin prick testing among children [43]. In vitro testing (RAST) should be performed using a validated method and should be related to the patient's clinical history. It should be used on the same basis as the skin prick test. A baseline program consisting of standard allergens such as house-dust mite, alternaria, birch, grass, cat is generally informative, younger preschool children (2–3 years) should also be tested for mixed foods. In case of a suspicious history of food allergy prick–prick testing can be highly informative and more reliable than RAST results.

Other tests, such as exhaled nitric oxide, exhaled breath condensate, eosinophil cationic protein (ECP) and histamine

release, may indicate the presence of (allergic) inflammation but are mainly research tools. However, exhaled nitric oxide is demonstrating its usefulness as an adjunct to routine clinical assessment in the management of asthma [42] and monitoring of treatment [48].

Lung function measurements are time-consuming and difficult to obtain reliably in the preschool child and not before the age of 4. Although it is possible to measure peak flows from the age of 4–5 years, there are some concerns about effort-dependent effects. The validity of PEF is clearly lower than standard spirometry data.

11. Managing the preschool asthmatic

This is based on four interacting strategies:

1. avoidance of allergens and other triggers;
2. appropriate pharmacotherapy;
3. allergen-specific immunotherapy;
4. asthma education programs for patients, parents and careers.

11.1. Avoidance of allergens and other triggers

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. Even if sensitization cannot be prevented, allergen avoidance improves lung function [47] and reduces severity of symptoms in high-risk children [9]. It must be stressed that avoidance of inhaled allergen such as pollen is difficult and that removal of an allergenic pet may become effective only after years as animal sheddings may be found for prolonged periods. Since it is difficult to avoid pollutants and triggering weather conditions, for example thunder storms, parents should be aware of these situations so that they can react accordingly.

11.2. Appropriate pharmacotherapy

Control of symptoms and prevention of exacerbations with a minimum of drug-related side effects are the main goals of pharmacotherapy. Treatment should be given in a stepwise procedure according to the severity and/or the frequency of symptoms and according to age.

Treatments currently available for mild to moderate childhood asthma include:

11.2.1. Reliever therapies (mild intermittent asthma)

- Short-acting inhaled β_2 -agonists (SABAs);
- other bronchodilators.

11.2.2. Controller therapies (mild persistent asthma)

- inhaled corticosteroids (ICS);
- long-acting β_2 -agonists (LABAs);
- leukotriene receptor antagonists (LTRAs);
- slow release theophylline;
- oral steroids.

11.2.3. Reliever medication for mild intermittent asthma

11.2.3.1. Short-acting β_2 -agonists. These are the treatment of choice for acute asthma episodes in children and for preventing exercise-induced asthma. 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 [37]. Terbutaline is the only other β_2 agonist with a safety and efficacy profile comparable to that of salbutamol; directions for use are similar.

SABAs are generally safe and earlier concerns about deaths when used for all ages on a regular base have not been substantiated [45]. The risk of tremor and electrolyte imbalances must be taken into account.

11.2.3.2. Ipratropium bromide. Ipratropium bromide is the only other reliever of any relevance. Its combined use with β_2 -agonists has resulted in favorable outcomes in children, although results were ambiguous in those less than 2 years of age [14]. Side effects are few and current evidence supports trial use when β_2 -agonists alone are not fully effective.

11.2.4. Regular controller therapy for mild persistent asthma

11.2.4.1. ICS. ICS are the cornerstone of persistent pediatric asthma management. They should be introduced as initial maintenance treatment (200 μg BDP equivalent) when the patient has experienced symptoms more than once per week during the past 6 weeks. It is difficult to predict which patients will respond to ICS, but atopy and low lung function favor their use [40].

If control is inadequate on a low-dose after 1–2 months, reasons for poor control should be identified. If indicated, additional therapy with LABAs, or LTRAs should be considered. However, there is no evidence that therapy with fixed combinations of LABAs and ICS has benefits over and above both agents given separately. In fact, LABAs are not recommended for children less than 5 years. New evidence does not support a disease-modifying role after cessation of treatment with ICS in preschool children [5,15].

At doses recommended for the majority of asthmatic children, a satisfactory safety profile has been established over 20 years of use. A 3-year treatment 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 [35]. However, only 40–50% of patients are still taking

the prescribed dose of ICS after 6 months of treatment, potentially biasing measures of their long-term effects.

Oral candidiasis, growth and hypothalamic-pituitary-adrenal axis suppression may arise [30], particularly at higher doses. After prolonged use, patients on doses ≥ 800 μg should be referred to a specialist.

11.2.5. LTRA

Although less effective than low-dose ICS, LTRAs are an alternative for patients who cannot or will not use ICS. Evidence suggests use of montelukast as an alternative second line treatment for mild to moderate asthma for children aged ≥ 2 years, and after failure of beta agonist alone [17] as it protects against bronchial challenges [4] and reduces airway inflammation as measured by nitric oxide levels in some preschool children with allergic asthma [39]. At present there is no clear-cut evidence of an indication to use LTRA as a first-line treatment in mild to moderate asthma. Ease of application and few side-effects may make montelukast, the only widely available LTRA, a future first option. Evidence is accumulating that montelukast and other LTRAs may be used as first-line treatment for virus-induced mild to moderate asthma.

11.2.6. LABA

LABAs are licensed for use in children above 4–5 years of age and as an adjunct to ICS. They are effective in adults, but their efficacy in children is much less well documented [44]. Safety concerns have been raised recently [21], suggesting that use of LABAs should be restricted to add-on therapy to ICS where indicated. Evidence of an increased risk of severe adverse events has led the FDA to issue a public health advisory concerning LABA use. Some studies suggest an increase in asthma exacerbations in children using LABA regularly, and an increased risk of hospital admissions [6]. Headache and gastro-intestinal upset are the most commonly encountered side-effects, skin rashes or flu-like symptoms are much less common.

11.2.7. Oral theophylline

This compound has now a very limited position in childhood asthma but 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. Due to its narrow therapeutic index, blood levels must be monitored closely.

11.2.8. Use of inhalers

The preferred method of administration of ICS and β_2 -agonists is a metered dose inhaler (MDI) with a spacer or a dry powder inhaler (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 [1].

Table 1
Age-dependent inhalant devices [32]

Inhalation device	Age group	Inhalation technique
Nebulizer	All	Tidal breathing
Pressurized MDI	0–2 years	5–10 tidal breaths through non-electrostatic holding chamber (small volume) with attached face mask/activation
	3–7 years	5–10 tidal breaths through non-electrostatic holding chamber (small or large volume) with mouthpiece/activation
	> 8 years	Maximal slow inhalation followed by 10 s breath hold through non-electrostatic holding chamber (small or large volume) with mouthpiece/activation
DPI	> 5 years	Deep and fast inhalation followed by a 10 s breath hold/activation

The Table 1 shows the age-dependent choice of appropriate inhalant devices, MDIs and spacer products that are at least equivalent to nebulizer delivery of β_2 -agonists in acute asthma [32].

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 [10].

11.2.9. New and future drugs for the preschool asthmatic

Initial studies in adults with mometasone, a new ICS, suggest there may be less suppression of the hypothalamic-pituitary-adrenal axis than with established ICS, but further studies, particularly in children, are required. Ciclesonide, another new formulation ICS is activated in the lung. Although it can be used in children and adolescents over 12 years of age, the pediatric literature is anecdotal. Omalizumab prevents free serum IgE from attaching to mast cells and other effector cells and prevents IgE mediated inflammatory changes. There are no reports on the use of anti-IgE in preschool children.

11.3. Allergen-specific immunotherapy

Allergen-specific immunotherapy is the administration of increasing doses of specific allergen(s) over prolonged periods of time until protection against allergic symptoms associated with natural exposure to the allergen is reached. Such immune modulation is the only way of modifying the disease process of allergic (atopic) asthma [27]. While there is no literature on subcutaneous forms of treatment in the age group 2–5 limited evidence suggests efficacy of sublingual therapy in children under the age of 5 years [12]. However, a systematic review concluded that sublingual immunotherapy 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 [38]. 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 [7]. The forthcoming immunotablet against

grass pollen may change the pattern of allergen-specific immunotherapy in the age range 2–5.

11.4. Education

Since education is an essential aspect of disease management, it should begin at an early phase of disease. Ideally, the level of education required should be determined at diagnosis. In addition, asthma should be included in continuing medical and professional education programs. Parents and important others should be made knowledgeable at an early stage.

12. Perspectives into the future—the key for the future

Asthma between ages 2 and 5 can be established with some certainty despite the lack of objective measurements such as lung function or non-invasive monitoring of airway inflammation. The diagnosis will be much more certain than in the first 2 years of life where virus-induced infections result in an asthma-like symptomatology. Support for the diagnosis is commonly derived from demonstration of allergy which in fact appears to be the prime dominant factor for symptom persistence and long-term treatment. Fortunately, a large number of pharmacotherapeutics including compounds such as oral montelukast or ICS offer a ready armamentarium. There is little news concerning the advent of new therapeutics for this age group but recent developments such as new inhaled steroids or advances in allergen-specific immunotherapy appear promising. The preschool period remains a key period for the future development of asthma. It remains to be seen whether asthma treatment commenced in or before the preschool time will alter the overall disease course.

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