

Pharmaceutical treatment strategies for childhood asthma

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Purpose of review

Although great improvement has been obtained in quality of life and mastering of illness by asthmatic children over recent decades, controversies still exist related to asthma treatment. The objective of the present article is to discuss such controversies.

Recent findings

Results from recent publications related to childhood asthma treatment question existing dogmas. Important for prescribing correct treatment to children is correct diagnosis. Phenotypes of childhood asthma related to treatment decisions are discussed. Early use of inhaled steroids in young children is still debated as well as the preference of inhaled long-acting β_2 -agonists versus leukotriene receptor antagonists as add on to inhaled steroids. When present, both allergic rhinitis and asthma should be treated to obtain improved control. Also as regards the treatment of exercise-induced asthma in children, new results concerning use of leukotriene receptor antagonists is discussed as well as the acute treatment in infants with bronchial obstruction.

Summary

There are still several controversies regarding treatment of the asthmatic child. New studies designed specifically for children are needed to solve these questions. One cannot rely on studies performed in adults for treatment in children. New studies designed for childhood asthma are needed to solve these controversies.

Keywords

acute asthma, asthma, asthma phenotypes, children, exercise induced asthma, pharmacological treatment

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Introduction

As reported from recent International Study of Asthma and Allergies in Childhood (ISAAC) trials, the allergic airways diseases are among the most common chronic disorders of childhood [1,2], in particular asthma with a reported dramatic increase in lifetime prevalence over the last 50 years. In Norwegian published studies childhood asthma prevalence increased from 0.4% in 1948 [3] to 12% in the 1990s [4] and further to over 20% in the most recent report from a birth cohort study [5]. Even if some reports suggest that the prevalence of childhood asthma starts to level out [6,7] recent published studies still report an increase [5,8], and the recent ISAAC report found that asthma still increased in most places [2]. Asthma often starts early in life and especially severe asthma [9]. One early international paediatric asthma consensus report [10] was published more than 15 years ago, followed by two later updates [11,12]. Lately paediatric asthma has been included into general guidelines covering both adult and paediatric asthma such as the Nordic consensus [13], the Global Initiative for Asthma (GINA) second revision [14] and recently updated (November 2006) as well as the British guidelines [15]. The British guidelines were developed with evidence-

based recommendations (SIGN criteria) [16]. Childhood asthma has often been regarded as adult asthma in young individuals, this, to some extent, being reflected in treatment guidelines. Due to the overall perspective several specific issues relevant to paediatric asthma may not be covered fully in the general guidelines. This includes issues such as asthma in the very young child, the changing clinical presentation and different causative factors throughout childhood, and specific issues such as exercise-induced asthma (EIA). The main objective of the present article is to address controversial aspects of treating asthma and allergic airways diseases that may influence the choice of therapy.

Definition and characterization of asthma and asthma phenotypes

The latest revision of the GINA guidelines (November 2006) defines childhood asthma in three entities as originally described by Martinez *et al.* [17]:

- (1) Transient early wheezing, often outgrown in the first 3 years. This is often associated with prematurity and parental smoking.

- (2) Persistent early-onset wheezing (before age 3). These children typically have recurrent episodes of wheezing associated with acute viral respiratory infections, no evidence of atopy and, unlike children in the next category of late onset wheezing/asthma, have no family history of atopy. The symptoms normally persist through school age and are still present at age 12 years in a large proportion of children. The cause of the episode is usually respiratory syncytial virus in children below 2 years, while other viruses predominate in older preschool children.
- (3) Late-onset wheezing/asthma. These children have asthma which often persists throughout childhood and into adult life. They typically have an atopic background, often with eczema, and airway pathology is characteristic of asthma.

These three phenotypes are useful for understanding asthma and obstructive airways disease in childhood. Through their retrospective way of describing childhood asthma, however, these definitions are not useful when treating a patient early in life, because you cannot know his or her outcome. Childhood asthma entities described should be easily recognized in the daily clinical situation. Table 1 shows some clinical phenotypes of asthma that are easily recognized, but needing different approaches as regards management and therapy.

International guidelines for the treatment of paediatric asthma

All guidelines for treating paediatric asthma relate to the same therapeutic principles. Previously grading asthma

Table 1 Different clinical characteristics and phenotypes of childhood asthma

Phenotypes of childhood asthma	Description
Infantile asthma	Asthma during first year of life with at least three episodes of verified bronchial obstruction
Virus induced asthma	Asthma most frequently and mainly exacerbated by respiratory virus infections with and without allergy
Allergen driven asthma	Allergic asthma with verified allergen contact causing exacerbation or allergic airways inflammation
Persistent episodic asthma	Asthma with persisting symptoms, but with exacerbations caused by virus infections, allergen contact, exercise and others
Exercise induced asthma	Symptoms of asthma provoked by exercise May be verified by exercise testing May occur as only symptom of asthma, but also in asthma with other precipitating factors
Severe, difficult to treat asthma	Asthma not responding to ordinary treatment, including inhaled steroids

in mild, moderate and severe, then later mild and moderate intermittent and persistent [14], it is common to start with intermittent inhaled short-acting inhaled β_2 -agonists as needed for mild asthma, going on with inhaled corticosteroids with recurrent or persistent symptoms. Previously high doses of inhaled corticosteroids were common, but dose-response studies [18,19] have indicated a different dose-response relationship for local anti-inflammatory effects and systemic effects [20]. This has caused a more cautious attitude towards high doses of inhaled steroids. Recently, there has been more focus on asthma control with regard to need of asthma medication.

Reliever and controller therapy

The allergic airways diseases are recognized as inflammatory diseases. Traditionally the therapeutic alternatives have been classified as anti-inflammatory or bronchodilating/symptomatic treatment. The main anti-inflammatory agents have been inhaled corticosteroids. New drugs have been introduced, and medication used to relieve symptoms (on an as required basis) has been reintroduced for control of symptoms. In the GINA guidelines the main treatment options have been renamed reliever and controller therapy [14]. The most important drugs for the treatment of childhood bronchial asthma are still inhaled corticosteroids. Adult studies have shown that early anti-inflammatory treatment is vital to reduce airways remodelling caused by inflammatory processes [21]. This has also been maintained for childhood asthma [22]. In a recent study of bronchial biopsies in childhood asthma [23], airways remodelling was not found in any child below 3 years of age irrespective of symptoms severity or the presence of atopy. Early anti-inflammatory treatment will be discussed later, whereas use of combination therapy, consisting of inhaled steroids and long-acting β_2 -agonists (LABAs) or leukotriene receptor antagonists (LTRAs), will be discussed below.

Long acting inhaled β_2 -agonists

Through later years it has become common to add inhaled LABAs to inhaled corticosteroids to obtain optimal symptom control. This type of treatment was demonstrated as beneficial in adult asthma [24], and it became common to give fixed combinations of inhaled corticosteroids and LABAs (seretide and symbicort). This spread to paediatric asthma, even if the effect was not as well documented in children as in adults [25]. One study [26] demonstrated a positive effect on lung function of adding formoterol to inhaled steroids, but not on symptoms. Because of the convincing adult studies, not enough weight was put on conducting relevant paediatric studies on their own [27]. Later, fixed combinations of LABAs and inhaled corticosteroids were found safe in children [28], improvement was shown in lung function and symptoms with salmeterol added to inhaled steroids [29]. A recent multicentre American study [30^{••}], however, reported better effect of a

higher dose fluticasone alone than of the combination of a lower dose fluticasone with salmeterol in children with mild–moderate persistent asthma. The so-called SMART-principle, using the combination of the inhaled steroids budesonide together with the LABA with rapid onset of action, formoterol, in regular maintenance dose with extra reliever doses as needed, was recently shown to be also successful in children [31].

Several studies, however, consistently report tolerance development with regular use of inhaled β_2 -agonists, both short and long-acting [32–37], and this should induce a need for regular follow-up of these patients. In adults a meta-analysis showed increased frequency of cardiovascular side effects in patients with asthma and chronic obstructive lung disease with the use of LABAs [38]. Furthermore, the recent large-scale study on the use of LABAs was stopped due to a report of asthma-related deaths (13 deaths out of 26 000 patients mostly in inner city Afro-Americans) [39•] and followed by a meta-analysis concerning LABAs and severe asthma exacerbations [40•]. Although this meta-analysis was later criticised [41], and the findings are not relevant to children, we should be aware of possible side-effects of LABAs in the long term. This should be born in mind before starting LABAs in young children who may use these drugs over a long time period.

Leukotriene receptor antagonists

LTRAs are recommended in addition to inhaled corticosteroids as an alternative to LABAs [42]. LTRAs exhibit both bronchodilator and anti-inflammatory effects that may add to the effect of inhaled steroids. The LTRA, montelukast, reduces EIA in children [43,44•]. De Benedictis *et al.* [44•] demonstrated that tolerance did not develop to the effect of montelukast on EIA, although many patients were nonresponders. Montelukast improves symptoms both in school [45] and preschool children [46]. It is beneficial when added to inhaled steroids [42]. One study [47] compared the effect of inhaled steroids and montelukast in children, and although inhaled steroids were superior in most children with asthma, also montelukast had a good controlling effect upon childhood asthma. In one adult study montelukast and salmeterol were compared in patients not optimally controlled on inhaled steroids alone, as an add-on therapy. Both salmeterol and montelukast improved bronchial hyperresponsiveness, symptoms and peak expiratory flow rate [48]. A similar study compared inhaled steroids, combination therapy of inhaled steroids and LABA and montelukast alone in children with mild-moderate persistent asthma, and both inhaled steroids and the combination therapy were superior for asthma control than montelukast [30••]. In the recent revision of GINA guidelines (November 2006) LTRAs have been upgraded to additional treatment to inhaled

steroids at the same level as inhaled β_2 -agonists [49•]. Very recently, the Practall guidelines for paediatric asthma suggest that LTRAs may occasionally be used even as a first line alternative treatment to inhaled steroids in special patients [50].

The respiratory tract as a continuum: the relationship between allergic rhinitis and asthma

Both allergic rhinitis and asthma are parts of the so-called 'allergic march' [51], starting out with atopic eczema and food allergy with specific IgE antibodies to food allergens during the first year of life [52]. As atopic eczema and the reaction to food allergens may subside from 2 years of age, specific IgE to inhalant allergens appears, as well as symptoms of allergic rhinoconjunctivitis and asthma [52]. Several reviews [53,54] have pointed out the relationship between asthma and rhinitis, and the Allergic Rhinitis and its Impact on Asthma guidelines are based on this relationship [55]. Allergic rhinitis, especially perennial rhinitis, is a risk factor for asthma [56]. Children with asthma have increased eosinophilic inflammation in their nasal mucosa [57], and there is increased bronchial responsiveness to methacholine in patients with allergic rhinitis [58].

When treating patients with mild asthma and rhinitis in a randomized placebo controlled crossover study, nonspecific bronchial responsiveness decreased during intranasal corticosteroid therapy [59]. Furthermore, treating mild asthma and allergic rhinitis with loratadine and pseudoephedrine, improved lung function [forced expiratory volume in 1 s (FEV₁) and peak expiratory flow rate] and asthma-related quality of life [60]. Oral inhalation of budesonide (Turbuhaler; AstraZeneca, Lund, Sweden) improved the symptoms of allergic rhinitis in a randomized double-blind placebo controlled study during the birch pollen season [61]. Two large retrospective cohort studies [62,63] demonstrated decreased risk of hospital admission from acute asthma in patients with allergic rhinitis and asthma, receiving treatment for their allergic rhinitis in addition to asthma treatment. Adams and coworkers [63] found decreased risk of asthma admissions when treating coexistent asthma and rhinitis with antihistamines and intranasal steroids, the larger effect with the latter.

Thus, it is important with co-existing allergic rhinitis and asthma that neither disease should be neglected, but both treated [55].

The asthma phenotype changes with increasing age

The asthma diagnosis may be difficult in infants and young children. The symptoms and presentation of acute bronchiolitis may be similar to symptoms of asthma, and there is a relationship between acute bronchiolitis and obstructive airways diseases later in childhood [64–66].

Martinez [67] discriminates between transient early wheezers, non/atopic wheezers and IgE/associated wheeze/asthma with respect to the long-term prognosis of childhood wheeze. During early life, however, it is difficult to discriminate between the groups, and the choice of controller therapy must be guided by severity and frequency of the symptoms. It has been difficult to agree on the use of both reliever and controller therapy in young children. This is due to doubts about effectiveness of treatment as well as concerns about possible side effects [68–70].

Inhaled steroids in infants and young children

In 1986 Maayan and coworkers [71] reported a beneficial effect of nebulized beclomethasone on lung function in 15–36-week old infants with postbronchiolitic wheeze after 2 weeks. One study reported beneficial effects upon episodes of bronchial obstruction by nebulized beclomethasone dipropionate for 12 weeks in infants with three recurrent obstructive episodes after acute bronchiolitis. The beneficial effect persisted for up to 1 year [72]. Wennergren and coworkers [18] found a similar effect on recurrent wheeze in young children using nebulized budesonide, whereas in a later study [73] no difference was found using high or low dose budesonide in infants with recurrent wheeze after bronchiolitis.

Whereas in severe infantile asthma benefit has been shown [74,75], there is more debate regarding a possible benefit on children with recurrent episodic wheeze. A systematic review reported positive effect with high-dose intermittent inhaled steroids, but not with continuous low-dose inhaled steroids [76]. A recent study from Oslo [77] reported from an observational case–control study within a prospective birth cohort study. This study observed the real life effect and not a strictly selected group of patients based upon accurate inclusion criteria. In this birth cohort study children younger than 2 years of age were included when having recurrent bronchial obstruction. Some received inhaled steroids from their regular doctor. It was found that cases with recurrent bronchial obstruction had lower lung function than their healthy matched controls. Furthermore, children who were given inhaled steroids by their regular doctor already had lower lung function than the nontreated cases before the start of treatment. Inhaled steroids improved lung function until the follow-up, and the improvement correlated significantly with the duration of inhaled steroid treatment [77]. Bisgaard treated infants within their first episode of wheeze intermittently with inhaled steroids. He found no beneficial effect, but the mean duration of treatment was only 2 weeks per year, and no effect can be expected of anti-inflammatory treatment of such a duration [78].

Early anti-inflammatory treatment according to the diagnosis of asthma

Inhaled steroids presently are the most effective treatment known for childhood asthma and reduce nonspecific bronchial responsiveness [79] and EIA [80] even in low doses [81]. Agertoft and Pedersen [22] reported that children commencing inhaled steroids within 2 years of the diagnosis of asthma, had significantly higher annual growth in lung function than children starting 5 years or more after the diagnosis. Their study was uncontrolled, but the findings were confirmed by König and Schaffer [82]. The Childhood Asthma Management Program (CAMP) study compared inhaled budesonide and nedocromil with placebo in 1041 children with mild to moderate asthma, treated for 4–6 years [83]. The budesonide treated group had significantly higher baseline FEV₁ than the two other groups, but the difference disappeared after administration of bronchodilator. At study entry, however, the patients had suffered from asthma for approximately 5 years [83], thus being similar to the late treatment group of Agertoft and Pedersen [22].

In school-age studies it has repeatedly been shown that inhaled steroids are effective in controlling symptoms and improving lung function [79]. Trying to stop the use of inhaled steroids after a treatment period of 28–36 months, however, led to recurrence of symptoms, decrease in lung function and more severe bronchial responsiveness [84]. This was also shown in preschool children in two recently published studies. One of these was a randomized placebo controlled trial in 2–3-year-old children based upon an asthma severity index indicating a severe long-term prognosis [85]. The young children were treated with a low dose inhaled steroid for 2 years and then followed for one more year without active therapy [86[•]]. The other study was a nested randomized placebo controlled case–control study conducted within a birth cohort with follow-up until 5 years of age [87^{••}]. In both these studies deterioration of symptoms and reduction in lung function until the level of the placebo group occurred after stopping inhaled steroids. The authors thus concluded that inhaled steroids improved symptom control and lung function in preschool childhood asthma, but did not improve the long-term prognosis when inhaled steroids were stopped [86[•],87^{••}]. These studies confirmed that inhaled steroids do not cure asthma. The authors did not discuss the possibility, however, of a continuing airway inflammation controlled by inhaled steroids and appearing again when stopping anti-inflammatory treatment, as discussed by the authors of the Dutch papers concerning school children [84].

Inhaled steroids, growth and systemic effects

Of concern to paediatricians treating asthmatic children with inhaled corticosteroids, are possible implications for longitudinal growth. Several studies indicated an effect

on growth using low to moderate doses of inhaled steroids [88,89]. The duration of growth suppression, however, seems limited to the initial phase of treatment and of small magnitude [90]. In the long-term follow-up of the CAMP study, growth reduction by inhaled steroids was only approximately 1 cm over 4–6 years treatment compared with nedocromil and placebo [83]. In another study following up children into adult life, there were no differences between measured adult height and targeted adult height in asthmatic patients treated with inhaled steroids, healthy controls and siblings of asthmatics [91].

Another concern is possible systemic effect of high doses inhaled steroids initially reported by Priftis *et al.* [92,93], and the more recently reported cases of symptomatic hypoglycemia by Drake *et al.* [94] and others [95–97]. Pituitary–adrenal suppression was reported in preterm very low-birth weight infants treated with fluticasone [98], and Kannisto *et al.* [99] reported mild adrenal suppression in children on moderate doses of budesonide and fluticasone. These studies demonstrate the need to individually assess all children treated with inhaled steroids, and in children with need of medium to high doses a stimulation test of the adrenals should be done. In a recent paper Priftis *et al.* [100•] reported on adrenal suppression and growth inhibition in asthmatic children treated with inhaled steroids. They found that growth inhibition and adrenal suppression did not occur in the same children, and the absence of one of these did not rule out the other [100•].

Concordance (compliance) with treatment and patient/parent education

Compliance with therapy is never optimal in children [101]. With continuous therapy, compliance seems to decrease with time. After 12 weeks treatment with inhaled budesonide, compliance was 77% [102], whereas after 27 months, it was 40 and 46% for morning and evening doses, respectively [103]. Specific education programs have been designed for asthmatic children and their parents [104] to encourage self-management and improve mastering of illness.

Treatment of exercise-induced asthma and physical exercise and training

Physical exercise and daily play are very important for asthmatic children and their growth and normal development [105]. One of the major objectives of treating asthmatic children is to help the patient master EIA [106].

Several studies examined the effect of physical training upon asthma disease activity. A meta-analysis, combining several studies [107] found no effect on lung function, bronchial responsiveness and disease control with regular physical training in asthma. Quality of life and physical

fitness improved, however. Low physical fitness may possibly predispose to later development of asthma [108]. A relationship may exist between development of asthma, body mass index, physical activity and the gene for the β_2 -receptor, influencing asthma severity by the level of physical activity undertaken, especially in females [109].

EIA in childhood is best controlled by inhaled steroids. With regular treatment symptoms may disappear and be excellently controlled [80,81]. Both LABAs and LTRAs control symptoms in children [44•,110,111], although often not completely, and combination of several drugs may be needed [112]. Regular use of LABAs may cause some tolerance development, but this is not so for LTRAs [44•]. The physician treating asthmatic children active within sports, should observe the regulations related to inhaled β_2 -agonists and inhaled steroids as issued by the World Anti-Doping Association and by the International Olympic Committee, Medical Commission and follow the latest regulations.

Severe difficult to treat childhood asthma

Also in older school children it is now possible to employ humanized anti-IgE (omalizumab) for severe difficult to treat asthma, not responding to inhaled steroids. Few studies have been performed in children. Silkoff *et al.* [113] showed an effect upon exhaled nitric oxide comparable to inhaled steroids. Bousquet *et al.* [114••] recently published a meta-analysis and systematic review from seven randomized controlled trials on omalizumab in severe persistent asthma demonstrating a positive response in 61% of the patients. A limitation at present is the restriction to patients with an upper limit of total IgE of 750 kU/l. Further childhood studies with regard to the effect of omalizumab on severe asthma are necessary to establish the role of anti-IgE in childhood asthma.

Acute asthma in children

Acute asthma is in many countries the most frequent cause of admission to hospital during childhood [115–117], especially during the preschool years [116,118]. A steady increase in asthma admissions for children over the 1980s and 1990s was reported from several countries [115,117] with levelling out and even reduction in readmissions and in children older than 5 years in the later part of the period [115,116,119].

Most importantly, acute asthma emergencies may be prevented by careful asthma management, but acute asthma admissions remain a problem especially in young children. Proper hospital treatment procedures of acute asthma remain an important issue.

Treatment of acute asthma

To be able to breathe freely is intimately connected with the feeling of life. Acute breathing difficulties will always be associated with fright. Fright may contribute to aggravating the dyspnoea. Health personnel in contact with the patient and the parents should behave considerately and be able to convey a feeling of safety. It is now extremely rare that children are dying from acute asthma, and when it rarely occurs, it is most often due to the lack of realizing the severity of the asthmatic attack and delay in initiating adequate measures [120–122]. The treatment principle of acute asthma usually employed, is to start up with bronchodilating treatment with a short acting inhaled β_2 -agonist, and then if necessary supply with other treatment. To give a detailed guide to the treatment of acute asthma falls outside the scope of this article, but some considerations will be given to choice of bronchodilating treatment in the young child with acute asthma.

Acute asthma treatment in children 0–2 years of age

The treatment principles of acute infantile asthma [123] are similar of those in older children, namely instant relief with bronchodilating agents, and in severe cases, systemic steroids. The most frequent differential diagnosis is acute bronchiolitis. Treatment of acute bronchial obstruction in asthma and in bronchiolitis is quite similar, however, and the acute bronchiolitis may represent the first episode of asthma. In young children the bronchial muscular spasm is not so prominent during acute asthmatic attacks, but bronchial mucous secretions and mucosal oedema are more important for treatment. The symptomatic bronchodilating effect of inhaled β_2 -agonists is much more questioned in infants than in older children [124], even a paradoxical deterioration has been described [125]. On the other hand, a symptomatic effect of inhaled racemic epinephrine (adrenaline) was found in several studies in infants with acute bronchial obstruction, either acute bronchiolitis [126,127] or infantile asthma [128]. Even in adults inhalation of racemic adrenaline had similar effects to inhaled salbutamol [129] as also in children 1–17 years of age [69,130].

Conclusion

Several treatment modalities are available for the asthmatic child. Each child should be assessed in order to have optimal therapy, and should be monitored in order to regulate treatment. Weight should be put on mastering illness and daily life. According to the new nomenclature of asthma treatment, controller therapy on its own is the most important treatment of asthma, reducing acute asthma exacerbations. Due to modern asthma treatment, the asthmatic child presently experiences a much higher quality of life than was possible only 15–20 years ago.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 199–200).

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