Review Article

Asthma in children under five years of age: problems in diagnosis and in inhaled corticosteroid treatment*

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The objective of this study was to review the literature, focusing on difficulties encountered in asthma diagnosis and in the establishment of initial inhaled corticosteroid treatment in children under five years of age. The search was limited to studies published between 1991 and 2002 in Portuguese, Spanish, or English and included in the LILACS and MEDLINE databases. Symptoms of asthma, the most common chronic childhood disease, typically appear in the first years of life. There are currently no diagnosis means of making a certain diagnosis of asthma in children under the age of five. Clinical manifestations, when present in toddlers and preschoolers, may require treatment such as that given for asthma, assuming that it is preceded by a critical evaluation. We can conclude that diagnosis of asthma in the first years of life is complex and predominantly clinical. Inhaled corticosteroid treatment is an effective tool, although its risks and benefits must be carefully evaluated.

INTRODUCTION

The chronic inflammatory nature of asthma and the role played by inhaled corticosteroid treatment (ICT) on disease control have been well established in the literature. Asthma is a high-prevalence entity whose clinical manifestations appear early. In more than half of all cases, symptoms appear in the first years of life. An international multicenter study showed that asthma prevalence in children ranges from 2% to 30% worldwide, although prevalence among 6- and 7-year-olds in some Brazilian cities included in that study ranged from 21.3% to 27.2%[1]. Diagnosis of asthma in this period of life is predominantly clinical since there are currently no satisfactory means of making a certain diagnosis. In view of the high prevalence, identifying those toddlers and preschoolers who will develop asthma should be considered a public health priority since it allows early intervention.

Aiming to contribute to the improvement of clinical treatment for asthma in the first years of life, we reviewed the literature regarding asthma diagnosis, as well as that related to the use and potential side effects of ICT in children under five years of age.

DIFFICULTIES IN DIAGNOSING ASTHMA IN CHILDREN UNDER FIVE YEARS OF AGE

Asthma is currently defined as a chronic inflammatory airway disease that causes, in susceptible individuals, recurrent wheezing episodes, respiratory difficulty and cough, especially at night and in the early morning. These episodes are usually accompanied by variable and diffuse airflow obstruction, which is generally reversible, either spontaneously or through treatment, although the resolution may be less than complete. Asthma-related inflammation also increases bronchial responsiveness to various nonspecific stimuli[2-4].

Diagnosis of asthma in toddlers and preschoolers is complex, and there is a constant need for such diagnostic services. It is documented in the literature that many children who wheeze before the two years of age do not develop asthma[5-7], and that approximately 40% of children experience at least one wheezing episode in the first three years of life[8]. Therefore, clinicians frequently find it difficult to distinguish between two conditions that appear in the first years of life: recurrent and persistent wheezing[9]. The difficulty increases when we consider the diversification of the clinical spectrum of symptoms related to asthma, which has occurred as a consequence of the multiple genes involved in the pathogenesis of this disease[10,11].

Diagnosing asthma in toddlers has long been a concern of pediatricians. In 1983, Akasaka[12] published a scoring system aimed at that goal. Since then, many other studies have made contributions. In a study carried out by Martinez et al.[7], two-thirds of the cohort presented recurrent wheezing episodes that disappeared before the three years of age. The continuity of this line of research made it possible to demonstrate that, if the symptoms persist after the three years of age, the chance of later being diagnosed with asthma is higher than 80%[13].

Young et al.[14] concluded that wheezing that starts or persists during the second year of life is usually correlated with airway abnormality, which makes the case for clinical suspicion and investigation of asthma.

Despite the advances in the understanding of the disease, a great number of pediatric pulmonologists still accept the clinical definition put forth by Tabachnik and Levison[5], in which at least three episodes of dyspnea and wheezing before the second year of life are considered indicative of asthma[15].

The Third International Pediatric Consensus Statement on the Management of Childhood Asthma[16] reports that the immunopathology of asthma in children under three years of age should be further studied. The statement includes the recommendation that recurrent episodes of wheezing, persistent cough, or both, in this age group, be considered highly suggestive of a diagnosis of asthma, assuming that other causes of wheezing have been ruled out. Charts 1 and 2 show, respectively, examples of alternative diagnoses and findings that are suggestive of these diagnoses[17].

Assuming that other respiratory diseases that lead to wheezing have been ruled out, children or toddlers who have a history of wheezing triggered by multiple determinants, have severe and prolonged respiratory symptoms after a viral infection, present evidence of underlying atopy or have a confirmed family history of atopy or asthma, as well as those who test positive on laboratory exams (for increased levels of IgE, eosinophils and serum eosinophil cationic protein), may be diagnosed with asthma[18]. However, this broad

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CHART 1

Differential diagnosis of bronchial asthma

Vascular ring
Obstructive sleep apnea
Bronchiectasis
Bronchiolitis
Laryngeal dyskinesia
Vocal cord dysfunction
Chronic respiratory disease of prematurity
Cystic fibrosis
Tracheoesophageal fistula
Deglutition disorders
Viral and bacterial infections
Heart failure
Hypopharyngeal masses
Mediastinal masses
Pronounced airway obstruction
Gastroesophageal reflux*
Loeffler's syndrome
Hyperventilation syndrome

*Common diagnosis in toddlers, usually physiological, not requiring any treatment

definition is controversial. For example, although the predictive value of family history of asthma plays an important role, a great number of asthmatic children have no asthmatic relatives[19].

Diagnosis is made more difficult by the current lack of tests that are sufficiently specific and sensitive to determine with certainty whether or not toddlers are asthmatic. However, in children who present wheezing but are not known to be asthmatic, administration of anti-inflammatory and bronchodilator medication may lead to control of the symptoms[18].

Another aspect to be considered is the early presence of the inflammatory process in children who have recurrent wheezing and who are later diagnosed with asthma[20]. Therefore, it is necessary that noninvasive techniques that make it possible to quantify the inflammatory process, such as the quantitative determination of airway inflammatory mediators in urine, blood and nasal secretions, be developed[21]. The importance of performing bronchoalveolar lavage and determining the concentration of exhaled nitric oxide, as well as collecting sputum samples for culture, is indisputable. However, due to the difficulty in routinely using these techniques in children under five years of age, they are not useful diagnostic tools in this context

CLINICAL AND LABORATORY PARAMETERS AND THE DIAGNOSIS OF ASTHMA

Strunk[22] correlated the diagnosis of asthma in children under three years of age with the following findings: onset of symptoms before the age of six months; symptoms induced by physical exertion, crying or laughing; eczema; recurrent otitis media; family history of asthma; and maternal smoking. The author made a cost-benefit analysis of the determination of chlorite counts in sweat, as well as of the use of chest X-rays, and concluded that these exams are particularly useful in making a diagnosis of asthma in this age group.

Castro-Rodriguez et al.[23] showed that a diagnosis of asthma in children who present wheezing within the three first years of life may be made with reasonable accuracy using simple parameters. The authors used clinical and laboratory testing data from children involved in a longitudinal study carried out in Tucson, Arizona. Subsequently, they created two indices, one more rigorous and one less rigorous, that made it possible, among wheezing children under three years of age, to identify those at increased risk for later presenting asthma symptoms (at six to thirteen years of

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CHART 2

Findings suggestive of a diagnostic alternative to asthma

History
  Wheezing or need for mechanical ventilation in newborns
  Early wheezing combined with vomiting or regurgitation
  Sudden-onset coughing or choking
  Chronic diarrhea or steatorrhea
Physical Exam
  Growth and development insufficiency
  Cardiovascular alterations
  Digital clubbing
  Focal alterations and unilateral wheezing upon auscultation
Lack of therapeutic response
  Refractory to bronchodilator treatment
Radiological findings
  Focal or persistent alterations

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age). The most significant risk factors were eczema and a parental history of asthma, whereas the least significant risk factors were peripheral eosinophilia, wheezing in the absence of a cold, and allergic rhinitis. It is important to bear in mind that the laboratory test used (determination of eosinophil counts in peripheral blood) is easily carried out and is more sensitive and specific than the determination of total serum IgE. The more rigorous index took into account frequent wheezing in the first three years of life combined with one of the most significant risk factors or with two of the least significant risk factors. The less rigorous index took into account any wheezing in the same period combined with two of the least significant risk factors. The more rigorous and the less rigorous indices indicated an increased risk of developing asthma between six and thirteen years of age ranging from 4.3 to 9.8 times and from 2.6 to 5.5 times, respectively, in the . The authors concluded that the more rigorous index has an acceptable positive predictive value and presents high specificity, although the sensitivity is very low. In contrast, the less rigorous index has high sensitivity, lower specificity and lower positive predictive value. The decision about which index to use should take into account the index sensitivity as well as the efficacy and the side effects of the preventive measure to be recommended.

When focusing on the diagnosis of asthma in toddlers, the formulators of the III Brazilian Consensus on Asthma Management[24] emphasized the importance of factors such as previous history of hospitalization for bronchiolitis or severe wheezing and the occurrence of at least three

episodes of wheezing in the first six months of life. The authors highlighted the relevance of taking into account factors such as parental history of asthma, presence of atopic dermatitis, wheezing or rhinorrhea not accompanied by a cold, peripheral eosinophilia equal to or greater than 5%, and being male.

DIFFERENT PHENOTYPES IN CHILDREN WHO WHEEZE

Another relevant factor is the heterogeneity of the clinical presentation of asthma. In the study carried out by Martinez et al.[25], three quite distinct phenotypes were established: transient wheezing; wheezing beginning after the three years of age; and persistent wheezing.

Transient wheezing was correlated with reduced bronchial diameter and, as a result of the growth of the airways, disappeared by the three years of age. It is important to emphasize that narrowed airways may be more easily obstructed when infected and increase from three to six times the risk of wheezing in the first year of life[26].

Wheezing beginning after the three years of age was found to correlate with factors such as maternal asthma, being male and presenting episodes of rhinitis in the first year of life.

In children with persistent wheezing, symptoms did not disappear by the three years of age, and the initial pulmonary function (PF) measurements were approximately 50% higher than in those with transient wheezing. However, in this group, reduced PF was observed by the six years of age. A similar situation was observed in children who presented wheezing later and became sensitized to airborne allergens.

ASTHMA AND ATOPY

In the cohort studied by Martinez et al.[25], the prevalence of atopy was significantly higher in children with persistent wheezing and in those who presented this symptom by the three years of age than in those who never wheezed. Symptom severity was higher among atopic children.

In children with persistent wheezing, high levels of IgE were found at nine months of age, suggesting a form of IgE-mediated sensitization. The authors suggested that such levels may be correlated with chronic bronchial inflammation, persistent bronchial hyperresponsiveness and the abnormal development of PF. It is important to emphasize that detection of antigen-specific IgE antibodies in order to diagnose atopy is totally unnecessary in the first year of life.

According to Ribeiro[27], the factor most frequently correlated with a high probability of recurrent wheezing is atopy and, more specifically, atopic dermatitis. However, even among toddlers with atopic dermatitis, only 50% to 60% will later develop asthma.

EXPOSURE TO CIGARETTE SMOKE

Maternal smoking during pregnancy is a significant determinant of impaired PF detected soon after birth, and reduced airway diameters are observed in children of smoking mothers[28]. This may explain the strong correlation between intrauterine exposure to cigarette smoke and the subsequent risk for a respiratory tract disease[29]. However, exposure to cigarette smoke after birth also correlates significantly with transient wheezing in children under three years of age. Ribeiro[27] reported that newborns who are underweight for their gestational age and children of smoking mothers have impaired PF, which improves with the growth of the lungs. Risk is proportional to length of exposure. Alterations in bronchial hyperresponsiveness are principally observed within the first ten weeks of life[26].

VIRAL INFECTIONS, WHEEZING AND ASTHMA

Viral infections of the lower respiratory tract - common complications in the first years of life - are capable of inducing temporary disturbances in PF, causing transient bronchial hyperresponsiveness in normal children[18]. Hyperresponsiveness may result from varioust mechanisms, such as increased permeability to antigens, decreased endogenous production of nitric oxide, exposure of cholinergic nerve fibers or damage caused by the use of bronchodilators[26].

The duration of altered PF may vary widely, from one month to one year, especially in the presence of pre-existing underlying alterations. It has been shown that viral-induced wheezing is uncommon before two months of age, and that the frequency decreases after the two years of age, not only due to immunological factors, but also due to the increased bronchial diameter.

Immunological mechanisms may act in an antagonistic way, contributing to the genesis of viral-induced wheezing. For example, although cellular immunodeficiency has an important protective effect, it may lead to permanent alterations. Although an intensified cellular response is necessary to eradicate the virus, it may also cause airway damage, which may persist even after the eradication of the pathogenic agent. It has been well established in the literature

that there is a correlation between a pronounced cellular response and severe pulmonary disease accompanied by wheezing. However, breast milk may provide a certain degree of protection against wheezing, especially wheezing induced by the respiratory syncytial virus (RSV). Neutralization of the lymphoproliferation response to the RSV seems to be correlated with the secretory IgA and the interferon-γ present in it[30]. Among the viruses that induce wheezing, RSV is the most commonly found[26].

Currently, there is well-established evidence that toddlers with bronchiolitis caused by RSV are at increased risk for the continuation of respiratory symptoms until reaching school age. The determining factor of this situation is poorly understood. Genetic and environmental factors seem to define the type as well as the intensity of the immune response to acute RSV infection, and this response affects the mechanisms that control muscle tonus. Among such responses is the cell-mediated defense mechanism. This mechanism is stimulated when the RSV infects respiratory epithelial cells such as macrophages and monocytes that produce cytokines and interleukins[28].

Stein et al.[31] found RSV infection before the three years of age to be correlated with a significant increase in the risk of subsequent frequent wheezing (OR: 4.3) and in that of infrequent wheezing (OR: 3.2) in the first ten years of life. However, this correlation was less than significant among children of thirteen years of age and was not observed in children with a history of allergy. Whereas RSV-induced wheezing tended to decrease with age, early allergic sensitization tended to increase rather than regress. The authors emphasized that the increase in the airway diameter may reduce the probability of wheezing unrelated to airway allergic inflammation. However, the alterations in airway tonus observed in children with a history of RSV infection tended to decrease with age. These children presented decreased bronchial responsiveness to methacholine at school age. In summary, wheezing in nonatopic children is often induced by viral infection, especially by RSV, whereas wheezing in atopic children is mediated by IgE.

The same view is shared by Ribeiro[27], who stated that most episodes of bronchial obstruction in wheezing toddlers are viral in origin, and that, when there is no concomitant atopy, such children remain asymptomatic between crises.

EARLY ALLERGIC SENSITIZATION AND ENVIRONMENTAL CONTROL

It is possible that the development of the persistent form of wheezing is dependent on genes and the action of certain environmental factors in early life. The identification of these factors would make it possible to devise a primary prevention strategy. Otherwise, we would contribute to the increased prevalence. However, it has been observed that early exposure to certain factors, including interaction with other children in day care centers or interaction with animals, decreases the risk of persistent asthma[32]. For years, the correlation between persistent asthma and the development of IgE antibodies in response to certain airborne allergens, such as dust mites, favored the hypothesis that the risk of asthma would be correlated with the degree of exposure to those allergens in early life[33]. Nevertheless, studies determining the concentration of dust mites in the home have failed to establish a causal relationship between this factor and the development of asthma by school age[34]. Similarly, no correlation has been found between low dust mite concentrations and a lower incidence of asthma. Paradoxically, increased exposure to cat and dog allergens in the first years of life has been correlated with a marked decrease in the subsequent risk of developing asthma[35]. In fact, high microbial burdens have been found in the dust of houses where there are pets. This burden elicits immune responses that do not involve Th2 cells, which is a characteristic of persistent asthma. The infection would thus protect against the subsequent development of atopy(26,36). The role played by exposure to animals in the development of allergic diseases needs to be further investigated.

In summary, genetic and environmental factors influence the expression and progression of asthma or atopy, or both. Among these factors are early sensitization to airborne allergens, premature birth, maternal smoking during pregnancy, exposure to smokers after birth, maternal asthma, growth and development of the respiratory system, and viral infections, such as RSV infection[28].

ASTHMA, A CLINICAL SYNDROME

According to the 1995 Global Initiative for Asthma[2], in 50% to 80% of asthmatic children, symptom onset occurs in the first years of life; a fact that has been corroborated by several authors[37,38].

Therefore, a significant percentage of asthmatics will have presented wheezing and required therapeutic care while still toddlers. In addition, there are no methods available that are both easy to use and present high sensitivity and specificity for making a certain diagnosis of asthma in children under five years of age. However, the fact that diagnosis is made almost exclusively through evaluation of simple clinical parameters, as proposed, among others, by Castro-Rodriguez in his study[23], makes it possible to diagnose such children in health centers presenting any level of complexity since no advanced technology is required. In addition, the fact that wheezing is triggered by numerous agents makes it possible to consider asthma to be, in terms of symptoms, a clinical syndrome that needs to be approached therapeutically, according to the severity of the manifestations[39]. In view of the difficulty in making a definitive diagnosis of asthma in children under five years of age, the British Guidelines on Asthma Management[40] recommend using the term wheezing disease as a substitute for the word asthma.

WHEN SHOULD INITIAL INHALED CORTICOSTEROID TREATMENT BE INITIATED? NORMALIZATION OF PULMONARY FUNCTION AND PREVENTION OF BRONCHIAL REMODELING

The controversy regarding diagnosis of toddlers is equaled by that surrounding the timing of ICT introduction in such patients. Oswald et al.[41] observed that PF in adulthood tended to remain altered in patients who had presented persistent asthma and frequent symptoms as an infant and to normalize in those who had presented infrequent viral-induced infantile wheezing.

Stein et al.[31] showed there was a statistically significant decrease in PF in children with persistent asthma at the six years of age in comparison to those in the control group. The authors stated that the acquired PF deficit could be explained by the chronic airway inflammation caused by the allergy.

Sears[33] observed PF deficit in patients with persistent asthma. This deficit increased after the development of the first symptoms. The author argued that it is plausible to suspect that the rapid growth of the lungs during the preschool period may be particularly susceptible to the effects of the more intense inflammation that accompanies persistent asthma.

In summary, chronic inflammation may cause bronchial remodeling, stunt airway growth and reduce PF. Therefore, delayed initiation of ICT would have a lesser effect on PF and bronchial hyperresponsiveness than would early initiation. Various authors have shown the response to ICT to correlate with time of treatment initiation, suggesting that initiation at the first clinical manifestations leads to better results since the inflammatory process occurs early in asthma[42-45]. Early initiation of ICT could reduce bronchial inflammation, thereby preventing the more severe form of the disease as well as protecting against the establishment of irreversible obstruction years later. Agertoft et al.[43] observed that PF was better in children who began ICT before having had the symptoms for two years (p < 0.05).

The Childhood Asthma Management Program Research Group[46] monitored 1041 children from five and twelve years of age over a period of four to six years. Patients were given three types of maintenance treatment: placebo, budesonide and nedocromil. The authors observed that clinical control and improvement in bronchial hyperresponsiveness, measured using the methacholine provocation test, were significantly greater in patients treated with budesonide; an advantage that was not maintained after the discontinuation of treatment. The results of the responsiveness to methacholine seen in the group receiving budesonide suggest that the beneficial effect of this treatment was due to alterations in the muscle tonus and in bronchial inflammation rather than in the prevention or in the resolution of the bronchial remodeling. After two months of budesonide use, there was an improvement in postbronchodilator forced expiratory volume in one second. However, the mean values for this parameter at the end of the treatment were similar to those obtained at the beginning of the treatment and to those found in the placebo group. The authors concluded that continuous treatment with budesonide in children five years of age or older with mild to moderate asthma did not present any therapeutic benefit in terms of PF, raising the hypothesis that, since the mean duration of the disease was five years at the beginning of the treatment, there is irreversible deterioration in PF prior to the initiation of treatment.

Further studies are needed in order to determine the effect of ICT on the normalization of PF and to assess the capacity of such treatment to prevent

alterations in the structure of the bronchial tree in asthmatic patients[45].

The positive effect of ICT on the control of clinical manifestations has been well established. In the Belo Horizonte Asthma Program[47], the frequency of hospitalizations and emergency room visits was evaluated prior to and after ICT in children with asthma or wheezing syndrome. The occurrences of such episodes in the twelve months prior to ICT were the parameters of comparison. The study sample consisted of 821 children under fifteen years of age. Mean age was 3.5 years. All were monitored in a clinical setting for at least twelve months after the initiation of ICT (beclomethasone dipropionate). Hospitalizations and emergency room visits were reduced by 75.8% and 85%, respectively. A statistically significant reduction in hospitalizations ($p < 0.05$) and in emergency room visits ($p < 0.05$) was observed in all age groups, including children under five years of age, suggesting that this prophylactic treatment has a beneficial effect in toddlers and preschoolers.

Sano et al.[48] observed a decrease in the length of hospital stay in 71 toddlers admitted with severe exacerbation and treated with budesonide.

Until the middle 1980s, ICT was not recommended for toddlers or preschoolers[49]. However, its efficacy in this age group has now been documented. Making a certain diagnosis of persistent asthma in children under three years of age remains the greatest difficulty.

In the cohort studied by Martinez et al.[17], one-third of the children presented wheezing in the first three years of life, and the symptoms persisted in only 40%. Price[49] stated that if all children underwent ICT in the first three years of life, 60% would be treated unnecessarily, but, for the rest of the children, giving no treatment could represent a lost opportunity to prevent abnormalities in PF.

Evidence suggests that ICT outcomes are better when asthma is diagnosed early, allowing the initiation of treatment within the first two years of illness[45].

According to Landau[50], ICT should be introduced when the symptoms occur more than once or twice a week, or when there are more than two attacks a month.

Ribeiro[28] enumerated possible situations and doses for use of ICT in toddlers and preschoolers. Based on the severity of symptoms, the author listed the following situations: continuous symptoms or symptoms manifesting themselves more than twice a week, attacks occurring more than twice a month,

life-threatening acute respiratory insufficiency in a toddler and abnormal PF between attacks (something that is difficult to evaluate in our milieu) in a toddler. Based on evidence of atopy, the author included toddlers with moderate and severe atopic wheezing. Based on evidence of recurrent wheezing after an episode of acute viral bronchiolitis, the author included patients admitted to intensive care units because of acute respiratory insufficiency, and who, after discharge, continue having persistent wheezing. In cases of severe wheezing, the author suggests starting with high doses and decreasing the dosage as soon as possible. In toddlers with moderate wheezing, he recommends starting with low doses and discontinuing the medication within three months. However, clinical evaluation is the principal parameter and, depending on the response obtained, the dose level should be maintained or increased.

INHALED CORTICOSTEROID TREATMENT IN VIRAL INFECTIONS

Viral infections constitute an aspect that deserves special attention. The benefits of ICT or oral corticosteroid treatment in toddlers presenting recurrent wheezing episodes are still unclear and seem to be dependent on age and on symptom severity[51]. According to Taussig[8], patients with recurrent viral-induced wheezing, even those without a certain diagnosis of asthma, may benefit from inhaled anti-inflammatory drugs. Intermittent use of high-dose ICT in preschoolers with episodic viral-induced wheezing has been correlated with modest improvement[52,53], whereas continuous use has proven ineffective[54].

Svedmyr et al.[55] treated patients with budesonide, started at symptom onset, and obtained better control of the exacerbations triggered by airway infections.

Connett et al.[53] used budesonide in toddlers and preschoolers with systematic viral-induced wheezing and obtained a reduction in wheezing time ($p < 0.05$).

The use of ICT in the treatment of RSV-induced bronchiolitis has also been studied. The findings of the study carried out by Kajosaari et al.[56], in which patients admitted to the hospital because of RSV-induced bronchiolitis were monitored, suggested that prescribing ICT during or after the acute phase produces a beneficial effect on disease evolution as well as on recurrent wheezing.

Another relevant aspect is hospitalization in children under five years of age. In studying 100 patients with a possible diagnosis of asthma, Wever-

Hess et al.[57] observed that hospital readmission rates were higher in the under one year age group than in the two to four year age group (p = 0.02). In children under one year of age, 60% of readmissions occurred within two months of the first hospitalization, and there was a tendency toward a positive correlation between ICT and fewer readmissions.

In the 2002 revision of the Global Initiative for Asthma[10] it is stated that "the clinical benefits of the use of inhaled or systemic corticosteroids in the treatment of viral-induced bronchospasm remain controversial. Some studies did not find, in the acute phase of the viral-induced bronchospasm, short or long-term clinical benefits of the use of this treatment in previously healthy toddlers, although there are studies that reported improvement." It also mentions that "although intermittent high dose ICT represents a partially effective strategy in the treatment of episodic mild viral-induced wheezing in children, there is no evidence to support the maintenance of ICT, even at low doses, in order to prevent it."

The ideal timing of ICT initiation is still under debate. Therefore, the use of ICT in toddlers and preschoolers should be preceded by a critical evaluation in which its risks and benefits are carefully evaluated. In summary, ICT should be prescribed to children who present severe exacerbations, hospitalizations, frequent use of -agonists, persistent symptoms that lead to impaired growth and development or to pulmonary hyperinflation between attacks[2,3,17,40]. The use of ICT in the treatment of bronchiolitis and exacerbation seems to bring positive results.

RISKS AND BENEFITS OF INHALED CORTICOSTEROID TREATMENT

The use of ICT in asthmatic patients is effective and safe. Although this treatment regimen allows minimal doses to be deposited in the lungs, some systemic absorption is inevitable. The risk of systemic side effects depends on the potency of the corticosteroid, the type of delivery device (inhaler) used, patient age, duration of treatment and the dose used, as well as on patient systemic bioavailability[58,59]. The cumulative effect should be taken into account when prescribing nasal ICT.

In regard to dosing schedules, studies suggest that doses of beclomethasone or similar drugs lower than 400 µg/day have no clinical significance[50]. According to Soren[60], low doses of inhaled corticosteroids, from 100 to 200 µg/day, have proven sufficient to obtain satisfactory clinical control in patients with mild and moderate asthma. Parameswaran et al.[45] suggested that ICT in children begin with doses between 200 and 400 µg/day of budesonide or equivalent, and that the duration of treatment be proportional to the duration of symptoms. In regard to maintenance, the authors emphasized the importance of identifying the lowest dose that results in clinical control.

The following are some of the rules laid down by Ribeiro[27] for the use of ICT in toddlers and preschoolers: use the lowest dose possible as soon as possible (Table 1); try not to use ICT for more than three months in toddlers with the severe forms; use Aerochamber® type valve spacers; avoid inhaled corticosteroid suspensions in ultrasonic nebulizers; hold the mask firmly to the face in order to avoid getting mist in the eyes, wash the face with water and soap after the use of the mask; and encourage older children to rinse their mouths with water after use of ICT.

LOCAL AND SYSTEMIC SIDE EFFECTS OF ICT

Adverse local effects, rare in children, include oral candidiasis and dysphonia, both of which can be reduced through the use of spacers and by developing the habit of rinsing the mouth after ICT administration.

Among the systemic effects, those related to growth have been more consistently studied. According to the 2002 Global Initiative for Asthma[10], there have been no studies showing clinically or statistically relevant adverse effects on growth caused by the use of 100 to 200 mg/day of an inhaled corticosteroid. Some studies have demonstrated that asthmatic children who are given ICT reach the final height expected in adult life. Therefore, alterations in the growth rate that

TABLE 1

Doses and estimated equipotencies of inhaled corticosteroids

Corticosteroid	Low dose (µg/day)	Medium dose (µg/day)	High dose (µg/day)
Beclomethasone	200-400	400-800	> 800
Budesonide	100-200	200-400	> 400
Fluticasone	100-200	200-400	> 400

Source: Global Initiative for Asthma - 2002 (revised)[10]

are induced in the first year of treatment seem to be temporary[46]. However, it is important to bear in mind that severe asthma, when not controlled, has an adverse effect on growth and height.

Ribeiro[27] comments on the potential risk of pulmonary growth being affected by ICT, especially within the first two months of life. The author also states that those who undergo ICT in infancy tend to lose more elastic fibers in old age.

FINAL CONSIDERATIONS

The importance of ICT in persistent asthma has been well established. Since its introduction in 1973, it has proven to be the regimen that best controls this entity.

Another relevant aspect is the early manifestation of asthma, higher than 50% in the first years of life. Diagnosis in this age group is predominantly clinical, and several causes may lead to similar symptoms. However, wheezing in the second year of life is highly suggestive of asthma. Noninvasive means of making a certain diagnosis of asthma in toddlers and preschoolers are currently in development. On the other hand, the fact that diagnosis is still predominantly clinical, not requiring advanced technology, allows its implementation in health care clinics of any level of complexity. It is important to emphasize that the indication for ICT, especially in children under five years of age, must be carefully evaluated.

Further studies attempting to clarify the period between the initiation of ICT and the bronchial remodeling - an important aspect for the prognosis of asthma - are required. In addition, the use of ICT in bronchiolitis needs to be further investigated. Bearing in mind the possible side effects, it is also imperative that children undergoing long-term ICT be monitored, and that the lowest effective dose be determined.

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