CHAPTER 17

Asthma in children

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Asthma is the most frequent chronic disease in childhood [1, 2], with increasing levels of morbidity in most of the countries worldwide [2]. Even if a recent paper predicted a possible end to this epidemic [3], it is undeniable that in the last decade asthma has become more and more frequent in children. Evidence for a real increase in asthma prevalence in childhood has been gathered in epidemiological studies performed in the same population at different times (fig. 1) [4–8]. Significant changes in the outdoor and indoor environment have been considered as possible causes for the increase of the disease. In Western countries there have been many changes in lifestyle such as structural building modifications, with more indoor humidity and consequent elevated levels of indoor allergens, modifications of the diet and of the infant intestinal flora, a reduction in the occurrence of early infectious diseases, widespread vaccination programmes, which have been, individually or in combination, implicated as causes of the increase [9].

However, differently from adulthood, the real prevalence of the disease in children is difficult to determine since there are uncertain relationships between viral infections, episodes of childhood wheezing and persistent asthma [10]. Wheezing can affect up to 40% of children aged <5–6 yrs [11, 12], but a lot of wheezing can resolve spontaneously during the school-age. Asthma will develop in ~30–40% of the total wheezing children [13]; in these subjects airway inflammation may occur very early in the natural history of the disease, with early inflammatory damage of the epithelium and airway remodelling [14].

Pathology

Most of the concepts regarding the pathogenesis of asthma in children are derived from studies performed in young adults. Obvious ethical reasons, have limited the application of invasive methods, in particular bronchoscopy, for the evaluation of inflammation in the airway of asthmatic children. However, from the available studies, the pathological finding of inflammation at the site of the airway in asthmatic children appears to be similar to that observed in adult patients, as suggested by studies of bronchoalveolar lavage (BAL) [15,16], induced sputum [17] and exhaled nitric oxide (eNO) [18,19]. In particular, it has been reported that the pathological findings are characterised by mucus plugs in the bronchi and bronchioles, loss of epithelium to varying degrees, goblet cell hyperplasia, thickening of the epithelial basement membrane, submucosal oedema and smooth muscle hypertrophy and, as a result, airway remodelling [17, 20]. These findings have been demonstrated even in mild asthmatic children [20]. Interestingly, in the recent study by ÇOKUĞRAŞ *et al.* [20] it has been demonstrated that in their group of mild asthmatic children the submucosa was infiltrated by lymphocytes in most patients, whereas only one subject presented eosinophilic infiltration. Thrombi were

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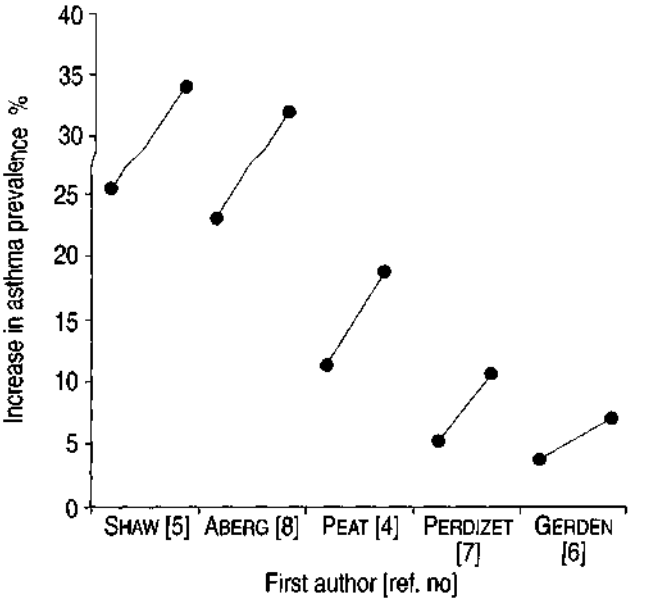

Fig. 1. - Childhood asthma prevalence in different countries.

found in capillaries and arterioles in some patients [20], thus confirming previous Findings in patients who died of asthma [21].

Recently, it has been demonstrated that neutrophils may play a pivotal role in inflammation in asthma, thus suggesting heterogeneicity of airway inflammation in the disease, indicating different mechanisms which may impact on treatment response [22].

In a group of children with difficult asthma who experienced frequent symptoms despite treatment with high-dose inhaled steroids it has been demonstrated that at least two subgroups of patients could be identified. Some of the children had persistently raised eNO levels despite treatment with oral prednisolone indicating ongoing steroid-insensitive inflammation, whereas some others presented normal levels of eNO. Both subgroups included patients with persistent symptoms, which suggests that different patterns of difficult asthma exist in children [23].

The finding that airway inflammation in asthma can be based on different mechanisms may be of critical relevance in the choice of treatment. Children with low eNO may have no evidence of airway inflammation or perhaps have noneosinophilic inflammation and they may need alternative treatment to steroids [24].

Wheezing from infancy to childhood

Wheezing is a nonspecific physical sign associated with restriction of airflow through narrowed airways and is believed to be generated by turbulent airflow which causes oscillation of the bronchial wall. Since many different mechanisms may induce noisy breathing, wheezing may simply be the final pathway for a variety of conditions associated with airway obstruction. In particular in preschool children anatomical abnormalities such as a reduced airway calibre may be responsible for the incidence and recurrence of this symptom [1, 25]. For this reason, in early childhood the definition of asthma is difficult, but the following has been proposed: "recurrent wheezing and/or

persistent coughing in a setting where asthma is likely and other rarer conditions have been excluded" [26]. Therefore, particularly if allergic sensitisation is absent, the diagnosis of asthma cannot often be made on the basis of wheezing only [26]. Beyond the age of 3 yrs, the diagnosis may become progressively more definitive and beyond an age of 6 yrs the National Heart, Lung and Blood Institute, National Institutes of Health, definition [27] can be accepted [26]. Indeed, wheezing illness in infants and young children are not a single disease. At least two distinct phenotypes have been described: subjects with wheezing episodes in association with viral infections, without parental atopy and personal allergic sensitisation; they have a reduced pulmonary functional residual capacity shortly after birth and they were more often exposed to tobacco during the foetal period [28, 29]. This group of patients present wheezing as the result of congenitally smaller airways and they represent the so-called "transient early wheezers", since wheezing may disappear with age [28]. However, out of the total early wheezers a percentage of ~30–40% will continue to wheeze after the first years of life. This is the second group of wheezers; the latter have good changes to present persistent wheezing to school-age. Children that present symptoms in age 0–6 yrs will reinforce the group. Their pulmonary function could be normal during the first years of life, but it will decrease by the age of 6 yrs, suggesting a deterioration induced by the persistence and severity of the disease [28]. For this group of "persistent wheezers", the recognised risk factors are: a maternal history of asthma, an atopic status characterised by the presence of eczema and/or rhinitis and early allergic sensitisation [30–34].

The two groups of wheezers are also characterised by different pathological findings: in the airways in the group of patients with lower basal pulmonary function and wheezing due to viral exacerbations there is usually prevalence of neutrophils. In children with persistent asthma associated to allergic sensitisation even in early childhood there are more eosinophils and mast cells in BAL [35, 36].

A strict correlation between early allergen exposure, the development of specific immunoglobulin (Ig)E sensitivity and progressive pulmonary deterioration has been shown [37]. Eighty-five per cent of asthmatic children have at least one positive allergen sensitivity. Therefore the exposure to allergens causes an increase in symptoms and bronchial hyperreactivity (BHR) with an increased risk of asthma exacerbations in most asthmatic children [38]. Correlation between allergen exposure and the severity of the disease has been clearly demonstrated not only for allergens of house dust mites [39], but also for cockroaches [40], grass pollens [41] and for Alternaria [42]. Reduction of allergen exposure leads to a decrease in symptoms, of BHR and rescue therapy [38]. Allergen avoidance is an essential part of the programme of asthma control; such avoidance may lead to a slowing of the progression of the "allergic march" in high-risk children and to the prevention of asthma exacerbations in sensitised asthmatic subjects [43, 44].

Asthma from childhood to adulthood

Early initiation of asthma symptoms is associated with more significant pulmonary deterioration and more persistence of symptoms into adulthood [45]. An annual decline of 1.3% in the forced expiratory volume in one second (FEV_1; per cent of predicted value) has been observed to occur in asthmatic children receiving therapy with bronchodilators only, ve 5 yrs [46]. Furthermore, asthma duration was associated with lower lung function, greater BHR, more asthma symptoms, greater use of rescue therapy, in other words with asthma severity [47]. As such, an early identification of subjects at high risk of developing persistent asthma may be necessary so that disease-controlling therapy may be initiated at an early age. Clinical indices defining the risk of asthma in young children

with recurrent wheezing has been proposed in epidemiological studies [48, 49]. A stringent index included frequent wheezing during the first 3 yrs of life and either one major risk factor (parental history 57 asthma and eczema) or two of three minor risk osinophilia, wheezing without colds, and allergic rhinitis). A less stringent index required any wheezing in the first 3 yrs plus the same combination of risk factors. Children with a positive loose index were 2.6–5.5 times and those with stringent index were 4.3-9.8-times more likely to have active asthma between the ages of 6–13 yrs than children with a negative index [48]. Using personal and family history of atopy and immune parameters a higher sensitivity was obtained in another smaller longitudinal study [49].

Other risk factors for the development of persistent asthma in school-age children are: exposure to cigarette smoke [11, 50-52], the degree of severity of the disease [53, 54], pulmonary function [55, 56] and BHR [57, 58].

Diagnosis

The clinical evaluation of a child with possible asthma requires a careful and comprehensive medical history. The most significant symptoms of asthma in children are wheezing, shortness of breath, chest tightness [25], and chronic cough [59, 60]. In a relevant number of children chronic cough represents the major symptom of the disease. Sometimes it is the primary or sole presenting manifestation of asthma in paediatric patients [59, 60]. Cough is characteristic of asthma in children when it is induced by upper respiratory tract infections, cold air, exercise or along with nocturnal exacerbations [61].

Exercise-induced bronchospasm (EIB) can be found in 70-80°/) of untreated asthmatic schoolchildren [62] and it represents a cause of limitation of normal activities at this age of life [63]. It is important for child's self-esteem to participate in play and sports therefore, mastering EIB is considered to be an essential part of the successful management of asthma [64]. Standardised exercise test represents a specific diagnostic tool for the evaluation of exercise-induced bronchoconstriction and it can be regarded as a means of monitoring asthma and BHR [65].

However, even in children, the diagnosis requires demonstration of the reversibility of bronchial obstruction, as observed after the administration of an inhaled pVagonist. A 15% increase in FEV_1 or 20% in peak expiratory flow (PEF) can be considered to be demonstrative of a reversible airway obstruction and diagnostic of asthma [66, 67]. For this reason all children suspected of having asthma should have a spirometry performed for assessment of airway function [68].

Since cough may be a symptom suggestive, but not specific for bronchial asthma [69-72], sometimes the administration of anti-asthmatic therapy can represent an *ex-adiuvantibus* criterium to confirm or exclude the diagnosis [73].

Since allergy appears to be an important factor in determining asthma in childhood, the diagnosis may be supported by a careful evaluation of parental history of atopy and asthma and by the presence of signs and symptoms of atopy in the subject [67]. The actual presence or a positive past history of eczema and/or rhinitis apart from colds should be investigated. In the management of asthmatic children the investigation for allergic sensitisation should be performed by more sensitive and economical skin-prick tests (SPT), or by evaluation of the serum-specific IgE by immunoassays (radio-allergosorbent test (RAST)) [72, 74]. SPT and RAST are entirely interchangeable and neither will replace the other [75]. IgE levels seem to correlate closely with inhaled challenge studies in cat and house dust mite sensitive children; specific IgE are expression

of allergen sensitisation over time and evaluate reactions of allergen exposure/avoidance [38, 75]. Finally, both methods may be useful to predict in the "allergic march" which food allergies are resolving and which inhalant sensitisations are developing [44].

Asthma diagnosis is particularly difficult in the younger children, where wheezing is not a specific marker of asthma and evaluation of pulmonary function is not easy and available to all clinical settings. It has been recently shown that the flow/volume loop evaluation by pneumotachography may yield considerable diagnostic information in young children presenting with persistent wheezing [76]. Other causes of wheezing are shown in table 1 divided according to their incidence. In particular cases, the differential diagnosis must exclude other causes of wheezing, such as cystic fibrosis, foreign body inhalation, anatomical abnormalities and the gastro-oesophageal reflux (GER). Cystic fibrosis has been diagnosed with a high incidence in children who were admitted to hospital with solely persistent wheezing and who did not necessarily present failure to thrive [77]. GER is more common in infants and younger children. The association between GER and asthma is well documented [78]; nocturnal cough is one of the peculiar manifestations of the pathological reflux and often requires a further investigation by 24-h pH probe, which is the most sensitive method for the diagnosis.

In a recent Paediatric Consensus Statement, chronic asthma in childhood has been divided into three different clinical patterns: infrequent episodic, frequent episodic and persistent asthma [26]. Infrequent episodic asthma (75% of asthmatic children) occurs less ffian once every 4-6 weeks without interval symptoms and normal lung function between episodes. Usually it does not require preventive therapy. Frequent episodic asthma (20% of asthmatic children) is associated with more frequent attacks and wheezing on moderate exercise. Symptoms occur less frequently than once a week and there is normal or near normal lung function between episodes. Prophylactic treatment is usually necessary. Persistent asthma (5% of asthmatic children) presents with frequent acute episodes, wheezing with poor exercise and interval symptoms with night wakening or chest tightness in the morning. Since there is always evidence of airflow limitation between episodes, prophylactic treatment is mandatory [26].

Lung function mea monitoring asthmatic children: both for recovery from an acute asthmatic episode and for guide optimal management of long-term disease. Some older children with frequent symptoms who are not well controlled can have poor perception of deterioration and may benefit from peak-flow monitoring at home [79]. Monitoring of infrequent episodic asthma requires a careful clinical history and examination with spirometry once or twice a year. In cases of frequent episodic asthma short periods of peak-flow measurements in addition to interval spirometry will suggest the therapy. In more severe disease with evidence of reduced perception of airflow limitation peak-flow monitoring should be recommended [26, 79]. It is noteworthy that there is no correlation between pulmonary function and symptoms [80, 81] and that children have a poorer perception of bronchial obstruction than adults, particularly in severe asthma [82] and long-lasting disease [83]. These subjects are at high risk of severe asthma attacks and required strict monitoring by spirometry and home peak flow [84].

Table 1. – Causes of wheezing in infants and children

Common	Uncommon	Rare
Asthma	Bronchosdisplasia	Vascular anomalies
Bronchiolitis	Foreign body	Tracheobronchial anomalies
Recurrent	Cystic fibrosis	Mediastinal masses
Aspiration		

Treatment

Although the therapeutic armamentarium may be similar in adult and paediatric patients, some peculiarity of the first years of life require specific care in the choice and application of treatment for asthma. The international guidelines prepared by the Expert Panel of the National Asthma Education and Prevention Programme convened by the National Heart, Lung and Blood Diseases, National Institutes Of Health, Bethesda, USA [27, 85] and the British Guidelines on Asthma Management [26, 86] give the indications for the long-term treatment of asthma in children aged <5 yrs.

Figure 2 is a flow chart showing the treatment of asthma in children under and over the age of 5 yrs according to the indications of the international guidelines [26, 27, 85, 86].

Cromones

Long-term control treatment starts with either low-dose inhaled steroids or cromones, *i.e.* cromolyn or nedocromil. The main reason for including a trial with cromolyn or nedocromil at the initial phase of a daily anti-inflammatory treatment in asthmatic children is the safety profile of these drugs [85]. In a recent review by TASCHE *et al.* [87] it was concluded that from the results of placebo-controlled studies in childhood asthma "there is insufficient evidence that sodium cromoglycate (SCG) has a beneficial effect as maintenance treatment in children with asthma" [87]. The methods and conclusions of the review by TASCHE *et al.* [87] have been criticised by an international panel of experts who concluded in favour of a beneficial effect of SCG in the treatment of children with asthma [88].

Corticostevoids

At present, inhaled corticosteroids (ICS) represent the most effective drugs for the control of chronic asthma [89]. They have been demonstrated to be effective in increasing lung function, reducing BHR, including EIB [90], allowing prolonged symptom-free periods [91], preventing exacerbations and hospitalisation in asthmatic children [92].

In children with moderate-to-severe asthma, low doses of inhaled steroids (budesonide or fluticasone propionate 100 $\mu g \cdot day^{-1}$) can achieve an increase in PEF values and control of symptoms after 1–2 weeks of treatment [93-95], whereas the maximum effect on bronchial responsiveness can be observed after 1–3 months of administration of higher doses [96, 97]. Only a minority of patients have demonstrated refractoriness to the treatment with inhaled steroids [98].

A critical, unresolved issue in the positioning of inhaled steroids in the treatment of asthmatic children is the question as to whether or not the early introduction of this class of drugs can be advantageous. A study performed in a group of 28 children with moderate-persistent asthma treated in a double-blind manner either with budesonide (0.4 $mg \cdot day^{-1}$) or placebo for 8 weeks and for further 20 weeks with open-label budesonide showed total lung capacity decreased along with budesonide treatment in both groups suggesting that early introduction of an inhaled corticosteroid may be useful in the prevention of asthma-related remodelling of the lung and thoracic cage [99].

These results have been confirmed more recently in a group of 31 mild asthmatics showing that inhaled steroids remarkably blunt the occurrence of gas trapping during induced bronchoconstriction in mild bronchial asthma, possibly due to their effects on airway wall remodelling [100].

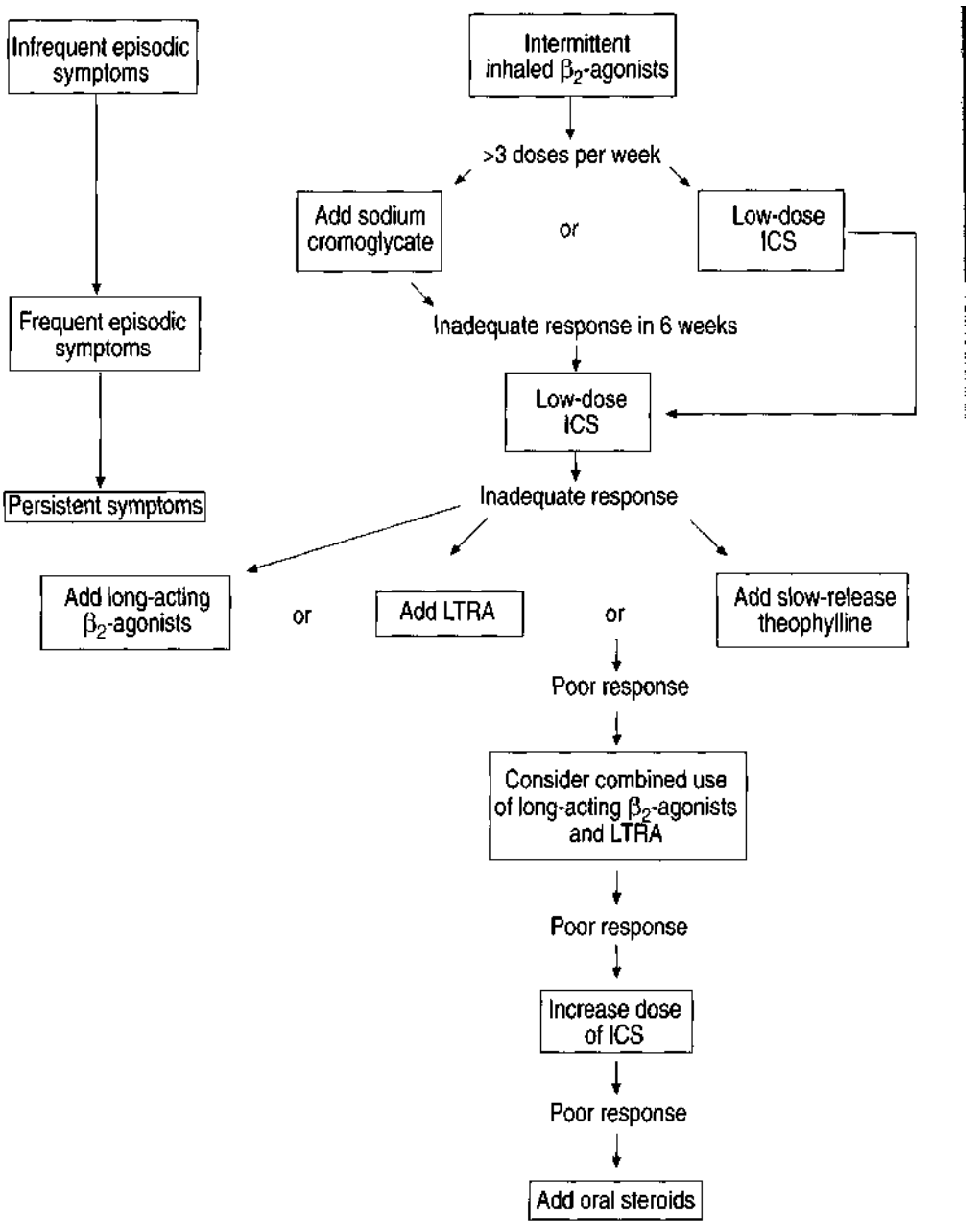

Fig. 2. Long-term treatment of asthma. ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonists. Modified from [26].

Bronchial biopsy studies have demonstrated that airway remodelling is present even before the first symptoms appear [101] and recently, there has been growing interest in the possible benefits of using ICS at an earlier stage in asthma, as soon as the condition is diagnosed [102]. The concept of early intervention is supported by the recognition that airway inflammation is common to all grades of asthma, including early and mild

disease. Observations from recent studies suggest that corticosteroid treatment in asthma can reduce the lamina reticular thickness by modulation of insulin-like growth factor (IGF)-I expression with consequent inhibition of the airway infiltration by inflammatory cells, and therefore may help to prevent remodelling of the airways [103]. In addition, treatment with ICS have been demonstrated to be able to reduced airway wall vascularity during airway remodelling [104]. Nevertheless, long-term treatment with corticosteroids may result in a significant suppression of the hypothalamic pituitary-adrenal (HPA) axis, which is a systemic effect that can be monitored. Corticosteroid derivatives mimic the natural corticosteroid hormone, cortisol, mainly through interactions with the glucocorticoid receptor, and as such may interfere with the activity of the HPA axis, which largely determines the rate of cortisol production [105]. Treatment with corticosteroids can reduce adrenal corticotropic hormone (ACTH) production. Despite numerous studies of HPA axis function in children treated with ICS, it is unclear which test best detects clinically relevant HPA axis suppression [106]. In a recent review on efficacy and safety of budesonide in childhood asthma it was concluded that dose-dependent alterations in sensitive measures of HPA function were evident but the clinical significance of these changes is unclear [107]. Although there is considerable inter-individual variability in adrenal suppression at a given dose of ICS, in general, the effects on HPA axis suppression are minimal <800 $\mu g \cdot day^{-1}$ in adults and <400 $\mu g \cdot day^{-1}$ in children [108]. In order to improve the control of asthmatic disease reducing the potential risk of side-effects, steroid sparing options have been proposed and are currently under evaluation.

Long-acting fi-agonists

The addition of long-acting β_2-agonist *or* leukotriene modifier drugs appears to be the most promising options for the purpose of achieving better asthma control in particular in those patients who cannot be controlled even at a high dose of inhaled steroids. Long-acting pVagonists, such as salmeterol and formoterol have been demonstrated to provide prolonged bronchodilation, reduced day and night-time symptoms and improved quality of sleep and a reduction in the requirement for short-acting pVagonists as relief medication. When added to ICS a greater improvement in lung function than when using an increased steroid dose alone is produced [109]. In a study by BYRNES *et a/.* [110] the effects of the addition of salmeterol in asthmatic children who were symptomatic despite treatment with ICS at a dose of at least 400 $\mu g \cdot day^{-1}$ over a 1 month period were compared. The authors concluded that in moderate-to-severe asthmatic children on ICS, salmeterol was significantly more effective at increasing the morning PEF rate over a 1-month period compared to salbutamol. Recently, the combination of long-acting β_2-agonists with inhaled steroids, namely formoterol with budesonide and salmeterol with fluticasone, has become available. The combination of salmeterol and fluticasone has been demonstrated to be safe and effective in a study of a large group of asthmatic children who were treated for 12 weeks [111].

Salmeterol and formoterol provided a prolonged protection against EIB. In a study in asthmatic children, a single dose of 50 ug salmeterol caused a >90% inhibition of EIB, after 1, 5 and 9 h [112]. Formoterol has been demonstrated to provide almost complete inhibition of EIB at 3 h and >60% inhibition of EIB at 12 h in children at a dose of 12 ug [113]. Despite the variation in the duration of protective effect in different studies, it can be suggested that a long-acting P-agonist given in the morning will offer some protection throughout the day against symptoms provoked by sport and other physical activity [114]. Prolonged use of a long-acting β-agonist is accompanied by a reduction in the duration of inhibition of EIB. In a study of a group of young adolescents aged 12 16 yrs

with asthma salmeterol was administered regularly for 28 days [115]. In this study on the first day of treatment there was effective inhibition of EIB with salmeterol at 1 and 9 h, but, after 28 days of treatment, while the protective effect of salmeterol at 1 h persisted, it was lost at 9 h [115]. All the patients were taking beclomethasone throughout the study, and therefore concomitant treatment with an inhaled steroid did not prevent the development of tolerance [115].

Leukotviene receptor antagonists

In contrast to long-acting pVagonists, there is no evidence that leukotriene receptor antagonists (LTRA) wane their effect when they are taken regularly. LTRA can be administered orally and they have been proven to be beneficial in asthma treatment.

In a study performed in a group of 336 asthmatic children who were treated with montelukast (5 mg once daily) a lower number of patients with asthma and a lower percentage of days free of symptoms have been reported [116]. In an extension of this study, with an open-label design during which children received either montelukast or an ICS for periods of up to 1.4 yrs, it was shown that the improvement in percentage of predicted FEV_1 values with montelukast was maintained and the change from baseline was similar to that in the ICS group, thus suggesting that tolerance does not develop to the effect of montelukast [117].

A more recent trial with oral montelukast (4-mg chewable tablet) administered once daily has suggested that this drug is effective in asthmatic children aged 2–5 yrs and is generally well-tolerated without clinically important adverse effects [118]. Thus, on the basis of studies showing the benefit of montelukast to younger children with persistent asthma, in the USA, LTRA have been approved for use in children, with montelukast starting from the age of 2 yrs and zafirlukast from 7 yrs. Since the formation of cysteinyl leukotrienes in the airways of asthmatic patients is not suppressed by corticosteroids, it is not unexpected that LTRA can exert complementary effects when given in association with ICS. SIMONS *et al.* [119] demonstrated that montelukast, 5 mg, added to budesonide can significantly improve asthma control in children, with a small additive effect on lung function and a clinically relevant decrease in asthma exacerbation days.

There has been no study comparing the effectiveness of inhaled salmeterol powder *versus* oral montelukast treatment in children with persistent asthma who remained symptomatic while receiving ICS.

Montelukast has been shown to be protective against exercise-induced asthma in children. In a multicentre study in children aged 6–14 yrs, montelukast was effective in protecting against the postexercise fall in FEV_1 at 20-24 h after administration [120]. In an adult study the protection against EIB by montelukast was consistent over 12 weeks, without development of tolerance [121]. The long-lasting protection against EIB and the absence of tolerance can be of particular interest in children, since they are active at frequent and irregular intervals throughout the day [122].

At present LTRA should be considered as add-on therapy to ICS for complementary therapy in those patients who are not satisfactorily controlled by low-to-moderate doses of ICS or who are poorly adherent to this therapy. In addition they should be considered as an interesting therapeutic opportunity to allow tapering of corticosteroid dose and reduction in β-agonist use.

The results of the studies on LTRA, showing efficacy, anti-inflammatory activity and safety for this class of drug, suggest a potentially important role in the treatment of asthmatic children [123]. However, despite the wide use of LTRAs for first-line prophylaxis in the USA and its recommendation in some international therapeutic guidelines [27], this approach has not yet been fully accepted in Europe [122].

Summary

Asthma is the most frequent chronic disease in childhood, with increasing levels of morbidity in most of the countries worldwide.
Wheezing can affect up to 40% of children aged <5–6 yrs, in most of which it will resolve spontaneously during the school-age. Asthma will develop in ~30–40% of the total wheezing children; in these subjects airway inflammation may occur very early in the natural history of the disease, developing early inflammatory damage of epithelium and airway remodelling.
A strict correlation between early allergen exposure, development of specific immunoglobulin E sensitivity and progressive pulmonary deterioration has been shown and the exposure to allergens causes an increase in symptoms and bronchial hyperreativity with an increased risk of asthma exacerbations in most of the asthmatic children.
The therapeutic armamentarium can mostly be the same in adult and paediatric patients, but some peculiarity of the first years of life require specific care in the choice and application of the treatment of asthma.

Keywords: Asthma, children, inhaled corticosteroid, leukotriene antagonists, wheezing.

References

1. Boner AL, Martinati LC. Diagnosis of asthma in children and adolescents. *Eur Respir Rev* 1997; 7: 3-7.
2. Myers TR. Pediatric asthma epidemiology: incidence, morbidity, and mortality. *Respir Cure Clin N Am* 2000; 6: 1-14.
3. Ronchetti R, Villa MP, Barreto M, *et al.* Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. *Eur Respir J* 2001; 17: 881 886.
4. Peat JK, Haby M, Spikier J, *et a/.* Has the prevalence of asthma increased? Results from two population study conducted at a nine year interval in Busselton, Western Australia. *BMJ* 1992; 305: 1326–1329.
5. Shaw RA, Crahe J, O'Donell TV. Increasing asthma prevalence in a rural New Zealand adolescent population: 1975-1989. *Arch Dis Child* 1990; 65: 1319–1323.
6. Gerden PJ, Mullaly DI, Evans R III. National survey of prevalence of asthma among children in the United States, 1976–1989. *Pediatrics* 1988; 81: 1-7.
7. Perdizet S, Neukirch F, Cooreman J. Prevalence of asthma in adolescence in various parts of France and its relationship to respiratory allergy manifestations. *Chest* 1987; 91: 104S–106S.
8. Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995; 25: 815-819.
9. Matricardi PM, Bonini S. High microbial turnover rate preventing atopy: a solution to inconsistencies impinging on the Hygiene hypothesis? *Clin Exp Allergy* 2000; 30: 1506-1510.
10. Valacer DJ. Childhood asthma. Causes, epidemiological factors and complications. *Drugs* 2000; 59: Suppl.l, 1-8.
11. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133–138.
12. Brooke AM, Lambert PC, Burton PR, *et al.* The natural history of respiratory symptoms in preschool children. *Am J Respir Crit Care Med* 1995; 152: 1872-1878.

13. Silverman M, Wilson N. Wheezing phenotypes in childhood. *Thorax* 1997; 52: 936–937.
14. Warner JO. Unmet needs in treatment of asthmatic children and adolescents. *Clin Exp Allergy* 2000; 30: Suppl.1, 70–72.
15. Ferguson AC. Wong FWM. Bronchial hyperresponsiveness in asthmatic children. Correlation with macrophages and eosinophils in bronchoalveolar lavage fluid. *Chest* 1989; 96: 988–991.
16. Ferguson AC, Whitelaw M, Brown H. Correlation of bronchial eosinophil and mast cell activation with bronchial hyperresponsiveness in children with asthma. *J Allergy Clin Immunol* 1992; 90: 609–613.
17. Twaddell SH, Gibson PG, Carty K, Woolley KL, Henry RL. Assessment of airway inflammation in children with acute asthma using induced sputum. *Eur Respir J* 1996; 9: 2104–2108.
18. Nelson BV, Sears S, Woods J, *et al.* Expired nitric oxide as a marker for childhood asthma. *J Pediatr* 1997; 130: 423-427.
19. Artlich A, Hagenah J, Jonas S, Ahrens P, Gortner L. Exhaled nitric oxide in childhood asthma. *Eur J Pediatr* 1996; 155: 698-701.
20. Çokuğraş H, Akckaya N, Seckin I, Camcioğlu Y, Sarimurat N, Aksoy F. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. *Thorax* 2001; 56: 25-29.
21. Schneider RC, Zapol WM, Carvatho AC. Platelet consumption and sequestration in severe acute respiratory failure. *Am Rev Respir Dis* 1980; 122: 445-449.
22. Gibson PG, Simpson JL, Saltos N. Heterogeneity of airway inflammation in persistent asthma: evidence of neutrophilic inflammation and increased sputum interleukin-8. *Chest* 2001; 119: 1329-1336.
23. Payne DNR, Wilson NM, James A, Hables H, Agrafioti C, Bush A. Evidence for different subgroups of difficult asthma in children. *Thorax* 2001; 56: 345-350.
24. Baraldi E, Zanconato S. The labyrinth of asthma phenotypes and exhaled NO. *Thorax* 2001; 56: 333-335.
25. Martinati LC, Boner AL. Clinical diagnosis of wheezing in early; childhood. *Allergy* 1995; 50: 701-710.
26. Warner JO, Naspitz CK, Cropp GJ. Third International Pediatric Consensus Statement on the Management of Childhood Asthma. *Pediatric Pulmonology* 1998; 25: 1-17.
27. Global Initiative for Asthma. Pocket guide for asthma management and prevention. NIH publication n. 96-3659B. Bethesda, MD, National Institutes of Health, 1998.
28. Martinez FD, Morgan WJ, Wright AL, *et al.* Diminished lung function as predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319: 1112–1117.
29. Lodrup Carlsen KC, Carlsen KH, Nafstad P, Bakketeig L. Perinatal risk factors for recurrent wheeze in early life. *Pediatr Allergy Immunol* 1999; 94: 750–755.
30. Clarke JR, Reese A, Silvennan M. Bronchial responsiveness and lung function in infants with lower respiratory tract illness over the first 6 month of life. *Arch Dis Child* 1992; 67: 1454-1458.
31. Halonen M, Stern D, Taussig LM, *et al.* The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illness and eczema in infants. *Am Rev Respir Dis* 1992; 146: 866–870.
32. Martinez FD, Morgan WJ, Wright AL, *et al.* Diminished lung function as predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319: 11 12–1117.
33. Stevenson EC, Turner G, Heaney LG, *et al.* Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997; 27: 1027–1035.
34. Marguet C, Jouen-Boedes F, Dean TP, Warner JO. Bronchoalveolar cell profiles in children with asthma, chronic cough, or cystic fibrosis. *Am J Respir Crit Care Med* 1999; 159: 1533-1540.
35. Speight ANP, Lee DA. Hey EN. Underdiagnosis and undertreatment *of* asthma in childhood. *BMJ (Clin Res)* 1983; 286: 1253–1256.
36. Silverman M. Out *of* the months of babies and sucklings lesson from early childhood asthma. *Thorax* 1993; 48: 1200–1204.

37. Boner AL, Bodini A, Piacentini GL. Environmental allergens and childhood asthma. *Clin Exp Allergy* 1998; 28: Suppl. 5, 76–81.
38. Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1994; 149: 1442–1446.
39. Peat JK, Tovey E, Toelle BG, *et al.* House dust mite allergens a major risk factor for childhood asthma in Australia. *Am J Resp Crit Care Med* 1996; 153: 141-146.
40. Rosenstreich DL, Eggleston P, Kattan M, *et al.* The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997; 336: 1356-1363.
41. Pollart SM, Reid M, Brown M, *et al.* Epidemiology of emergency room asthma in Northern California: association with IgE antibody to rye grass pollen. *J Allergy Clin Immunol* 1988; 82: 224-230.
42. O'Hallaren MT, Yunginger JW, Offord KP, *et al.* Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *New Engl J Med* 1991; 324: 359-363.
43. Warner JA. Controlling indoor allergens. *Pediatr Allergy Immunol* 2000; 11: 208-219.
44. Wahn U. What drives the allergic march? *Allergy* 2000; 55: 591-599.
45. Grol MH, Gerritsen J, Jonk SM, *et al.* Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. *Am J Respir Crit Care Med* 1999; 160: 1830–1837.
46. Agertoft L, Pedersen S. Effects of long term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 88: 373-381.
47. Haatela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S. Effects of reducing or discontinuing budesonide in patients with mild asthma. TV *Engl J Med* 1994; 331: 700-705.
48. 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: 1402 1406.
49. Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999; 160: 1473-1480.
50. Sears MR. Evolution of asthma through childhood. *Clin Exp Allergy* 1998; 28: Suppl. 5, 82-89.
51. Lundback B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998; 28: Suppl. 2, 3-10.
52. Halken S. Environmental causes of asthma in children. *Pediatr Allergy Immunol* 1994; 5: Suppl. 1, 57-60.
53. Blair H. Natural history of childhood asthma. 20-year follow-up. *Arch Dis Child* 1977; 52: 613-619.
54. Tuchinda M. Childhood asthma in Thailand. *Act a Paediatr Jap* 1990; 32: 169–172.
55. Kelly WJW, Hudson I, Raven J, Phelan PD, Pain MCF, Olinsky A. Childhood asthma and adult lung function. *Am Rev Respir Dis* 1988; 138: 26-30.
56. Gerritsen J, Koëter GH, Postma DS, Schouten JP, Knol K. Prognosis of asthma from children to adulthood. *Am Rev Respir Dis* 1989; 140: 1325–1330.
57. Roorda RJ, Gerritsen J, van Aalderen WMC, Schouten JP, Veltman JC, Weiss ST. Risk factors for the persistence of respiratory symptoms in childhood asthma. *Am Rev Respir Dis* 1993; 148: 1490-1495.
58. Gerritsen J, Koëter GH, de Monchy JGR, van Lookeren Campagne JG, Knol K. Change in airway responsiveness to inhaled house dust from childhood to adulthood. *J Allergy Clin Immunol* 1990; 85: 1083-1089.
59. Hannaway PJ, Hopper DK. Cough variant asthma in children. *JAMA* 1982; 247: 206–208.
60. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979; 300: 633-637.
61. Li JTC, O'Connell EJ. Clinical evaluation of asthma. *Ann Allergy Asthma Immunol* 1996; 76: 1-14.
62. Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise-induced asthma. *Thorax* 1985; 40: 481–487.

63. Lenney W, Well NEJ, O'Neill BA. The burden of paediatric asthma. *Eur Respir Rev* 1994; 4: 49-62.
64. Carlsen KH, Engh G, Mork M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000; 94: 750–755.
65. American Thoracic Society. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Mecl* 2000; 161: 309-329.
66. McKenzie S. Clinical features and their assessment. *In:* Silverman M, ed. Childhood asthma and other wheezing disorders. Chapman & Hall Medical 1995; pp. 175–200.
67. Motala C, Kling S, Gie R, *et al.* Guideline for the management of chronic asthma in children - 2000 update. Allergy Society of South Africa Working Group. *S Afr Mecl J* 2000; 90: 524-528.
68. National Asthma Education Program. Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. U.S. Department of Health and Human Services. Public Health Service, National Institutes of Health. Publication No. 91-3042, August 1991.
69. McKanzie SA. Cough but is it asthma? *Arch Dis Child* 1994; 70: 1-2.
70. Schidlow DC. Cough in children. *J Asthma* 1996; 33: 81–87.
71. Wright AL, Holberg CJ, Wayne J, *et a/.* Recurrent cough in childhood and its relation to asthma. *Am J Respir Crit Care Mecl* 1996; 153: 1259-1265.
72. Sear M, Wensley D. Chronic cough and wheeze in children: do they all have asthma? *Eur Respir J* 1997; 10: 342-345.
73. Warner JO, Neijens HJ, Laudau LI, *et al.* Asthma: a follow-up statment from an international paediatric consensus group. *Arch Dis Child* 1992; 67: 240-248.
74. Menardo JL, Bousquest J, Rodiere M. Skin test reactivity in infancy. *J Allergy Clin Immunol* 1985; 75: 646-651.
75. Yunginger JW, Ahlstedt S, Eggleston PA, *et al.* Quantitative IgE antibody assays in allergic diseases. *J Allergy Clin Immunol* 2000; 105: 1077–1084.
76. Filippone M, Name S, Pettenazzo A, Zacchello F, Baraldi E. Functional approach to infants and young children with noisy breathing. *Am J Respir Crit Care Med* 2000; 162: 1795-1800.
77. Kerem E, Reisman J, Corey M, Bentur L, Canny G, Levison H. Wheezing in infants with cystic fibrosis: clinical course, pulmonary function, and survival analysis. *Pediatrics* 1992; 90: 703-706.
78. Faubion WA, Zein NN. Gastroesophageal reflux in infants and children. *Mayo Clin Proc* 1998; 73: 166-173.
79. Sly PD. Peak expiratory flow monitoring in pediatric asthma: is there a role? *J Asthma* 1996; 33: 277-287.
80. McFadden ER, Kiser R, DeGroot WJ. Acute bronchial asthma. Relations between clinical and physiologic asthma. *N Engl J Med* 1973; 288: 221–225.
81. Isles AF, Robertson CF. Treatment of asthma in children and adolescents: the need of a different approach. *Med J Aust* 1993; 158: 761-763.
82. Bijl-Hofland ID, Cloosterman SGM, Folgering HTM, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. *Thorax* 1999; 54: 15–19.
83. Santanello NC, Davies G, Galant SP, *et al.* Validation of an asthma symptom diary for interventional studies. *Arch Dis Child* 1999; 80: 414–420.
84. Stableforth DE. Asthma mortality and physician competence. *J Allergy Clin Immunol* 1987; 80: 463-466.
85. Guidelines for the diagnosis and management of asthma. National Asthma Education Program. Expert Panel Report II. Bethesda, MD, National Heart, Lung, and Blood Institute/National Institute of Health, Publication no. 97–4051; 1997.
86. The British Guidelines on Asthma Management. *Thorax* 1997; 52: S1–S22.
87. Tasche MJA, Uijen JHJM, Bernsen RMD, *et al.* Inhaled sodium cromoglycate (SCG) as maintenance therapy in children with asthma: a systematic review. *Thorax* 2000; 55: 913–920.
88. Edwars A, Holgate S, Howell J, Warner J, *et al.* Sodium cromoglycate in childhood asthma. *Thorax* 2001; 56: 331-332.

89. De Jongste JC. Prophylactic drugs in asthma: their use and abuse. *Bailliere's Clinical Paediatrics* 1995; 3: 379–398.
90. Hofstra WB, Neijens HJ, Duiverman EJ, *et al.* Dose-response over time to inhaled fluticasone propionate treatment of exercise- and methacholine-induced bronchoconstriction in children with asthma. *Pediatr Pulmonol* 2000; 29: 415–423.
91. 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.
92. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997; 277: 887–891.
93. Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. *J Allergy Clin Immunol* 1995; 95: 29–33.
94. Jonasson G, Carlsen KH, Blomqvist P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids. *Eur Respir J* 1998; 12: 1099–1104.
95. Katz Y, Lebas FX, Medley HV, Robson R. Fluticasone propionate 50 micrograms BID versus 100 micrograms BID in the treatment of children with persistent asthma. Fluticasone Propionate Study Group. *Clin Ther* 1998; 20: 424–437.
96. Shapiro GG. Childhood asthma: update. *Pediatr Rev* 1992; 13: 403-412.
97. Henriksen JM. Effect of inhalation of corticosteroids on exercise induced asthma: randomized doubled blind crossover study of budesonide in asthmatic children. *BMJ (Clin Res Ed)* 1985; 291: 248-249.
98. Cypcar D, Busse WW. Steroid-resistant asthma. *J Allergy Clin Immunol* 1993; 92: 362-372.
99. Sekerel BE, Tuncer A, Saraclar Y, Adalioglu G. Inhaled budesonide reduces lung hyperinflation in children with asthma. *Aeta Paediatr* 1997; 86: 932-936.
100. Corsico A, Pellegrino R, Zoia MC, Barbano L, Brusasco V, Cerveri I. Effects of inhaled steroids on methacholine-induced bronchoconstriction and gas trapping in mild asthma. *Eur Respir J* 2000; 15: 687-692.
101. Warner JO. Unmet needs in the treatment of asthmatic children and adolescents. *Clin E.xp Allergy* 2000; 30: Suppl. 1, 70-72.
102. Redington AE. Step one for asthma treatment: Beta2-agonists or inhaled corticosteroids? *Drugs* 2001; 61: 1231-1238.
103. Hoshino M, Nakamura Y, Sim JJ, *et al.* Inhaled corticosteroid reduced lamina reticularis of the basement membrane by modulation of insulin-like growth factor (IGF)-I expression in bronchial asthma. *Clin Exp Allergy* 1998; 28: 568-577.
104. Hoshino M, Takahashi M, Takai Y, Sim J, Aoike N. Inhaled corticosteroids decrease vascularity of the bronchial mucosa in patients with asthma. *Clin Exp Allergy* 2001; 31: 722-730.
105. Orth DN, Kovacs WJ. The adrenal cortex. *In*: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. Williams textbook of endocrinology. Philadelphia, WB Saunders; 1998; pp. 517–664.
106. Brown PH, Blundell G, Greening AP, Crompton GK. Screening for hypothalamo-pituitary-adrenal axis suppression in asthmatics taking high dose inhaled corticosteroids. *Respir Med* 1991; 85: 511–516.
107. Adams N, Bestall J, Jones PW. Budesonide at different doses for chronic asthma (Cochrane Review). Cochrane Database Syst Rev 2001;4:CD003271.
108. Boner AL. Effects of intranasal corticosteroids on the hypothalamic- pituitary-adrenal axis in children. *J Allergy Clin Immunol* 2001; 108: Suppl. 1, S32-S39.
109. Sears MR. The evolution of beta2-agonists. *Respir Med* 2001;95: Suppl. B, S2-S6.
110. Byrnes C, Shrewsbury S, Barnes PJ, Bush A. Salmeterol in paediatric asthma. *Thorax* 2000; 55: 780-784.
111. Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/ fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with ashtma. *Pediatr Pulmonol* 2000; 30: 97-105.

112. Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. *Arch Di.s Child* 1992; 67: 1014–1017.
113. Boner AL, Vallone G, Chiesa M, Spezia E, Fambri L, Sette L. Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children. *Am J Respir Crit Care Med* 1994; 149: 935–939.
114. Price JF. Choices of therapy for exercise-induced asthma in children. *Allergy* 2001; 56: Suppl. 66, 12–17.
115. Simons FE, Gerstner TV, Cheang MS. Tolerance to the protective effect of salmeterol in adolescents with execise induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997; 99: 655–659.
116. Knorr B, Matz J, Bernstein JA, *et al.* Montelukast for chronic asthma in 6– to 14-year old children. A randomized, double-blind trial. *JAMA* 1998; 279: 1181–1186.
117. Knorr B, Noonan G, McBurney J, Shingo S, Nguyen HH, Reiss TF. Evaluation of the long-term effect of montelukast in adult (> 15 years) and pediatric (6- to 14-years) patients (abstract). *Eur Respir J* 1999; 14: Suppl. 30, 290s.
118. Knorr B, Franchi LM, Bisgaard H. *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001; 108: E48.
119. Simons FE, Villa JR, Lee BW, *et al.* Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001; 138: 694-698.
120. Kemp JP, Dockhorn RJ, Shapiro GG, *et al.* Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; 133: 424-428.
121. Leff JA, Busse WW, Pearlman D, *Bronsky* EA, Kemp J, Hendeles L. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl JMed* 1998; 339: 147-152.
122. Warner JO. The role of leukotriene receptor antagonists in the treatment of chronic asthma in childhood. *Allergy* 2001; 56: Suppl. 66, 22-29.
123. Bisgaard H. Leukotriene *modifiers in pediatric asthma management. Pediatrics 2001; 107:381–390.*