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Asthma in Preschool Children

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Abstract

A proper diagnostic and therapeutic approach in children under 5 years who have symptoms of respiratory distress, of varying intensity, more or less continuously or in acute and repeated episodes must be observed. In many cases, the dominant symptom is cough, which has been linked to the existence of asthma ('equivalent asthmatic coughing'). As respiratory symptoms are common to many processes that affect this system, an appropriate differential diagnosis is required before starting treatment, which is often not appropriate.—Concept. Epidemiology—Predisposing factors, risk factors and triggers—Respiratory symptoms addressed from a pathogenic point of view, in order to better understand the possibilities of these symptoms to appear: Pathogenesis of dyspnea, cough, secretion and bronchial breath sounds.—The inflammatory reaction is the pathogenetic basis of asthma, and hence, anti-inflammatories are the most appropriate treatment. But there is no evidence that inflammation is a permanent fact from the start of the disease or that it exists in other respiratory processes. The appropriate methods to assess inflammation in children under 5 years and the evaluation of results in published studies will be presented. The conclusion is that it has been shown that in mild to moderate and sporadic cases, inflammation persists.—Atopy and asthma: onset and evolution—Clinical and allergologic diagnosis—Diagnostic evaluation of the dominant symptoms, relating directly to their pathogenesis.—Exploration of respiratory function, according to age: younger and older than 2 years.—Differential diagnosis based on the dominant symptoms.—Treatment. (a) Etiologic: immunotherapy in <5 years: standards. (b) Pathogenic: anti-inflammatory (corticosteroids). Indications of pre-inflammatory: chromones and anti-leukotriene: montelukast. (c) Treatment regimens: treatment of seizures.

Keywords: preschool children, diagnosis, treatment, immunotherapy, genetic and trigger factors

1. Introduction

Episodes of breathlessness or wheezing are common in preschool children primarily in the first 2 years, being estimated that 50% of infants have episodes of this nature, and their causes are needed to be known. The insufficient development of the immune system opens up to frequent viral infections, but other factors can contribute, such as the home environment, particularly if the mother is a smoker. Given the importance of genetic predisposition, family history of allergic diseases and asthma in particular is always to be known, taking into account the famous expression 'all that wheezes is not asthma'.

2. Epidemiology

Some anatomical and physiological characteristics of the infant and young child's airways predispose to the development of processes that lead to the narrowing or bronchial obstruction, manifested by common symptoms, such as coughing, dyspnoea and noisy or wheezing breathing.

The *narrower airway calibre* is a basic fact, which contributes to the obstruction due to the inflammation of the mucosa, the smooth muscle constriction or the increased secretion of tracheobronchial mucus glands.

Infant *physiological increase of vagal tone*, which continues during the first years of life, as Montgomery and Tepper [18] demonstrated by methacholine inhalation, is known. Pathologically, bronchial hyperresponsiveness (BHR) is a key element in the pathogenesis of asthma. Having certain anomalies in the protein chain of the beta-receptors of the smooth muscle, such as the substitution of glycine for arginine at position 16 and glutamate for glutamine at position 27, is a characteristic of individuals with atopic predisposition. But in non-predisposed subjects, BHR is usually secondary to the inflammatory reaction that occurs in various circumstances in the bronchial mucosa.

Regarding bronchopulmonary infectious pathology, it is the well-known *immaturity of the immune system*, which in some children continues for several years (infant transient immunodeficiency), facilitating the development of bronchial inflammation processes.

It is not always easy to establish the true diagnosis of asthma in early life, as the evolution of symptoms over the years will confirm the diagnosis by excluding other possible causes of dyspnoea or wheezing, supported by immuno-allergological and respiratory function studies.

In line with these concepts, Martinez et al. [16] distinguish the different phenotypes of the bronchospastic pathology in preschool children, identifying asthma and transient bronchitis (wheezy bronchitis) that encompass various processes suffered by a group of children who, after preschool age, do not show no broncholability, all a consequence of the predisposing factors cited above. However, it is not always easy to determine the phenotype of a particular patient, and in the course of time, as they evolve, the criteria may even have to be modified. Hence, the need to pay attention to the characteristics of the symptoms and their evolution, in addition to a number of circumstances, such as the suffering from other allergic processes by

the same child (eczema, allergies to milk proteins), a precocious start of symptoms, or the existence of similar pathologies among siblings, parents or other close relatives, or environmental pollutants, climate, etc. The lack of a family history in approximately 20% of cases adds another obstacle to the diagnosis.

In most children, asthma begins in the first 5 years of life. A study in Spain in 1982 showed that in 76% of asthmatic children, the process had started before 4 years of age. Several studies indicate that between 15 and 35% of preschool children have had an episode of respiratory distress, with or without wheezing or other breathing noises; however, 60–65% of these children would not suffer crises after the third year. The high diagnostic confusion in this group of children with 'transient bronchitis' comes not only from symptomatic similarity but also from the terminology that has been used to label the process. The appearance of these temporary symptoms can be due to various causes, such as viral infections (respiratory syncytial virus (RSV), parainfluenza, influenza), causing bronchiolitis, which may recur, even more in immunodeficient children. Other possible causes can also be household pollutants (tobacco smoke, cleaning chemicals or industrial products) or weather changes (sudden cooling), among other.

3. Predisposing factors, risk factors and triggers

Prevention of diseases is one of the challenges that medicine faces, therefore knowing the risk factors for each of the processes we aim to prevent is essential to carry out effective measures to achieve the proposed objectives. The best known risk factors and triggers that lead to allergic diseases, especially asthma and related bronchopaties, are as follows.

3.1. Atopy: genetic bases

The hereditary component in allergic diseases is well known, being asthma the most important, so that in approximately 70–80% of patients, close family members with the same or other allergy-related pathologies are identified. Allergic (atopic) predisposition is polygenic, that is there are several genes that support polymorphisms, which prompt the abnormal response of the organism to allergens.

In infants and pre-schooler children, the diagnosis of asthma is based on demonstrating the causality of allergic symptoms, and BHR, which is an essential condition for the diagnosis of the disease at any age. Polymorphisms in genes that lead to variants of the β_2 -adrenergic receptor in the bronchial smooth muscle are the basis for congenital BHR (primary BHR), which may be also due to the harmful influence of certain exogenous factors such as when smoker women do not drop the habit during pregnancy, thereby harming the normal development of the lung. The existence of congenital BHR is the first precursor of asthma in young children. Moreover, also in these early years, BHR may worsen or appear by the inhalation of pollutants present at home or in the exterior, being this cause of BHR (acquired BHR) the most prominent at later ages.

In children with wheezy bronchitis (transient), such family circumstances are not given, but the causes are different, such as pulmonary immaturity, viral infections or environmental pollution (micro-habitat).

3.2. Foetal immunity and atopy: intrauterine sensitization

The influence of the mother in the transmission of atopic predisposition is greater than the father's, possibly because of the intimate connection between the former and the foetus. Pregnancy maintenance requires an immune environment with predominance of activity of Th2 lymphocytes, which prevents the rejection of the foetus. Thus, the foetus develops in an environment in which cytokines from that lymphocyte subclass, especially interleukin (IL)-4, IL-10 and IL-5, are predominant, increased if the pregnant woman is atopic, suffering or not from any allergic disease. Although IL-13 is a cytokine of the Th2 group, it has been observed that it is produced to a lesser extent in foetuses and neonates at risk of atopic disease, which could be related to the immaturity of the development of the activity of T cells [27]. Along the same lines, low production of IFN- γ by mononuclear cells could be related, thereby reducing the suppression of Th2 activity, defect that is maintained for at least the first 2 years of life [24].

Sensitization to food allergens or pneumoallergens may occur already during pregnancy, as the foetus can produce IgE from the 11th week of gestation, even IgE specific to antigens, as has been shown to occur against parasites (helminths, filaria) in some countries.

What is yet to be clarified is the route by which the allergens that have passed to the mother by inhalation or digestion are brought into contact with the foetus for the immune stimulation that promotes IgE production to occur.

What it is also to be elucidated is the relationship that may exist between the degree of maternal exposure to allergens and the possibility that the foetus becomes sensitized. It does not seem that an environment rich in pneumoallergens cause a greater number of foetuses affected or that the diet of pregnant woman devoid of the most allergenic foods reduce the number of sensitivities.

3.3. Risk factors

Lung development

Regardless of atopic predisposition, various circumstances constitute an added risk for the early onset of asthma, which can also promote the development of wheezing transient bronchitis. Some of these facts can act on the lung during foetal life affecting both the development and maturation of the immune system, but also after birth, especially in the first year of life.

Lung development can be affected by certain circumstances. Prolonged stress of the mother can affect the imbalance of Th1/Th2 activity, due to the excessive production of cortisone that occurs in this emotional condition, since the hormone exerts its immunomodulatory activity in favour of Th2 activity [11]. Similarly, some incidents during pregnancy can affect the

development of the lung, such as uterine bleeding, placental insufficiency or other processes that alter the physiology of the uterus favouring premature birth and a consequent low birth weight. Also, prolonged malnutrition of the pregnant mother is detrimental to the overall development of the foetus and particularly of the lung, increasing the risk for prematurity in which many of these pregnancies end.

Smoking during pregnancy and lactation

Among the risk factors that affect lung development in both its structure and mechanisms of immune defence, the greatest interest is focused on the smoking habits of the mother during pregnancy and the first year of life, including also other smokers in the vicinity of the newborn and infant.

There are no doubts about the relationship between smoking and respiratory disease of the small child, with an increase in the prevalence among children of school age. Nevertheless, it is difficult to prove whether the functional changes are already initiated in the foetus or if this occurs later during lactation. Gilliland et al. [9] found decreased respiratory function (FEF₂₅₋₇₅) in children whose mothers smoked during pregnancy, but not after birth, suggesting that the injuries already started in the foetus.

Modern methods to assess respiratory function allow the study of BHR already in the first months of life, having shown a slight but real increase in the children of smoking mothers. Regarding immunity, several studies in cord blood appear to show that tobacco produces some changes in the immune response of the foetus, having found higher levels of IgE and a significant production of Th2 cytokines (IL-13, IL-5mRNA, IL-6), after *in vitro* stimulation of lymphocytes with allergens (ovalbumin, mite).

Environmental chemical pollutants

Various common contaminants at home may act as irritants that can cause or increase bronchial reactivity or produce an inflammatory condition of the airways. This may precipitate both sensitization to environmental allergens and be the cause of respiratory symptoms of varying intensity, from irritative cough to wheezing bronchitis. The most common environmental pollutants have a variable influence, in logical dependency on the concentration of chemicals, ventilation, housing characteristics and location (urban, suburban, rural).

It seems less likely that the outside environmental irritants may cause the same problems in young children, perhaps because the degree of exposure is lower than in later ages. However, in big cities or in the vicinity of industrial areas, pollution can be a serious risk, from which only small infants that spend little time outdoors will be protected.

3.4. Trigger factors

Early sensitization

As already mentioned, sensitization to allergens seems possible already during foetal life, although the onset of symptoms of asthma may take some time, depending on the degree of

exposure and environmental conditions in addition to the genetic load. But it is after birth when the child is more exposed to common domestic allergens, being mites the most common (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), but sensitization and subsequent development of allergic symptoms in the respiratory tract are associated with atopic predisposition, concentration of allergens and allergenic potency of each of them, and their ability to release the antigens when the particles are deposited on the wet surface of the mucosa, as well as the involvement of adjuvants, as are the aforementioned pollutants or the intercurrent respiratory infections.

Viral infections

Respiratory tract infections caused by viruses are responsible for a high percentage of bronchospasm in young children, for which their characteristic tendency for allergic symptoms in their upper respiratory tract or even crises of wheezing and/or dyspnoea had already been revealed. But also in non-atopic children, RSV mainly can cause lesions of the bronchial mucosa that facilitate contact with allergens, causing sensitization to them, with a simultaneous increase in broncholability. Also in not-predisposed children, RSV infections and other viruses trigger wheezing crisis or broncho-obstruction, as a pathogenic base for transient or wheezy bronchitis. The cause of these disorders lies in diverse mechanisms, dependent some on the injury of the mucosal epithelium and others on the activation of the cells involved in the immune–allergic response (**Table 1**).

RSV belongs to the *Pneumovirus* genus of the *Paramyxoviridae* family. Through a protein (G), the virus attaches to the surface of target cells, resulting in the fusion of the lipids of the cell membrane by another protein (F), which facilitates the insertion of RNA into the invaded cell. The G protein promotes a Th2 response, whereas the F protein stimulates the production of cytokines in Th1 lymphocytes. In connection with the predominance of one or other protein, it has been established the existence of two types of RSV, A and B, whose variety may depend on the different clinical manifestations [13].

The metapneumovirus is responsible for 10–15% of the respiratory infections in children, with the same clinical impact than the VRS, with which shares a certain genotypic and epidemiological similarity. They also belong to the *Paramyxoviridae* family and are genetically similar to the pneumovirus of the avian flu.

The influenza virus A and B, and parainfluenza 1, 2 and 3 are less aggressive but also cause obstructive crisis in atopic and non-atopic children, because they cause desquamation of trachea–larynx–bronchial epithelial cells and bronchial submucosal oedema with infiltration of neutrophils and mononuclear cells, lesions that are reversible within 6 weeks [3].

Moreover, it is possible that in healthy children, RSV infection may be the cause of asthma to be developed later, but is more likely to result in the wheezing bronchitis process that will persist for some time. It is shown that, after severe infection, deterioration of the lung function occurs with increased bronchial reactivity to methacholine or histamine and to physical exercise, as well as the existence of specific IgE antibodies against the virus, which decreases over time, which could be related to the transience of broncho-obstructive crises.

More recently, rhinovirus, with its three subgroups A, B and C, has been identified as the main cause of respiratory infections which will later trigger half of asthma attacks in early childhood. The *in vitro* rhinovirus contact with blood mononuclear cell from adult asthmatics, compared to healthy subjects, demonstrates the production of IL-4 only in patients and less IFN γ in these than in controls, with a IFN γ (gamma interferon)/IL-4 ratio over three times lower in asthmatics, which shows that rhinoviruses directly induce the activity of Th2 cells, which does not rule out a greater responsibility of rhinoviruses in the pathogenesis of asthma.

Bacterial infections

Unlike viruses, bacteria do not exercise such a harmful function. Some bacterial antigens have an immunomodulatory capacity and repeated infections are what promote the predominance of the activity of Th1 versus Th2 lymphocytes, preventing sensitization to allergens.

Although the protective action against sensitization to pneumoallergens and food in children under 2 years of age seems confirmed, there are studies that nuance the findings, as is the potential adjuvant effect of endotoxins with sensitization to mites and perhaps other pneumoallergens.

-
- Epithelial lesions
 - Increased neuronal sensitivity
 - Increased penetration of allergens
 - Decreased ciliary clearance
 - Neural endopeptidase reduction and increased tachykinins
 - Increase in mediators from mast cells
 - Histamine
 - Arachidonic acid metabolism: prostaglandins, leukotrienes
 - Increase of cellular mechanisms involved in inflammation
 - Increased production of cytokines
 - Stimulation of chemotaxis: eosinophils, neutrophils
 - Regulation of β_2 receptors
 - Production of specific IgE against viruses
 - Allergic sensitization
 - Mediators release
-

Table 1. Mechanisms responsible for bronchobstructive crises caused by viruses.

Moreover, at very low concentrations (10 ng/ml), endotoxins are able to activate alveolar macrophages and promote bronchial inflammation, increasing bronchoreactivity both in asthmatic and healthy people; therefore, it is possible that in the severity of asthma, environ-

mental endotoxin levels may have an outstanding role not only in adults but also from school age, causing especially wheezy bronchitis or non-atopic asthma (6,10).

Conversely, if the asthmatic has a bacterial infection with respiratory location, it is most likely that obstructive symptoms will be intensified by the action of bacterial enterotoxins that act as superantigens, which promote the mechanisms by which the inflammation of the respiratory mucosa is established.

4. Pathogenesis of common symptoms in obstructive bronchopathies

The mechanisms by which the symptoms of asthma occur in preschool children do not differ from those that cause the process at any age. The permeability of the bronchial lumen is maintained by a neuro-chemical mechanism, but airway calibre may be affected either by an imbalance in this mechanism or by the intervention of certain cells and their biochemical mediators involved in the inflammatory reaction, usually triggered in childhood by an allergic reaction or an unfavourable home environment. In the obstruction of the wider bronchi, the dominant mechanism is the constrictor one, of neuro-chemical cause, whereas in the peripheral bronchi (small airways), inflammation is the greatest cause, through cellular mediators that are also constrictors.

BHR and inflammation are the pathogenetic basis of asthma. BHR is usually present already in the newborns of atopic families, although it is true that certain exogenous harmful agents can increase it. Similarly, the regular or intense exposure to these pollutants and also viral infections can cause broncholability in non-predisposed children. This increased broncholability occurs as the result of inflammation that such elements, including allergens, produce in the bronchial mucous membrane. These facts are demonstrated in adults and children from school age, but in preschool children under five, the immediate influence of these exogenous factors is less certain. The injured bronchial epithelium is restored after the aggression that leads to crises of dyspnoea or wheezing, and the permanence of the injury can depend on the intensity of the aggression and the repetition of the same, leading to more or less severe and repeated symptoms. Therefore, there is doubt whether the inflammatory reaction is established from the onset of the first symptoms or whether that permanence occurs after the recurrence of the crisis or after the most serious crises, on which the therapeutic approach may depend. Various conventional methods are used to study bronchial inflammatory reactions, although in younger children, it is not always easy to conduct them. The most common are the following:

Direct methods: (1) Cell study from sputum obtained by bronchoalveolar lavage (BAL), induced sputum, forced cough or aspiration. (2) Bronchial biopsy.

Indirect, non-invasive methods: (1) Exhaled nitric oxide measurement. (2) Exhaled breath condensate: evaluation of several measurements of the inflammation. (3) Blood eosinophilia assessment and eosinophil cationic protein (ECP) in serum levels.

The inflammatory reaction is a key event in the pathogenesis of asthma, as it is evident in adults and children from school age. It seems certain that inflammation is present even in the first

episodes of dyspnoea in children who later go on to develop allergic asthma, but there is no unanimity in the recognition of this fact. In the work of Maclennan et al. [14] in preschool children with episodes of severe dyspnoea repeated between 2 and 12 times in the previous year (it is known that from the third episode, asthma can be diagnosed in young children), it is found that a percentage of them had an increased serum IgE levels although it is not significant in relation to a control group.

It is needed to know whether the persistence of inflammation and its intensity corresponds with the frequency and severity of the crisis, that is, if the mucosal lesions are restored after mild episodes that occur at long intervals of time, with implications in the therapeutic approach aimed at preventing recurrences.

5. Initiation and evolution

The precocity of the onset of episodes of respiratory distress may be related to the severity of the process and its evolution over time. Although in some children, the first crisis occurs in the first months of life, the process has a markedly evolutionary nature, not presenting the first crisis of dyspnoea but after a period of time, which varies from child to child.

5.1. Asthma crisis: early onset

For the suspected allergic asthma to be well-founded, it is necessary that the crisis is repeated for at least three times, as it is known that a large number of infants suffer an episode of dyspnoea, possibly of infectious cause, estimating that this happens in between 15 and 32% of children under 5 years, who cannot be labelled as asthmatics until the atopic cause is confirmed, related to the progressive evolution of the process.

The first episodes of dyspnoea are usually caused by viral infections and occur most frequently in the cold months, and it is not uncommon that they are accompanied by light fever. Associated symptoms are similar to asthma: rhinitis, dry cough, shortness of breath, wheezing, dyspnoea, intercostal retractions.

Depending on the intensity and the phase of the crisis, auscultation will show from wheezing to silent areas as well as fine or coarse crackles, indicative of bronchoalveolar involvement.

In any case, it is necessary to make sure there is a bronchiolitis, by RSV, of which prognosis and treatment can differ from that of a simple catarrhal process.

After the first year, it is likely that crises are not triggered by viral infections, but that other environmental factors are responsible, not ruling out weather conditions changes, even in atopic children.

The repetition of three episodes of dyspnoea should alert of the possibility that those are the first manifestations of asthma, which will continue in the following years. It is therefore necessary to assess in each case the various predisposing and boosting elements of atopy and

asthma, such as the incidence of allergic disease in parents or close relatives, the coincidence in the child of other allergic processes or the environment in which the patient lives.

5.2. Atopic processes precursors of asthma

In chronological order, but not occurring in all cases, the first manifestation of atopy might be the sensitization to foods, mainly cow's milk when breastfeeding is absent, with symptoms in the first weeks of life. Eczema associated with sensitization to foods, from the third month, and rhinitis, as the first manifestation of respiratory allergy, that usually precedes asthma, both identities related with the persistence and increased intensity of the other two previous allergic processes.

The correlation between early sensitization to foods and later development of asthma is difficult to determine, but in these cases, given the repeated respiratory crisis by possible viral infection, the allergy study must be expanded.

Atopic eczema

Although atopic eczema may be the only manifestation of atopy in many children, there is no question about the relationship between eczema that start of in childhood and asthma, of which the first symptoms sometimes coincide with a cutaneous process, although in most cases, respiratory symptoms appear months or years later, even after skin lesions have disappeared or been attenuated, as it happens in many children before their third year.

To predict the risk of respiratory disease in children with eczema, an early allergologic study is advised. An elevated total serum IgE will be the early sign that will alert of the atopic nature of the process, but skin tests and assessment of serum IgE specific to foods and to the most common aeroallergens at home (mites, animal epithelium), which will alert about the risk of respiratory disease, which will start later.

Besides eczema, it is frequent that allergy to cow milk protein is revealed by digestive (vomiting, diarrhoea) or anaphylactic symptoms, which are also indicative of atopic predisposition and might be a precedent of asthma.

Rhinitis, rhinoconjunctivitis, rhinosinusitis

Not surprisingly, allergic sensitization is initially produced in the respiratory mucosa, as it is directly accessible to airborne allergens present in the air we breathe; and therefore, very often, respiratory pathology of allergic cause starts with symptoms of rhinitis. The frequency and persistence of nasal symptoms in early childhood are well-known fact, and their causes are diverse, from adenoiditis to allergic rhinitis.

Because of the proximity of the conjunctival mucosa, with similar characteristics to the respiratory one, it is not uncommon the concurrence with conjunctivitis (rhinoconjunctivitis). From the second or third year, it is neither uncommon the simultaneous conditioning of maxillary sinusitis, which may be limited to the inflammatory reaction of the mucosa, but that is often complicated by superinfection. Greater doubts arise in the relationship of rhinitis with

otitis media present in some children, although it seems that nasal provocation with pollen can cause a dysfunction at the inner ear level.

6. Clinical and allergologic diagnosis

The diagnosis of asthma in the first years of life is based on a thorough questioning (anamnesis) and in the allergologic study. Given the difficulties and controversies surrounding the concept of the disease at a such early age, the issue is to obtain data that, with the smallest possible doubt, may allow on one hand to establish the syndromic diagnosis, that is, the existence of intermittent episodes of bronchial obstruction and, on the other, allergic causality, in most cases, or the responsibility of other exogenous factors able to increase bronchial reactivity, which usually occurs at later ages. When the allergologic study is negative, the questioning may provided valid information to guide diagnosis to some other of the process in which coughing or signs of bronchial obstruction often dominate the case history, having to complete the study in accordance with the suspected diagnosis.

Physical examination is essential, since even if the child is asymptomatic while being examined, important data, such as a chest deformity, the presence of paradoxical breathing with depressed abdomen on inspiration, or the pathologic auscultation when the child breathes deeply, among other information, can be obtained. Moreover, functional exploration will also provide data that can be decisive for the definitive diagnosis.

6.1. Anamnesis

A good interrogation often provides critical data to guide the diagnosis. It should include information about family precedents and medical history, diseases of probable allergic cause cited above, symptomatology, chronology of symptoms, medication use and its effectiveness.

6.2. Other medical history

Primary immunodeficiencies also occur in repeated bronchopaties, by viral or bacterial infections, with symptoms that may remind those of asthma; hence, the need for information on whether there have been relatives with any of these diseases (Wiskott–Aldrich, Hypo or agammaglobulinaemia, Di George, etc.), processes in which predisposition is transmitted by recessive inheritance.

6.3. Symptomatology: chronology

It is not enough to know that the child has episodes of cough or dyspnoea, but it must be also known if the cough is dry or soft, if breathing difficulty improves or worsens after a coughing spell, if there is expectoration, or if it is predominant at night, among other features. It is also necessary to know the intensity of respiratory distress, if it is accompanied with nasal flaring, or if it disrupts sleep. The existence of fever is also a point of great interest because an infectious trigger can be assumed.

The chronology of the succession of symptoms in each episode is another fact of interest, as it is whether dyspnoea appeared abruptly or was preceded by nasal or pharyngeal symptoms, as well as at what time it began, for example, if it was at night or after eating some food. The biggest interest is in the chronology of the process, taking very much into account the age at which symptoms started and whether they were intense from the beginning (mucoviscidosis could be suspected of).

6.4. Medication: use and effectiveness

Usually, when a child presents some of the symptoms that characterize bronchial obstruction, some medication is usually given, and their effectiveness must be critically evaluated, in order to better guide the diagnosis. It is not always possible to reduce or eliminate breathing difficulty with a bronchodilator, when mucous secretion is predominant, or preventing relapse with an inhaled corticoid, when there is no inflammation because the airway obstruction is of another nature.

6.5. Allergologic study

Skin tests

They may already be positive even in the second month of life, to cow's milk protein (casein, β -lactoglobulin). At 4 months, it is possible to show sensitization to other foods, especially egg proteins, increasing the percentage in the coming months, as new foods are introduced. Sensitization to pneumoallergens comes later. It is estimated that approximately 40% of atopic children under 3 years are sensitized to dust mites, reaching 70% in those over 4 years. Figures for animal epithelia range from 3 to 5% in the younger, being 6–8% at around 4–5 years of age. Sensitization to pollens also depends on the place of residence, in relation to the time and intensity of exposure.

The *prick test* is the least traumatic and totally reliable and reproducible technique that has replaced intradermoreaction. It is virtually painless, very well accepted by young children and easily performed with the same technique at any age.

Usually, the study is limited to dust mites, the most common being *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, but others can be added, such as *B. tropicalis*, *Acaro siro* or others that are common in the geographical area of residence: animal epithelia, cat and dog (the most frequent, even if they are not present at home) or other animals with which they may have contact. Fungi can be found anywhere at home. The most important, that allow conducting immunotherapy, are *Alternaria tenuis* and *alternata*, and *Cladoporium* ssp. At homes with high humidity, other fungi must be tested, such as *Aspergillus*, *Penicillium*, *Fusarium*, *Mucor*, etc. Earlier than at 3–4 years of age, sensitization to pollens is unlikely, although there is no objection to include in the list of allergens a mixture of pollen from wild grasses (*Poa pratensis*, *Festuca*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*) that are most often sensitizing. Other pollens depend on the geographic area in which they reside.

Total serum and specific IgE

From birth, the serum non-specific IgE level increases to reach figures close to those of the adult into adolescence (**Table 2**). IgE has some physiological functions, such as defence against helminth parasites, although it is supposed to participate in other defence mechanisms. In the atopic individual, the regulator mechanism of IgE production is genetically altered by the prevalence of the activity of Th2 lymphocytes already mentioned. Therefore, it is common in these patients to find an elevated serum IgE level, not having yet been specifically produced against any allergen. Hence, the finding of an elevated total serum IgE may be linked to symptoms suggestive of allergic disease, and in consequence, this finding has considerable guidance significance. However, in any case, it must be taken into account that the possibility of elevated total serum IgE, especially if the figure is very high, might be related to other processes such as parasites or certain immunodeficiencies (**Table 3**).

The assessment of total and specific to allergens IgE is based on radioimmunoassay, fluorometric or enzyme techniques. As a first step, in a suspected allergic disease, a method that includes a mixture of allergens that are suspected to be frequent in childhood (food and airborne allergens: Phadiatop[®] infant, Immuno-CAP, 3gAllergy) can be used, the positivity of which may indicate specific sensitization to any of the antigens included. Subsequently, the allergen that led to the positive test must be identified in order to establish the preventive and specific treatment as appropriate.

Comparing the diagnostic value of skin tests and the specific IgE, it can be said that both are equivalent; however, it is always advisable to check the diagnosis with both tests. To complement the immunoallergologic study, it is required to assess other serum immunoglobulins, IgG, IgM and IgA, as it is not uncommon that the deficit of some of them may favour respiratory infections. It is not unusual that this happens when there is selective deficiency of IgA, a common immunodeficiency (1/700 in the general population and 1/200 people with allergies) that sometimes goes unnoticed by a low clinical expression in most cases.

Eosinophilia: cationic protein

In peripheral blood, increased eosinophils above 500 cells/mm³ may indicate allergic reaction in any organ system (lung, skin, digestive tract) where the process is in an acute phase or immediate to clinical reaction. The presence of eosinophils in the bronchial exudate or tissue obtained by biopsy reveals the characteristic inflammation of an allergic reaction. When not in these cases, eosinophilia may be normal, and very high levels are usually due to many processes, parasitosis most of the time.

More valuable is the elevation of serum level of the enzymes from eosinophils, mainly ECP, easy to determine. It is necessary to be cautious when assessing the increased serum ECP as a marker of a certain bronchial inflammation, given the variability of the figures that can be found. According to Koller et al. [12], it could be a good marker even after the first episode of dyspnoea, finding a higher ECP in infants which a year later were diagnosed with asthma than in those who did not developed the disease, estimating that figures higher than 20 µg/l

could have a strong prognostic value. However, Pohunek et al. [23] found no differences in ECP levels in children under 3, between both diagnoses when children were asymptomatic, as opposite to when they were suffering a crisis. From his work, it can be deduced the interest to assess the enzyme during a bronchobstructive crisis, in yet not diagnosed children, especially during the first episode, for the possibility of establishing prophylactic measures to prevent or delay the establishment of asthma.

Age	Geometric mean kU/l	+1 SD	+2 SD
Umbilical cord	0.3	–	–
6 weeks	0.7	2.1	6.1
3 months	0.8	1.8	3.8
6 months	2.7	6.6	16.3
9 months	2.4	4.2	7.3
12 months	7	21	58
2 years	11	26	61
3 years	11	21	40
4 years	20	37	70
7 years	26	75	221

Table 2. Normal serum IgE levels (Kjellman and Johanson, 1976).

Parasitic infections

Ascaris lumbricoides

Toxocara canis

Entamoeba haemolítica

Echinococcus

Trichinella spiralis

Filaria

Others

Immunodeficiency disorders

Wiskott-Aldrich S.

Di George S.

Hiper IgE S.

Selective IgA deficiency

Table 3. Non-allergic process more frequents in small children that occur with high IgE.

Since allergic rhinitis often precedes the onset of bronchial symptoms, eosinophil count and ECP in nasal mucus can be a good indicator of allergic predisposition and the possible progression of the disease to the lower airways. Presence of allergy will be suspected if the percentage of eosinophils of the total cells of the smear exceeds 10%. In the same sample, ECP and even total and specific IgE can be assessed, in which variation after immunotherapy can be a good indicator of the effectiveness of the treatment [15].

7. Respiratory function exploration

7.1. Children under 2 years of age

In the diagnosis of asthma or of wheezy bronchitis, exploration in the infant has a relative utility. However, the greatest value of early exploration is focussed on distinguishing the processes that occur with breathing difficulties of various kinds, some of bronchopulmonary origin (cystic fibrosis, bronchopulmonary dysplasia, primary ciliary dyskinesia, bronchitis obliterans, malformations) or extrapulmonary (vascular rings, ductus persistence, other heart disease), which can raise the differential diagnosis with severe asthma or resistant to habitual treatment. Exploration in infants should be restricted due to the risk involved in the need to sedate the child, requiring hospital environment, which should be restricted to the following indications, in order to diagnose other possible diseases with apparent symptoms of asthma, although symptoms can have a different origin:

1. Presence of tachypnea, hypoxia, cough or dyspnoea of unexplained causes that cannot be studied with other techniques.
2. Serious and chronic obstructive diseases that do not yield to the usual treatment of corticoids and bronchodilators, both inhaled.
3. Non-characteristic respiratory symptoms, with the likelihood of an extrabronchial origin, in order to assess the origin and severity of the symptoms (e.g. vascular rings).
4. Research, necessary in all diagnostic or therapeutic procedures, but risk must always be assessed and therefore have the corresponding parental consent and approval by ethics committees.

Methodology

The most common method is the rapid thoracoabdominal compression at ordinary volume. As the child breathes normally and at the end of an inspiration, an insufflation of the jacket is provoked to induce maximal forced expiration, thus obtaining the parameter of the maximum flow at functional residual capacity (V_{maxFRC}). Both the figure obtained and the appreciation of the layout of the flow-volume curve will provide information on the permeability of the airways and the degree of obstruction, if any.

Less suitable is the one based on thoracoabdominal compression provided by a pneumatic jacket, a kind of inflatable vest connected to an air compressor through a non-distensible thick

tube. The exhaled airflow is measured with a pneumotachograph of appropriate size that adapts to the mouth through a mask. The biggest drawback is the need to sedate the child with chloral hydrate orally, which is not without risks.

As forced expiration is provoked during a normal respiratory movement, that is ordinary volume, this technique does not provide the value of the forced vital capacity (FVC) obtained with a spirometry, and therefore, no FEV_1 or the FEV_1/FVC ratio and $FEV_1\%$ can be obtained. To acquire these values, we must perform the technique known as rapid thoracoabdominal compression with previous insufflation, which is artificially forcing a deep breath, for which, by a compressor connected to an oral–nasal mask, air is blown into child up to the maximum vital capacity and requiring a pressure of 2–3 kPa (20–30 cm H₂O). Afterwards, a rapid inflation of the jacket is performed to provoke the forced expiration. This way, valuable data comparable to those provided by spirometry, can be obtained.

7.2. Children over 2 years of age

Although the following techniques are used in older children who do not cooperate during the exploration, some of them are also used in infants with devices adapted to their size (plethysmograph), requiring sedation of the child. With them, precise information on airway resistance (AWR) and compliance can be obtained.

The AWR is defined by the difference of pressure between both ends of the airways, that is the mouth and alveoli when an air flow of 1 l/s occurs. The circumstantial narrowing of the bronchi increases resistance, deducing the intensity of the obstruction by the degree of the increase in the value of the AWR.

Compliance refers to the intensity of the rigidity of the respiratory system, defined by the increase of the volume produced divided by the increase of the pressure unit, so that the less pressure necessary to produce an equal increase in volume, the higher the compliance.

The resistance can be measured through well-known techniques, such as interruption of flow (R_{int}), forced oscillation and its oscillometric impulse variation and plethysmography, a technique which also allows the compliance to be known.

Flow interruption (R_{int})

The interruption of the airflow during normal breathing causes rapid and complete occlusion of the airways, enabling the measurement of the pressure in the oral cavity immediately before the interruption and during the normal respiratory cycle using a pneumotachograph. The measurement of the alveolar pressure is deduced from the pressure value established in the mouth when the momentary interruption of flow occurs. If this is suddenly interrupted, for a split second, an immediate rise in pressure occurs in the mouth. The pressure measured this way is very similar to that found in the alveoli, allowing the measurement of *resistance*, comparing this pressure with that prevailing in the mouth just before shutting off the flow. The Unit used to measure the resistance is Pascal in litres per second. In short, R_{int} is the most simple and affordable method to learn the AWR in young children, with the only requirement

being that they breathe normally through the tube that is fitted into the mouth, preventing nasal breathing by pinching the nose.

Forced oscillation: impulse oscillometry

Forced oscillometry is based on the application of oscillatory pressure changes and therefore airflow, measuring the resistance from the relationship between the two. Easy to perform, it only requires that the child breathe calmly through a tube—not longer than 1 m—attached to the mouth and a volume of 100 ml, having inserted a pneumotachograph in between. The patient's air flow is superimposed with a oscillating flow of 2 ml at a frequency of 10 Hz coming from a sinusoidal generator, thereby leading to pressure variations which are not perceived by the child and are proportional to the 'total' patient breathing resistance.

Best results are obtained with a newer variation of this process, the *impulse oscillometry* (IOS). A controlled deviation of the membrane of a loudspeaker, which is adapted to a nozzle, leads to the excitation of the airflow generating pressure impulses, from which ratio, the value of the central airways resistance and the lung elasticity is obtained; and therefore, the values result from the relationship between the exerted pressure and the airflow [4].

Plethysmography

A plethysmograph measures the changes in volume of the thorax. Its principle is the law of Boyle and Mariotte, whereby the volume occupied by a mass of gas, at constant temperature, is inversely proportional to the pressure. By plethysmography, intrathoracic gas volume (TGV) through the volumetric variations of the thorax is measured simultaneously with the AWR, and from these values, conductance can be calculated.

Bronchodynamic tests

The above techniques report on the current state of the permeability of the lower airways but do not provide information on the level of BHR, the increase of which is significant in the diagnosis of asthma. Hence, the need to carry out tests to make it evident, that is bronchoconstrictor (methacholine, histamine) and bronchodilator (β -mimetic) tests. The three technical variations mentioned can be used for this purpose

8. Differential diagnosis based on the dominant symptoms

Many processes that start at preschool age manifest similar symptoms to those of bronchitis or asthma. The too early start of these symptoms, sometimes shortly after birth or in the first months of life, is a matter of warning about the possibility of a process less frequent than those, but even if the process has a late start, the other possible causes of cough or dyspnoea should never be forgotten, avoiding the comfortable position of starting a routine treatment, which may not always be beneficial and could even delay the establishment of appropriate therapeutic measures.

The assessment of cough as a symptom, that in the case of asthma is often maintained between the crises of dyspnoea or wheezing, has some characteristics that can guide to others diagnosis not uncommon at preschool age, with symptoms that may be common to those of asthma, and therefore is mandatory to take them into account in order to conduct a correct differential diagnosis (**Table 4**).

Dominant symptom: cough	Pseudoasthmatic bronchial symptoms	LESS common processes
Maxillary sinusitis	Immunodeficiencies	Congenital anomalies
Adenoids	Bronchiolitis	—Laringo and tracheomalacias
Rhinopharyngitis	Bronchitis obliterans	—Vascular rings
Whooping cough (pertussis)	Wheezy bronchitis	Alpha-1-antitrypsin deficiency
Primary ciliary dyskinesia	Tracheobronchial foreign body	Hypersensitivity pneumonitis
Eosinophilic bronchitis	Mucoviscidosis (cystic pancreatic fibrosis)	Pulmonary hemosiderosis
	Gastroesophageal reflux	Alveolar proteinosis
	Tumour or mediastinal adenopathy	Eosinophilic lung

Table 4. Most significant processes in the differential diagnosis.

9. Practical summary for diagnostic approach

1. Medical history
 - a. Family history: allergic pathology, respiratory or genetic pathology.
 - b. Own background: allergic comorbidity (eczema, allergies to milk proteins, etc.), recurrent infections
 - c. Symptomatology: for each one of the symptoms, it is necessary to specify the characteristics, age of onset, duration, severity, recurrence, association between them.
 - d. Environment: smoking, irritating substances, pets, rural area
2. Clinical examination
 - a. In a symptomatic stage or during an interval
 - b. General inspection: development, nutrition, colour of skin and mucous membranes, acrocyanosis. If there is coughing: characteristics. Nasal or mouth breathing.
 - c. Thoracic inspection: circulation, retractions, respiratory rate, dyspnoea. Auscultation: wheezing, rhonchus, crackles, localized or generalized, changing or not present when coughing. Localized hypophonia. Percussion: localized dullness.
 - d. Nasopharyngeal: nasal flaring, anterior or posterior rhinorrhea, appearance of mucus. Size and appearance of the tonsils: visible adenoids?
3. Initial Investigations in all cases

- a. Complete blood count. ESR
 - b. Immunoglobulin G, M, A and E
 - c. Paranasal sinuses X-ray. Adenoid RX if hypertrophy is suspected
4. If all the above rules out the existence of a pathology different of asthma or wheezy bronchitis, continue the study to confirm it.
 5. If the above tests fail to lead to that conclusion, if the symptoms are important or if after an initial diagnosis of asthma or bronchitis no improvement is achieved with standard therapy (inhaled bronchodilators and corticoids) the following tests should be made:
 - a. Sweat test. Also required in the initial study, if symptoms are of an early onset, severe, with general deterioration or a family history of cystic fibrosis
 - b. Esophageal pH monitoring
 - c. Thoracic X-ray, front and profile: assessing abnormal masses, adenopathy, condensation, etc. Mediastinal swaying following the suspicion of a foreign body aspiration, especially in children under 3 years
 - d. Other imaging techniques based on radiological findings or presumed diagnosis: computed tomography, magnetic resonance, gammagraphy.
 - e. Serum antibodies against RSV, influenza, parainfluenza and other
 6. If the above tests do not lead to a diagnosis in accordance with the clinical suspicion or in case of uncertainty, it is recommended that, successively:
 - a. Lung function study
 - b. Serum precipitin against actinomycetes
 - c. BAL: hemosiderophages (also in gastric contents), PAS+ protein, eosinophil
 - d. Alpha-1-antitrypsin serume
 - e. Bronchoscopy
 - f. Lung biopsy

10. Treatment

Although asthma treatment at any age is based on the same principles, the characteristics of the disease and the pathophysiology in pre-scholar children require adjusting each of the measures available to the peculiarities of the age.

Overall, these measures aim primarily to combat the cause of the disease, that is *etiological* treatment based, in one part on environmental measures (reduction of household allergens and reducing environmental pollutants) and on the other in desensitization by immunother-

apy. The *pathogenic* treatment is based on fighting the bronchial inflammation, trying to prevent or eliminate it, being chromones, anti-leukotrienes and corticoids the appropriate medications, and finally, the *symptomatic* treatment with short-acting bronchodilators, mainly β_2 -agonists.

10.1. Etiological: specific immunotherapy

Immunotherapy is the only therapeutic procedure, for its widely proven effectiveness, which decreases the sensitivity (desensitization or hyposensitization) to the responsible allergens, in which its mechanisms of action are essential to prevent further sensitization, as is well known (in short, the Th1/Th2 balance).

WHO supports the term 'allergy vaccine' and considers this as the only treatment that can alter the natural course of allergic diseases and also prevent the development of asthma in patients with allergic rhinitis.

Although the age to initiate immunotherapy has been questioned, multiple studies and the own experience show the need for an early start, from the third year of age, provided that the requirements set out in **Table 5** are met.

Recent and extensive literature reviews conclude that it is a serious need to consider the start of immunotherapy in children under 5 years of age that fulfil the required conditions ([7, 8])

– Correct clinical diagnosis

- In case of asthma:
 - mild to moderate intensity
 - respiratory function within normal limits: parameters not <70% of those foreseen
 - Accurate allergologic diagnosis, skin tests and serum specific IgE are sufficient
 - Exceptionally provocation with allergen will be used
 - Right choice of allergen/s to be included
 - Extract quality: purity, standardization, coadjuvants
 - Correct therapeutic regimen monitoring: dose, intervals
 - Periodical clinical controls
 - Minimum period of 3 years, and at least 1 year without onset of symptoms
 - Prescription and control by a allergy and paediatrics expert
 - Early onset
-

Table 5. Premises for immunotherapy for optimal results in paediatrics.

Some of the few problems that can cause subcutaneous immunotherapy could be avoided if administered by sublingual channels, which is virtually risk-free. A problem in young children is the difficulty of successfully administering the pharmaceutical preparation, keeping it under

their tongue for the right time, which is likely to be simplified with the most recent preparation in tablets or in atomiser (spray) (WAO).

10.2. Pathogenic: antiinflammatories

Chromones

Under this description, cromolyn sodium and nedocromil are included. Both act by blocking the chloride channels of the membrane in the cells involved in the allergic reaction, especially mast cells and eosinophils, but also epithelial and nerve cells. On the activation of chloride channels depends the crossing of Ca ions into the cell, required for the activation thereof to occur. When these cells are stimulated (allergens, non-specific agents), there is a release of mediators (mast cells) and the commencement of the elements involved in the allergic reaction. When idle, chloride channels are closed and this is what is achieved with chromones, the blocking of the channels, thereby preventing activation of the cells that would lead to the allergic reaction. For this reason, we must consider that chromones act more like preventive agents of inflammation than anti-inflammatories.

Although currently they are less used as inflammation preventives, cromolyn could be indicated in preschool age, before asthma reaches a significant degree of severity, that is in mild intermittent or persistent asthma and in moderate asthma, in which case an inhaled corticoid or salbutamol could be added.

Anti-leukotrienes

These are medications that block the action of cysteinyl leukotrienes that might prevent the onset of one of the most important mechanisms involved in the production of the inflammatory reaction of the bronchial mucosa. They specifically avoid the activity of those on specific receptors localized in bronchial smooth muscle and in bronchoalveolar blood vessels. This is intended to prevent the development of inflammation in the initial period of obstructive bronchial disorders and also contribute to avoid the swelling to persist or increase, once present when asthma has been clinically established.

Knowledge of the receptors of the leukotrienes is a key for the intended purpose. Pharmacological studies have determined that cysteinyl leukotrienes activate at least two types of receptors, named CysLT1 and CysLT2, being the first found in the bronchial muscle and the second in the pulmonary venous system. Depending on the consequences of the activation of these receptors by the corresponding leukotriene, the antagonists used therapeutically will produce diverse positive effects, even more prominent in children than in adults. On one hand, they achieved a discrete bronchodilation resulting as a consequence of counteracting the prolonged constrictor effect of leukotrienes.

In short, anti-leukotrienes behave more like inflammation preventives than as anti-inflammatories, an activity that is better performed by inhaled corticoids, and therefore, both treatments can be used simultaneously.

Of the preparations available (pranlukast, zafirlukast and montelukast), only the latter is indicated in children under 5 years of age, available in chewable tablets and granules. Since the permanence of the inflammatory reaction in all probability depends on the recurrence of episodes of dyspnoea and their intensity, montelukast may prevent the progression of the process in milder cases without resorting to inhaled corticoids. The advantage of oral administration and the single daily dose make this drug of easy acceptance and secure compliance. In asthma of moderate or severe intensity, it will be necessary to combine the treatment with inhaled corticoids.

Several studies confirm the efficacy of the treatment with montelukast in children between 2 and 5 years of age even reducing the number of episodes caused by viral infections (5). Respiratory function improves from the early days of treatment, even in children under 2 years of age as a result of the reduction of the inflammation.

Corticoids

Physiologically, corticoids activate the cytoplasmic receptors that most cells have; the same which corticoids administered therapeutically act upon, with a power that depends on the affinity of each product with these receptors, entering into competition with the natural hormone. They are known to inhibit various cytokines, especially ILs (IL-1, IL-2, IL-3, IL-4, IL5, IL-6 and IL-13), tumour necrosis factor alpha (TNF- α) and the colony stimulating factor in granulocytes and macrophages (GM-CSF), while increasing the IFN- γ and IL-12, that is they reduce the action of Th2 leukocytes, and consequently, the number of basophils, eosinophils and mast cells in bronchial epithelium is reduced. The risk of any side effects resides on the fact that only between 10 and 40% of the drug administered by inhalation reach the bronchi, depending on the inhalation system. The rest of the substance remains in the mouth and is swallowed, getting into the general circulation via the gastrointestinal tract. They are mostly metabolized in the liver, being removed, but another part remains in the bloodstream, reaching the lung, where they produce the same effect as corticoids administered by other means. At the same time, part of the fraction that reached the lung by inhalation passes into the bloodstream, following the same path as the ingested portion. Some of these drawbacks are avoided with ciclesonide, with little oral bioavailability (only 10% of the active molecule is generated in the oropharynx), so that the pharmacotherapy is mainly dependent on deposit and pulmonary absorption.

The most prominent undesirable effects are the hypothalamic-pituitary-adrenal (HPA) axis suppression and growth retardation that, although it seems to be compensated in years not affecting final adult height, it must be considered in order not to fall into the usual trend of increasing doses when the desired effects are not achieved. Prolonged treatments or higher doses may result from severe hypoglycemia to cushingoid features. In children, it is rare that osteoporosis occurs. Depression of immunity caused by corticoids may increase the risk of infections. Other less important effects are of cutaneous nature, such as oral thrush or skin atrophy, less common in children.

A weighting between dose/guideline/efficacy/duration of therapy/adverse effects should be established. Effective maximum doses of inhaled corticoids in children have been established,

which is 400 µg/day for beclomethasone dipropionate and budesonide, and 200 µg/day for fluticasone propionate. Despite the better tolerance with ciclesonide, only studies from 4 years of age have been published, with a maximum dose of 160 µg/day. Higher doses of any of them do not improve results and increase the risk of side effects. The daily dose is usually divided into two intakes, but can be simplified without losing efficiency, administering once the total daily dose in the morning, as the physiological hormone production would be reduced if taken at night. In mild-moderate asthma, there is an increased permeability of the airways, and therefore, the drug penetrates with greater ease making the most of the administered dose, hence the recommendation to use lower doses in milder cases.

The oral or intravenous administration of corticoids is reserved for asthma crises of medium or severe intensity, either at home or in hospital. The dose of 1–2 mg/kg/day of prednisone, prednisolone or methylprednisolone should not be prolonged for more than 5 days, but if more time is required, it should be progressively reduced.

Although inhaled corticoids may show a symptomatic improvement, in the long term, the course of the disease does not seem to change; therefore, the duration of the treatment will depend on the results and even a diagnostic review should be considered.

10.3. Symptomatic: bronchodilators

Beta 2-agonists

The indication of short-acting β_2 -agonists (salbutamol, terbutaline) is the bronchospasm crisis, whatever its intensity. The most appropriate route of administration is inhalation, achieving improvement in a few minutes, in the case of acute asthma attacks. Continued inhalation is indicated for the inpatient treatment of severe crisis. Other routes of administration are subcutaneous and, above all, continuous intravenous to which we must turn in severe crisis. The oral route may be useful in mild cases or after achieving a significant improvement with the inhaler.

In preschool children, the most common is the metered-dose inhaler (MDI) with a spacer or with a nebulizer when it is necessary to continuously administer the drug. Otherwise, the efficacy appears to be similar with both inhalation systems. Powdered formula, for which there are different systems (turbuhaler, diskhaler, accuhaler), is less useful at this age, because a greater degree of collaboration is required.

Anticholinergics

Ipratropium bromide, is a derivative of atropine, which does not produce the side effects of atropine. Because of its low lipid solubility, it hardly passes biological membranes and produces an effect almost exclusively in the bronchial tree, when administered by inhalation. The recommended dose for all ages is 0.04 mg three or four times daily. The greatest benefits are achieved in asthma attacks triggered by non-specific agents, which may act via vagal.

The bronchodilator action is more deferred with this product, but it remains longer than with the β_2 -mimetic, and in some cases might be administered simultaneously, for which there are

even preparations with formoterol or salbutamol and ipratropium bromide, although it is preferable to dispense them separately.

11. Therapeutic schemes

11.1. Treatment of crises

The therapeutic approach in episodes of respiratory difficulty should be preceded by a reflection on the different diagnostic possibilities, since various acute processes may manifest common and sometimes confusing symptoms, needing different treatments, care and control. The severity of the case will be visible by observation and by assessing dyspnoea, intercostal, subcostal or supraclavicular retractions, colouring and sensory. The assessment of breath sounds that can be discernible by auscultation is essential for diagnosis as it can indicate the location of the process (trachea, central or peripheral bronchi, alveoli), if bronchospasm, condensation or atelectasis are present, which can be deduced from the presence or prevalence of wheezing, stridor, crackles or coarse crackles, decreased murmur, among other respiratory noises. Other causes of severe respiratory distress that may resemble an asthma attack, should also be considered, especially the frequent aspiration of a foreign body, which requires radiological confirmation, and bronchiolitis, both of a sudden onset and which can also occur in children that already suffer from asthma. Once it is concluded that it is a bronchospasm crisis, its severity will be assessed and of this assessment will depend the therapeutic activities:

1. Mild: β -mimetic inhaled: according to severity: 2 doses \times 20 min, maximum 3 doses, or every 4–6–8 h depending on severity; maximum 24–36 h.
2. Moderate: add oral corticosteroids: 1–2 mg/kg/day: 3–4 days
3. In both situations, after the improvement, treatment with β -mimetic continue orally (\pm 1 week) or mucolytic and expectorant, if required.
4. Grave whose intensity, more complex processing conditions outlined in **Table 6**.

Immediate:

Oxygen inhalation by flow of a β -mimetic:

Salbutamol: 2.5–5 mg

Terbutaline: 5–10 mg

(Half dose in children under 1 year)

Intravenous hydrocortisone 100 mg

In more severe cases, adding:

Aminophylline e.v.: 5 mg/kg in micro-drip (20 min) followed continuous infusion of 1 mg/kg/h

(Investigate whether there were received a dose above)

Inhaled ipratropium bromide 0.25 mg (0.125 in infants)

Controls:

Symptomatology

Oximetry: to reach $\text{SaO}_2 > 92\%$

Monitoring

If no improvement in 15–30 min:

Salbutamol: Continuous inhalation or every 30 min until

to get better. After follow the evolution every 1–4–6 h
 Aminophylline: continuous infusion (monitor serum)
 Ipratropium bromide: every 6 h
 Hydrocortisone repeated every 6 h, or
 Methylprednisolone ev: 1–2 mg/kg/day (spread in 4 doses)
 If there is no improvement or worse:
 Admission to Intensive Care Unit:
 Protocol status asthmaticus

Leaving the hospital:
 Salbutamol or terbutaline inhaled or oral, to a week
 Methylprednisolone oral, decreasing doses, depending on the dose
 and previously administered treatment days

Medical surveillance: 2–4days

Table 6. Treatment of severe asthma attacks in children under 5 years of age (Abridged outline various guides).

11.2. Maintenance treatment

Pharmacological treatment mainly depends on the frequency and intensity of the symptoms, the severity of which is deduced for each single case (**Table 7**).

When symptoms occur sporadically (occasional episodic) unless there is a crisis, a treatment is not usually needed. When the frequency is higher (frequent episodic), it is recommended to start with montelukast, which will act as an inflammation preventive and if there is a failure to control the symptoms, a low-dose inhaled corticoid will be added.

If symptoms occur more frequently, with intermittent crises (moderate persistent), apart from montelukast, inhaled corticoids without exceeding the maximum recommended dose will be added. If control is not reached, cromolyn sodium nebulizer three times a day will often achieve satisfactory results. Once symptoms are controlled, continue with montelukast and inhaled corticoids.

From the third year of age, when the allergic causality of the process is certain and the responsible allergen has been identified, immunotherapy is the fundamental etiological treatment, provided that the above criteria are met, following WHO recommendations.

Occasional episodic	Infrequent episodes: 1 every 4–6 weeks or less Asymptomatic intercrisis
Frequent episodic	Over 1 episode in 4–6 weeks Intercrisis-isolated symptoms, which do not affect the child’s activities or sleep
Moderate persistent	Very frequent exacerbations Frequent intercrisis symptoms that interfere with daily activities and sleep
Severe persistent	Daily or nearly daily symptoms, with frequent episodes of respiratory distress Disrupted daily activity and sleep

Table 7. Classification of asthma in children under 6 years of age.

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