Arch Bronconeumol. 2009;**45(Supl 7)**:2-35

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

GEMA (Spanish Guideline on the Management of Asthma)

Method

In order to standardize the method for finding and classifying evidence and the recommendations in this guide, all the editors were given training in methodological aspects by collaborators from the Cochrane Latin American Center. In order to identify publications, the usual procedure for preparing clinical practice guidelines was followed[1] and the reference lists of the main international clinical practice guidelines were reviewed[2-4] in order to identify the main systematic reviews and clinical trials. These guidelines were found in specialized databases (National Guideline Clearinghouse, National Library of Guidelines) and in the TRIP medical literature meta-search engine database. The databases of the Centre for Reviews and Dissemination (DARE and HTA database) and The Cochrane Library were consulted to identify systematic reviews and evaluations of additional technologies. To complete the search the data was updated to include any systematic reviews and relevant studies in the major electronic databases of original studies (MEDLINE, CENTRAL and EMBASE) that were published after the search dates.

To assess the quality of the evidence, an alphabetical classification, which graded the quality of the information into four categories (A, B C, D), was employed (Table 1). This classification reflects the level of confidence in the results that were obtained in the studies available[2]. Category A corresponds to a high level of quality and category D to a very low level of quality. The confidence in the results, in the case of category A, is high and it is improbable that subsequent studies could modify their findings. In contrast, in the case of the lower categories, such as C or D, confidence is low or very low, and it is very likely that later studies could alter the results or even the rationale underlying them.

However, as the editors of this guide, we understand that although this classification is very useful for categorizing evidence designed to assess the therapeutic efficacy of drugs or other interventions, it tends to underrate other equally important studies, such as trials on the diagnostic efficacy of certain tests or epidemiological data. This is why in this guide much of the evidence available for evaluating important studies on the suitability of certain diagnostic tests has been graded with a C.

Given the recent appearance of new approaches to classifying the quality of evidence based on other aspects in addition to study design[5], future updates of GEMA will try to reflect these changes in the way it develops its recommendations. This time certain conceptual aspects and basic features of the GRADE system (http://www.gradeworkinggroup. org/) have been included, although this system has not been applied in any strict sense [5].

Once the quality (confidence in the results) of the studies at our disposal had been classified, the strength of our recommendations had to be classified, meaning our confidence that compliance with a particular recommendation would lead to more benefits than risks. To establish the strength of recommendations, the quality of the information (based on the above mentioned classification), the risk-benefit ratio of interventions, the costs and the values and preferences of patients were considered. Then, the recommendations were classified into two types: strong and weak recommendations (in favour of or against). Strong recommendations (R1 recommendations) are those the group that drew up the guidelines are convinced will be associated with more benefits than risks. For this type of recommendation the text uses expressions such as "it is recommended" or "we ought to". Weak recommendations (R2 recommendations) are those for which there is uncertainty as to whether their application would entail more benefits than risks and the language they use includes expressions such as "it might be considered" or "it could be regarded as".

Table 1
Classification of the quality of the evidence obtained from searches

Evidence category	
A	SR of RCT with or without MA and RCT with a low risk of bias. The evidence is based on a substantial number of well designed studies with consistent results.
B	SR of RCT with or without MA and RCT with a moderate risk of bias. The evidence is based on a limited number of studies and/or inconsistent results.
C	The evidence is from non-randomized, observational or uncontrolled studies.
D	Clinical experience or scientific literature hat cannot be included in category C.

RCT: randomized clinical trials; MA: meta-analysis; SR: systematic reviews (modified from GINA 2006[2]).

Introduction

Definition

Asthma is a syndrome that includes various phenotypes that share similar clinical manifestations but have etiologies that are likely to be different. This makes it difficult to propose a precise definition; the commonly used definitions merely describe its clinical and physiopathological features. From a pragmatic point of view, it could be defined as a chronic inflammatory disease of the respiratory tract, whose pathogenesis involves various types of cells and inflammation mediators. It is a process that is partly determined by genetic factors and is characterized by bronchial hyperresponsiveness and varying degrees of airflow obstruction, which is total or partially reversible, either as a result of pharmacological action or spontaneous.

Prevalence

Asthma prevalence varies ostensibly worldwide, ranging from 2% in Tartu (Estonia) to 11.9% in Melbourne (Australia). The prevalence

Table 2
List of Acronyms

ACQ	Asthma control questionnaire	LRA	Leukotriene receptor antagonist
ACT	Asthma control test	mg	Milligram
API	Asthma predictive index	mmHg	Millimetres of mercury
AR	Allergic rhinitis	MT	Methacholine test
ARIA	Allergic rhinitis and its impact on asthma	n	Sample population
Bd	Bronchodilation	NARES	Non-allergic rhinitis with eosinophilia syndrome
BDT	BronchodilatoryBronchodilator test	NEB	Nebulized
BHR	Bronchial hyperresponsiveness	NIMV	Non-invasive mechanical ventilation
CAN	Asthma control in children	NKTC	Natural killer T cell
COPD	Chronic obstructive pulmonary disease	NSAID	Non-steroidal anti-inflammatory drug
COX	Cyclooxygenase	O_2	Oxygen
CT	Clinical trial	OA	Occupational asthma
CT	Computerized tomography	OR	Oral route
DCA	Difficult to control asthma	$PaCO_2$	Arterial carbon dioxide pressure
e/	Each	PaO_2	Arterial oxygen pressure
EAACI	European Academy of Allergology and Clinical Immunology	PEF	Peak expiratory flow
ECRHS	European Community Respiratory Health Survey	RADS	Reactive airway dysfunction syndrome
ED	Emergency department	RCT	Randomized clinical trial
ELISA	Enzyme linked immunosorbent assay	Rint	Measurement of resistance by the interruptor technique
ER	Endovenous route	RR	Relative risk
FDA	Food and Drug Administration	SAE	Severe asthma exacerbation
$FEF_{25-75\%}$	Forced expiratory flow from 25 to 75% of FVC	SaO_2	Oxyhemoglobin saturation (percentage)
FE_{NO}	Fractional exhaled of nitric oxide	$SA\beta_2AA$	Short-acting β_2 adrenergic agonist
FEV_1	Forced expiratory flow during the first second	sBCT	Specific bronchial challenge test
FVC	Forced vital capacity	SEAIC	Spanish Allergology and Clinical Immunology Society
GC	Glucocorticoids	SEICAP	Spanish Clinical Immunology and Paediatric Allergy Society
GEMA	Spanish Asthma Management Guide	SEMERGEN	Spanish Society of Primary Care Doctors
GINA	Global Initiative for Asthma	semFYC	Spanish Family and Community Medicine Society
GRAP	Primary Respiratory Care Society	SEMG	Spanish Society of General and Family Practitioners
H	Hour	SENP	Spanish Paediatric Respiratory Disease Society
HEPA	High-Efficiency Particulate Air	SEORL	Spanish Otorhinolaryngology Society
HTL	Helper T lymphocyte	SEPAR	Spanish Respiratory Disease and Thoracic Surgery Society
ICSIGC	Inhaled glucocorticoids	SMART	Strategy of Maintenance and Reliever Therapy
ICU	Intensive care unit	TL	T lymphocyte
Ig	Immunoglobulin	TLC	Total lung capacity
IL	Interleukin	TNFα	Alpha tumoral necrosis factor
IOS	Impulse oscillometry	WAA	Work-aggravated asthma
IP	Pressurized inhaler	WAO	World Allergy Organization
ISAAC	International Study of Asthma and Allergy in Childhood	x'	Per minute
IT	Immunotherapy	β_2AA	β_2 adrenergic agonist
Kg	Kilogram	µg	Microgram
$LA\beta_2AA$	Long-acting β_2 adrenergic agonist		

of wheezing in the last 12 months varies from 4.1% in Mumbai (India) to 32% in Dublín (Ireland)[6,7]. [c]

In Spain the prevalence of asthmatic symptoms in children has remained constant over the last eight years in those aged 13-14 years, while there has been a significant increase in the 6-7 year age group (Tables 3 and 4). In adults the prevalence is lower than in Britain, Ireland, America and central European countries. In this country the European Respiratory Health Study identified rates of 4.7% in Albacete, 3.5% in Barcelona, 1.1% in Galdakano, 1% in Huelva and 1.7% in Oviedo; 52% of the people who had asthma had not been diagnosed and up to 26% of these, despite having frequent symptoms, did not receive any treatment[8,9]. In the IBERPOC study, which assessed people from 40 to 69 years of age, 4.9% declared that they had been diagnosed as having asthma, and the prevalence was higher in women[10].[c]

Table 3
Prevalence of asthma symptoms in children aged 13-14 years in the ISAAC Study in Spain[11]

	BOYS		GIRLS		TOTAL	
	1993	2002	1993	2002	1993	2002
Prevalence in the last year						
Wheezing	9.0	9.3	9.6	9.2	9.3	9.2
Number of wheezing episodes	...					
1-3	5.9	1.8	0.7	6.4	2.1	0.8
4-12	6.6	1.7	0.7	6.4	1.9	0.8
> 12	6.2	1.8	0.7	6.4	2.0	0.8
Disturbed sleep as a result of wheezing						
< 1 night/week	2.4	0.8	2.9	0.8	2.5	0.7
> 1 night/week	3.0	0.8	2.5	0.7	2.9	0.8
Wheezing which impairs speech	2.0	2.0	2.2	2.0	2.1	2.0
Prevalence at some stage in life						
Wheezing	18.5	17.7	17.5	18.0	18.0	17.8
Asthma Diagnosis	11.7	13.8	9.0	11.8	10.4	12.8

Values expressed in percentages

Pathogenesis

The inflammation of the respiratory tract is associated with bronchial obstruction and hyperresponsiveness, which causes the symptoms. However, how these phenomena are interrelated has not been clearly established, as occurs in the case of the relationship between the intensity of the inflammation and asthma severity[12]. The inflammatory process is quite consistent in all asthma phenotypes, although there may be certain differences between patients and at different stages of the disease[13]. [c]

The pattern of inflammation in asthma is similar to that of other allergic diseases. It involves the activation of mastocytes, an increase in the number of activated eosinophils and the cooperation of T lymphocytes with a predominantly Th2 cytokine profile and natural killer cells (Table 5). The structural cells of the respiratory tract have a vital role in its pathogenesis, as they not only serve as a target, but

Table 4
Prevalence of asthma symptoms in children aged 6-7 years in the ISAAC Study in Spain[11]

	BOYS		GIRLS		TOTAL	
	1993	2002	1993	2002	1993	2002
Prevalence in the last year						
Wheezing	7,0	10.7	5.3	8.2	6.2	9.4
Number of wheezing episodes	...					
1-3	5.0	8.5	4.0	6.2	4.5	7.4
4-12	1.2	1.7	0.8	1.5	1.0	1.6
> 12	0.3	0.5	0.2	0.4	0.2	0.4
Disturbed sleep as a result of wheezing						
< 1 night/week	2.6	4.3	1.9	3.2	2.3	3.7
> 1 night/week	0.8	1.4	0.6	1.3	0.7	1.4
Wheezing that impairs speech	1.2	1.9	0.8	1.4	1.0	1.6
Prevalence at some stage in life						
Wheezing	21.0	32.9	17.8	26.2	20.9	29.5
Asthma Diagnosis	7.7	12.9	4.9	9.0	6.3	10.9

Values expressed in percentages

Table 5
Inflammatory cells involved in asthma

T lymphocytes (TL): their numbers are increased in the respiratory tract and there is an imbalance in the TLh1/Th2 ratio, with a predominance of Th2[12]. Levels of TL regulators are reduced and levels of NK T lymphocytes are increased.
Mastocytes: their numbers are increased in the epithelium and there is infiltration of the smooth muscle of the wall of the bronchial tubes, which is linked to the development of bronchial hyperresponsiveness[17]. Their activation prompts the release of mediators that have a bronchoconstrictor and pro-inflammatory effect. They produce cytokines that maintain and promote inflammation.
Eosinophils: their numbers are increased in the respiratory tract of the majority of people with asthma and their number correlates with its severity. They are activated and their apoptosis is inhibited. They contain inflammatory enzymes responsible for epithelial damage and they produce mediators that intensify the inflammatory response[18].
Neutrophils: their numbers are increased in the respiratory tract of some patients with severe asthma during exacerbations, in patients who are smokers and in cases of work-related asthma[19].
Dendritic cells: they present antigens that interacts with cells that regulate the lymphatic glands and stimulate the production of Th2 lymphocytes.
Macrophages: they can be activated by allergens by means of receptors with a low affinity for IgE and they release mediators that boost the inflammatory response[20].

Table 6
Cells and structural elements of the respiratory tract involved in asthma

Bronchial epithelium: it is damaged with a loss of ciliated and secretory cells. The epithelium releases mediators that promote inflammation. Pollutants and viral respiratory infections can stimulate their production and damage the epithelium. The repair process after epithelial damage is usually abnormal, increasing the obstructive lesions that occur in asthma[21].
Bronchial smooth muscle: it contributes to obstruction as a result of its hypertrophy, contraction and production of pro-inflammatory mediators, which are similar to those of epithelial cells.
Endothelial cells: in bronchial circulation they participate in the recruitment of inflammatory cells from blood vessels to the respiratory tract by expressing adhesion molecules.
Fibroblasts and myofibroblasts: these are stimulated by inflammation mediators and growth factors. They are implicated in the remodeling of the respiratory tract.
Cholinergic nerves of the respiratory tract: they can be activated, causing bronchoconstriction and mucus secretion. Sensory nerves can cause symptoms, such as coughing and chest tightness, and can release inflammatory neuropeptides[22].

also play an active part in the inflammatory and repair processes that take place in the respiratory tract (Table 6). The cellular interactions that make this inflammatory process possible occur via cell mediators and molecules with a wide range of functions (Table 7).

Table 7
Molecules involved in the asthma inflammatory process

Chemokines: these are expressed by epithelial cells and are important in the recruitment of inflammatory cells to the respiratory tract.
Cysteine leukotrienes: potent bronchoconstrictors released by mastocytes and eosinophils.
Cytokines: they direct and modify the inflammatory response in asthma and possibly determine its severity. The most important cytokines are derived from Th2 L: IL-5 promotes eosinophil activation; IL-4 is necessary for the differentiation of Th2 L and IL-13, in conjunction with the latter, is important for IgE synthesis.
Immunoglobulin E (IgE): the antibody responsible for the activation of the allergic reaction. It binds to the cell surface by attaching itself to a high-affinity receptor, found in mastocytes, basophils, dendritic cells and eosinophils.

Table 8
Mechanisms of airway obstruction in asthma

Contraction of bronchial smooth muscle: this is the predominant mechanism underlying the narrowing of the airways that is reversed by bronchodilators.
Edema of the airways: a result of the microvascular exudate produced in response to inflammatory mediators.
Hypersecretion of mucus: the results of an increase in the number of caliciform cells in the epithelium and the increased size of the submucous glands. Moreover, there is an accumulation of inflammatory exudates that can form mucus plugs.
Structural changes of the respiratory tract: subepithelial fibrosis, as a result of the deposition of collagen and protein-glucan complexes beneath the basal membrane; smooth muscle hypertrophy and hyperplasia, and an increase in blood vessel circulation and greater permeability of the bronchial wall.

Table 9
Trigger factors for asthma exacerbations

Direct Factors	
– Viral respiratory infection	– Allergens
– Tobacco	– Atmospheric pollutants
– Cold and humid conditions	
Indirect Factors	
– Physical exercise	– Drugs
– Food allergens and additives (e.g.)	– Sinusitis
	– Menstruation
– Pregnancy	– Gastroesophageal reflux
– Storms and thermal inversion	

There is known as often a thickening of the reticular layer of the basal membrane, known as subepithelial fibrosis[14], hypertrophy and hyperplasia of bronchial smooth muscle[15], blood vessel proliferation and dilation[16], and hyperplasia of the mucous glands and hypersecretion, which are associated with a progressive loss of lung function that cannot be prevented or is not entirely reversible using current therapy[23]. This phenomenon, known as "remodeling", meaning that the patient responds only partially to treatment[24]. [c]

Physiopathology

The main physiological feature of an asthma exacerbation is narrowing of the airways and subsequent obstruction of the airflow, which is characteristically reversible. It is produced as a result of contraction of the bronchial smooth muscle, edema and the hypersecretion of mucus (Table 8).

Various trigger factors (Table 9) can cause an exacerbation. Acute allergen-induced bronchoconstriction occurs as a result of the release of mastocyte mediators. NSAIDs can also cause acute airway obstruction in some patients by means of a mechanism which is not dependent on IgE. Other stimuli, such as exercise, cold air or non-specific irritants can cause acute airway obstruction. The intensity of the response to these stimuli is related to the underlying inflammation.

The variation or fluctuation of symptoms and lung function over time, even on the same day, in excess of circadian physiological changes, is a typical feature of asthma that can be determined by

Table 10
Mechanisms of bronchial hyperresponsiveness

Excessive contraction of the smooth muscle of the respiratory tract. It may be the result of an increase in the volume and/or contractility of bronchial smooth muscle cells.
Decoupling of airway contraction as a result of bronchial inflammation. It may lead to excessive narrowing and a loss of the peak contraction threshold when bronchoconstrictor substances are inhaled.
Thickening of the walls of airways. This increases narrowing, due to the contraction of bronchial smooth muscle.
Sensitized sensory nerves. As a result of the inflammation, they may stimulate exaggerated bronchoconstriction in response to sensory stimuli.

Table 11
The most common asthma processes associated with wheezing in children

Newborn and very young infants (0-3 months)
– Bronchopulmonary dysplasia
– Congenital abnormalities of the laryngeal region (laryngomalacia, paralysis of the vocal cords, laryngeal angiomatosis, cysts and tumours).
– More serious congenital defects of the trachea and airways (tracheomalacia, bronchomalacia, tracheal or bronchial stenosis and tracheoesophageal fistula).
– Vascular rings or laryngeal membranes
Older b-b (3-12 months)
– Croup
– Cystic fibrosis
– Gastroesophageal reflux/aspiration
– Cardiac abnormalities
Children over 12 months of age
– Aspiration of a foreign body
– Primary ciliary dyskinesia
– Bronchiolitis obliterans
– Congenital lung and respiratory tract abnormalities
– Vocal cord dysfunction (adolescents)

daily peak expiratory flow (PEF) measurement and is known as variability.

As the disease becomes more persistent and the inflammation progresses, other factors contribute to the restriction of airflow: oedema of the airways, hypersecretion of mucus and the formation of plugs composed of cell exudates and mucous remains (Table 8).

A characteristic, although not exclusive, feature of the disease is the phenomenon known as bronchial hyperresponsiveness (BHR). Inflammation is a crucial factor for determining the level of BHR, which is defined as an "exaggerated bronchoconstrictive response to a range of physical, chemical or biological stimuli", but it is not the only one. The level of BHR partially correlates with the clinical severity of asthma and with inflammation markers, although not very closely[25]. Structural changes, neuroregulatory dysfunction and hereditary factors also have an influence[26]. Anti-inflammatory treatment improves asthma control and reduces BHR, but does not eradicate it entirely[27] (Table 10). [C]

Differential characteristics of childhood asthma

Although asthma symptoms are similar at any age, in childhood there are features which distinguish it from its adult form. The differences are more relevant in infants and pre-school children and they affect the diagnosis, the estimation of severity, the degree of control, and the development of the disease and its treatment. The most appropriate definition in this age group is the one agreed upon by the Third International Paediatric Consensus: "recurrent wheezing and/or persistent coughing in a situation in which there is a likelihood of asthma and other less common diseases have been ruled out"[28]. From the age of 6-7 years the definitions of general consensuses can be applied. An asthma diagnosis must take into account certain considerations and exclude other respiratory diseases that can also be expressed by wheezing symptoms, which means diagnosis must be differential (Table 11). [D]

Table 12
Phenotypes or developmental models of children with wheezing symptoms[29]

Early-stage transitory wheezing
– Onset during the first year of life, remitting when the child is about 3 years old
– Negative IgE and/or prick tests with no atopic features or history
– Impaired lung function at birth with low values at 16 years of age.
– Bronchial hyperresponsiveness and peak expiratory flow (PEF) variability tests are negative at age 11.
– Risk factors: mother smoked during pregnancy, male, premature birth, living with older siblings and/or attending a nursery.
Persistent non-atopic wheezing
– Wheezing generally starts during the first year of life and persists when the child is 6 years of age.
– Both sexes are equally affected
– Negative IgE and prick tests, with no atopic features or history
– Lung function is normal at birth and has deteriorated from 6 to11 years
– Bronchial hyperresponsiveness that lessens with age
– Wheezing usually disappears during adolescence
Atopic wheezing
– The first episode occurs after the first year of life and it predominates in males
– Raised IgE levels and/or positive prick tests, atopic family traits and history.
– Lung function is normal at birth, but worsens until the child is 6 and then stabilizes below normal levels
– Bronchial hyperresponsiveness
– Tends to persist during adolescence

Table 13
Asthma Predictive Index (API). Criteria and characteristics[30-32]

Major criteria
– Medical diagnosis in one of the parents
– Medical diagnosis of atopic eczema
– Sensitization to some form of aeroallergen
Minor criteria
– Presence of allergic rhinitis diagnosed by a doctor (at 2-3 years of age)
– Wheezing not related to colds
– Peripheral eosinophilia equivalent to or higher than 4%
– Sensitization to milk, eggs or peanuts
Characteristics of the Asthma Predictive Index (API)
– Infants, with more than 3 wheezing episodes a year during the first 3 years of life, who meet one of the major criteria or two minor criteria
– Sensitization 16%-specificity 97%
– Positive predictive value of 77%– Negative predictive value of 68% with respect to the likelihood that babies with recurrent wheezing will develop asthma by the time they reach school age (6-13 years).

Longitudinal epidemiological cohort and population studies in children have demonstrated that there are different models, also known as "phenotypes", for the development of recurrent bronchial obstruction that takes the form of a cough and wheezing symptoms throughout childhood (Table 12)[29]. The classification of a child into a particular phenotype is useful for establishing treatment and prognosis. [C]

There is currently a Predictive Index for defining asthma risk (API). It is used to predict the likelihood that a baby with recurrent wheezing will develop persistent atopic asthma by the time he or she reaches school age [30-32] (Table 13).

Diagnosis

Clinical features

A diagnosis of asthma should be considered when there are characteristic clinical symptoms and signs, such as dyspnoea, coughing, wheezing and tightness of the chest. These symptoms are usually variable, occurring predominantly at night and early in the morning, and are caused by different trigger factors (viral infections, allergens, cigarette smoke, exercise, etc.). Seasonal variations and a family and personal history of atopy are important aspects to be considered[33,34]. However, none of these symptoms and signs are specific for asthma,

Table 14
Differential diagnosis between asthma and COPD

	Asthma	COPD
Age of onset	At any age	After the age of 40
Smoking	Irrelevant	Virtually always a feature
Presence of rhinitis, conjunctivitis and dermatitis	Frequent	Infrequent
Family history	Frequent	Cannot be evaluated
Variability of symptoms	Yes	No
Reversibility of obstruction	Significant	Usually less significant
Response to glucocorticoids	Very good	Indeterminate or variable

Table 15
Reversibility and daily variability criteria recommended for asthma diagnosis

Reversibility	FEV_1 post Bd – FEV_1 pre Bd ≥ 200 ml and $\frac{FEV_1 \text{ post Bd} - FEV_1 \text{ pre Bd}}{FEV_1 \text{ pre Bd}} \times 100 \geq 12\%$
Daily variability	$\frac{\sum\left(\frac{\text{maximum PEF} - \text{minimum PEF}}{\text{maximum PEF} + \text{minimum PEF} / 2}\right)}{\text{No of days}} > 20\%$

FEV_1: forced expiratory volume during the first second; PEF: peak expiratory flow; Bd: bronchodilation.

which is why an objective diagnostic test, usually a respiratory function test, needs to be included. The physical examination may be normal, wheezing being the most characteristic sign, although it is not specific to asthma and may even be absent in severe attacks. [C]

When asthma is suspected, a differential diagnosis that admits the possibility of other obstructive respiratory diseases, including COPD, must be made. Table 14 includes some of the most relevant differences between these two diseases.

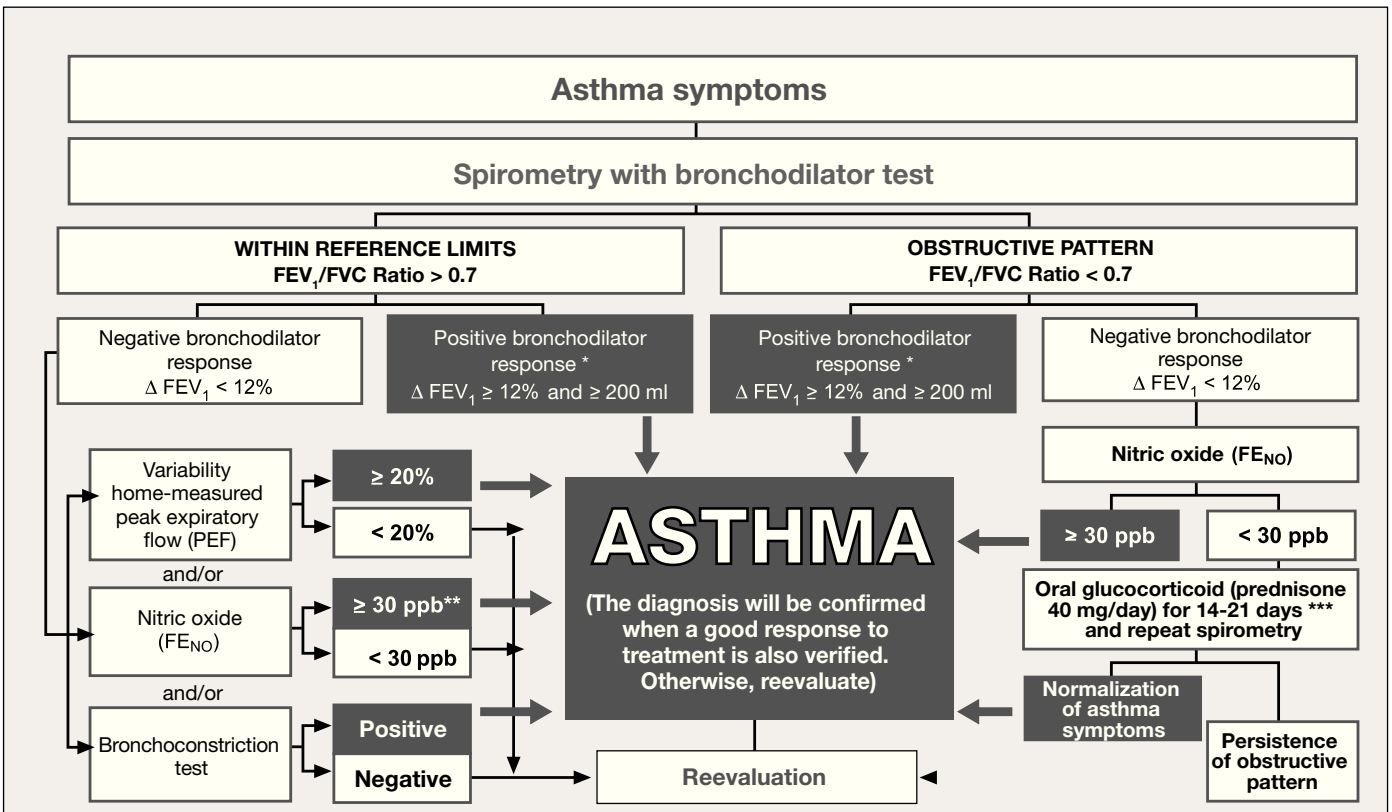
Pulmonary Function

Adults

The main functional changes that occur in asthma are airflow obstruction, its reversibility and variability, and bronchial hyperresponsiveness. [C]

Spirometry is the diagnostic test of first choice, as the algorithm for the proposed diagnostic process indicates (Fig. 1). The main parameters to be determined are forced vital capacity (FVC) and forced expiratory volume during the first second (FEV_1). The reference values must be adjusted to the age and ethnic group/race of each patient. Obstruction is defined as "a FEV_1/FVC coefficient which falls below the lower cut-off point for the reference values, which are arbitrarily set at 0.7"[35]. However, this criterion may result in the obstruction being overestimated in elderly people[35]. A reduced FEV_1 confirms obstruction, helps to establish its severity and indicates a greater risk of exacerbations[36]. Nevertheless, many asthma patients have a spirometry test result with readings that approximate reference values or that may even show a non-obstructive (restrictive) pattern due to air entrapment. [C]

For the bronchodilation test we recommend administering four successive puffs of 100μg of salbutamol, or its equivalent, using a



*In children an increase of 12% is sufficient for the response to be regarded as positive, even if it is less than 200 ml.
**In cases in which the bronchoconstriction test is negative, a diagnosis of eosinophilic bronchitis should be considered.
***As an alternative inhaled glucocorticoids can be used at very high doses (1,500-2,000 μg of fluticasone) taken three or four times a day over a period of 2-8 weeks.

Figure 1. Algorithm for asthma diagnosis.

Table 16
Recommendations

The diagnosis of asthma must be based on objective measurements of functional impairment. Spirometry is the test of choice.	R2
An asthma diagnosis should be considered when there is daily variability of PEF (peak expiratory flow) exceeding 20% or a raised exhaled nitric oxide fraction (FE_{NO}) in patients who have not used glucocorticoids, especially if it is associated with a reduced FEV_1.	R2
Non-specific bronchoprovocation must be taken into consideration to rule out a diagnosis of asthma.	R2

Table 17
Recommendations

Spirometry in conjunction with a bronchodilator test is recommended to confirm a diagnosis of asthma and to objectively assess its severity in all children who are able to cooperate appropriately.	R2
It is advisable for asthmatic children who require continuous treatment to undergo regular spirometric evaluations at least once a year.	R2
The measurement of FE_{NO} must be considered in the diagnosis and monitoring of asthma in children. A high FE_{NO} value in a child with symptoms suggestive of asthma makes the diagnosis more reliable. A high FE_{NO} value in a child who is being treated with inhaled glucocorticoids should lead us to suspect non-compliance. In a child, a FE_{NO} value above 49 ppb, when treatment has been withdrawn, should lead us to suspect a possible relapse.	R2

pressurized inhaler with a spacing chamber, and then repeating the spirometry test 15 minutes later. A positive response (in other words, significant bronchodilatation) is regarded as an increase in FEV_1 of 12% or more and of 200 ml or more with respect to the baseline value (Table 15)[35]. An alternative criterion of bronchodilatation is an increase in peak expiratory flow (PEF) greater than 60 l/minute or 20%[37]. Reversibility can also be identified by an improvement in FEV_1 or PEF after two weeks of systemic glucocorticoid treatment (40 mg/day of prednisone or its equivalent) or 2-8 weeks of inhaled glucocorticoids (1,500-2,000 mg/day of fluticasone or its equivalent)[38]. Although characteristic of asthma, reversibility of bronchial obstruction is not found in all patients. [C]

Excessive variability or fluctuation in pulmonary function over time is essential for the diagnosis and control of asthma. The most recommendable daily variability index is the amplitude of PEF with respect to the mean average over a minimum of 1-2 weeks and recorded prior to medication (Table 15)[39]. A PEF variability exceeding 20% is indicative of asthma[40]. [C]

The identification of an excessive response to a bronchoconstrictor (bronchial hyperresponsiveness) may be useful in patients with normal pulmonary function who are clinically suspected of having asthma. Direct agents, such as methacholine or histamine, or indirect agents, such as adenosine monophosphate, manitol or hypertonic saline solution can be used[41]. The latter show a better correlation with inflammation and greater sensitivity to the effect of glucocorticoids[42]. Furthermore, manitol offers the advantage that it can be administered using a dry powder inhaler[43]. [C]

Bronchial hyperresponsiveness is analyzed in terms of sensitivity or threshold values, by determining the dose or concentration that produces a 20% decrease in FEV_1 with respect to its post-dilution value[44]. Bronchial challenge is highly sensitive but exhibits limited specificity[45], so it is more useful for excluding than for confirming a diagnosis of asthma. Bronchial hyperresponsiveness is also present in other diseases, such as allergic rhinitis, COPD, bronchiectasis, cystic fibrosis or cardiac insufficiency. [C]

Exhaled nitric oxide fraction (FE_{NO}) is a non-invasive way of measuring eosinophilic inflammation of the respiratory tract. The procedure for its determination has been standardized[46] and, although there is a certain level of discrepancy amongst different studies, the upper limit for normal values is from 20 to 30 ppb[47]. It is highly sensitive and specific for diagnosing asthma in non-smokers who do not take inhaled glucocorticoids[48], especially if it is associated with a reduced FEV_1[49]. However, a normal FE_{NO} value does not exclude an asthma diagnosis, especially in non-atopic individuals[47]. [C]

Children

Respiratory function tests are less useful for classifying asthma severity in children than in adults; most children with asthma, even moderate or severe forms, have a FEV_1 which falls within the range of reference values[50]. [C]

Respiratory function in children who cooperate. The functional diagnosis of asthma in children who cooperate (children over 6 years of age) is similar to that of adults. Forced spirometry combined with a bronchodilator test is the most useful procedure for diagnosing and monitoring asthma. The FEV_1/FVC ratio correlates better with asthma severity than FEV_1 in children[50]. [C]

In children, a bronchodilator test is regarded as positive when the increase in FEV_1 with respect to its baseline value is greater than or equivalent to 12%. The requirement to exceed 200 ml cannot be met because the pulmonary volume in children is smaller and depends on their height. [C]

In children with obstruction and no bronchodilator response it may be useful to administer a cycle of oral glucocorticoids at a dosage of 1 mg/kg for two weeks to confirm the reversibility of the obstruction[35].

Only a small percentage of children aged 5 to 19 years are able to use a spirometer in accordance with ERS/ATS regulations when expiration lasts longer than six seconds. Children are able to exhale all the air in 2-3 seconds so an expiration lasting this long can be treated as valid as long as the flow/ volume curve does not tail off abruptly or the volume/time curve has no plateau, even though it may be short. Less demanding criteria of reproducibility are also acceptable: 100 ml or 10% of FEV_1[51]. [C]

$FEF_{25-75\%}$ correlates with the degree of non-specific bronchial hyperresponsiveness[51-53]. Its inter-subject reproducibility over time is much less than for FEV_1, which reduces its usefulness in clinical practice[54]. [C]

If a child undergoes a spirometry test together with a bronchodilator test and the diagnosis of asthma is inconclusive, bronchial challenge tests can be used to demonstrate bronchial hyperresponsiveness. The bronchoprovocation test during exercise is of special interest with children, as it is relatively easy to perform, reproducible and highly specific for diagnosing asthma, although not very sensitive[55]. [C]

Respiratory function in pre-school children. Until recently it was considered impossible to perform forced spirometry in children under the age of 6. However, with the right methodology it is possible to conduct reliable spirometric tests in children as young as three. It is essential to use appropriate reference values and not to extrapolate the values of older children[56-57]. Sometimes the expiration time in these children may be less than a second, so the most useful value will be $FEV_{0.5}$ and not FEV_1[58]. [C]

Other tests that may be useful in managing pre-school children with asthma include forced impulse oscillometry (IOS), the measurement of occlusion resistances (Rint), flow volume/tidal volume curve analysis or the measurement of resistances by plethysmography, although these procedures are usually used in specialized laboratories. Recently, the ATS/ERS regulations on lung function in pre-school children were published[58]. In infants the most widely used technique is rapid thoracic-abdominal compression. Baseline tests of pulmonary function are not very useful for diagnosing asthma in pre-school children, since it is more helpful to demonstrate a bronchodilator response or to employ a bronchial challenge test using one of the techniques mentioned above. [D]

Table 18
Standard aeroallergen battery* used for prick tests

Mites	*Dermatophagoides pteronyssinus* *Dermatophagoides farinae* *Lepidoglyphus destructor*
Epithelia	Cat, dog
Cockroaches	*Blatella orientalis* *Blatella germanica*
Pollen	Cypress, plane trees, olive, grass mixture, *Artemisia, Parietaria, Salsola*
Fungi	*Alternaria, Cladosporium, Aspergillus, Penicillium*

*Other allergens that are suspicious because of clinical history or geographical prevalence can be added (modified by Heinzerling[62]).

Table 19
Comparison of *in vivo* (prick) and *in vitro* (specific IgE) diagnostic tests

Advantages of the Prick Test	Advantages of the Specific IgE Assay
More sensitive	More specific
Cheaper	Knowledge of the technique is not required
Immediate assessment	Allergenic extracts are not required
Results are visible to the patient	No risk of systemic reactions
Safe and minimally invasive	Does not interfere with taking medication
Extensive battery of allergens	Can be performed in patients with eczema or dermographism

Table 20
Recommendations

In persistent asthma it is advisable to assess the potential role of aeroallergens by clinical evaluation and prick or IgE tests. It is important to base the diagnosis on the concordance between the clinical history and diagnostic tests.	R2

In order to conduct reliable lung function tests in children, especially pre-school children, it is essential to have access to nursing personnel who have been specially trained in pulmonary function techniques designed for children and laboratories adapted for testing children. [D]

The FE_{NO} measurement is useful for determining levels of eosinophilic bronchial inflammation in children[59]. A FE_{NO} value above 17 ppb offers a sensitivity of 81% and a specificity of 80% for predicting eosinophilic phenotype asthma[60] [C]. If nitric oxide is measured using electrochemical analyzers, FE_{NO} values are slightly higher (range 20-30 ppb). Inhaled glucocorticoid treatment reduces FE_{NO} concentration and its measurement after treatment helps to assess the degree of compliance. A FE_{NO} value less than 49 ppb four weeks after withdrawal of inhaled glucocorticoids shows a sensitivity of 71% and a specificity of 93% for estimating whether asthma is in remission; a higher value increases the likelihood of relapse[61]. Its usefulness in children who cannot or who fail to cooperate is still under investigation. It is essential to perform measurements following a correctly standardized methodology[46]. [C]

Allergy diagnosis

The aim of an allergy test is to determine the allergens that influence the development of asthma or its exacerbations, and it should be performed on every asthma patient with persistent symptoms. On the basis of clinical records, exposure to aeroallergens, the seasonal variation of symptoms and when and where they appear (at home, at work/school, in the patient's free time) are assessed, together with the patient's personal history (especially rhinitis) or a family history of atopy (asthma, rhinitis, eczema, food allergies). The selection of suspected aeroallergens (pollen, mites, fungi, animal epithelia or occupational allergens) varies, depending on the patient's clinical history and the geographical region in question[62] (Table 18).

Prick tests are the diagnostic method of choice (Table 19)[63], even in small children[63]. They have a high predictive value and show good correlation with other *in vitro* or bronchoprovocation diagnostic tests. For their correct interpretation it is necessary to know the variables that affect both their results (drugs, age, seasonal variations, dermographism, etc.) and their assessment (crossreactivity between allergens, panallergens, etc[64]. [C]

The measurement of serum IgE specific to individual allergens has the same clinical significance as the prick test, but is less sensitive and more specific[65]. Although its titration does not correlate with severity, it is more likely that symptoms will be persistent when specific IgE levels are raised for prolonged periods[66]. Although its predictive value is good, the determination of IgE to different allergens in the same assay is only justified when screening for allergic disease, given its cost-effectiveness profile[67]. [C]

The results of prick tests or the measurement of specific circulating IgE determine the sensitization to allergens, but they do not predict their clinical transcendence, just as in some asymptomatic patients positive results can be obtained. This is why, in the end, it is necessary to evaluate the clinical relevance of the sensitizations to allergens identified. Similarly, a specific bronchial challenge tests can be performed when there is a discrepancy between the clinical history and the sensitization results obtained, and in the case of occupational asthma[68]. [C]

Classification of adult asthma

Asthma Severity

Asthma has generally been classified in accordance with its severity[69-71], although it is difficult to assess, especially when the patient is already receiving anti-inflammatory treatment. Its severity is an intrinsic aspect of the disease and it reflects the intensity of any physiopathological abnormalities[72]. It is important to remember that the severity of the disease includes both the intensity of the process and its response to treatment[73]. Traditionally, the disease has been divided into four categories: intermittent, mild persistent, moderate persistent and severe persistent asthma[71]. [D]

The classification of asthma in accordance with its severity is useful in the initial assessment of an asthma patient because the choice of treatment, dosage and treatment regimen depend on the severity of the disease[69-71]. [D]

Severity is a feature of asthma that is not necessarily constant, but can vary over time (months or years), so it is necessary to reevaluate it regularly. Severity is easier to establish in a patient who is not receiving maintenance treatment or treatment to control asthma. Nevertheless, severity can also be determined in a patient whose asthma is controlled, depending on the therapeutic stage to which he has been assigned, in other words on the basis of the amount of medication which is required to keep the disease under control[74-75]. Asthma severity is determined by the most affected parameter. Table 21 shows the different levels of adult asthma.

Control

Asthma control is the extent to which the manifestations of asthma are absent or reduced by therapeutic interventions and to which treatment targets are met[74-75]. To a large extent, control reflects the suitability of asthma treatment[76] (Fig. 2). However, there is another factor that differs from one patient to another that must be taken into account. This factor is the response to treatment or the ease and speed with which control is achieved[73]. Although the term "control" is broad in meaning and can include all clinical and physiopathological aspects of asthma, for practical purposes it includes the clinical features of the disease (symptoms and exacerbations) and lung function tests. [D]

Depending on its level of control, asthma has been arbitrarily classified into: well controlled, partially controlled and poorly

Table 21
Classification of asthma severity in adults

	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Daily symptoms	No (2 days or less a week)	More than 2 days a week	Daily symptoms	Continuous symptoms a week) (several times a day)
Relief medication (short-acting β_2 adrenergic agonist)	No (2 days or less a week)	More than 2 days a week, but not every day	Every day	Several times a day
Nocturnal symptoms	No more than twice a month	More than twice a month	Quite often	Often
Limitations on activity	None	Some limitation	A fair degree of limitation	Considerable
Pulmonary function (FEV_1 or PEF) theoretical percentage	> 80%	> 80%	> 60% - < 80%	≤ 60
Exacerbations	None	One or none a year	Two or more a year	Two or more a year

FEV_1: forced expiratory volume in the first second; PEF: peak expiratory flow.

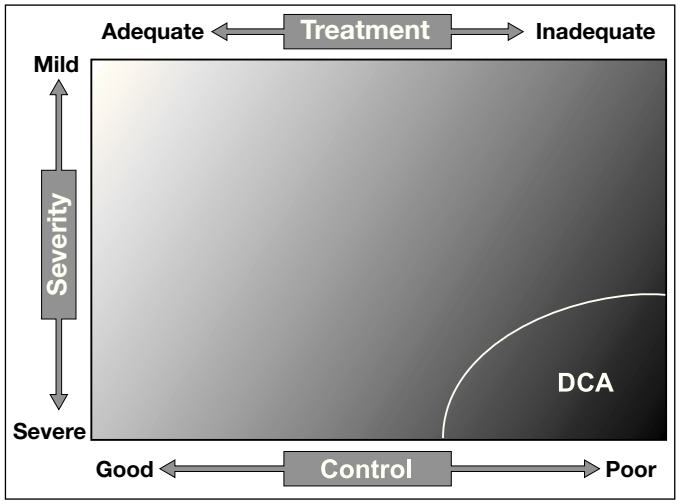


Figure 2. How asthma severity and control are related. To a large extent the level of control reflects the suitability of treatment. Some patients have severe asthma that is difficult to control (DCA). (Modified by Osborne[76]).

controlled asthma, in accordance with the criteria in Table 22[2]. However, this classification has not been validated from a clinical point of view. Some asthma patients can achieve good control of symptoms and pulmonary function and at the same time experience frequent exacerbations, while other patients have daily symptoms and very few exacerbations. When severity or control is assessed, these factors must be taken into account. [D]

Therefore, when we try to minimize the clinical expression of asthma, we need to bear in mind two key aspects[3]: on the one hand, the manifestations of the disease which are present on a day-to-day basis (current control) and, on the other, its future consequences (future risk), as indicated in Figure 3. [D]

When we use the term "current control", control is defined as the ability to prevent the presence of symptoms during the day or at night and the frequent use of rescue medication to relieve these symptoms, the maintenance of lung function within or close to normal limits, the absence of limitations on daily life, including family, social, occupational or school activities and physical exercise and finally the satisfaction of the expectations of the patient and his family with regard to the care he receives. [D]

With respect to the term "future risk", control includes the absence of severe exacerbations, the avoidance of visits to emergency departments and hospitalizations, the prevention of a progressive loss of lung function or, in the case of children, abnormal lung development and finally the prescription of optimal pharmacotherapy with minimal or no side effects. [D]

The concepts of severity and control are used as follows in the treatment of asthma:

- Determination of severity before initiating treatment. When the disease is first assessed, if the patient is not receiving maintenance treatment its severity must be evaluated (see previous classification) and used for guidance purposes in choosing the pharmacological treatment and making other therapeutic decisions. Once the patient is being treated, the severity of the disease is determined in accordance with the minimal medication requirements needed to maintain control[75]. Thus, controlled patients in therapeutic stage 1 will have intermittent asthma, in stage 2 mild persistent asthma, in stages 3 and 4 moderate persistent asthma and in stages 5 and 6 severe persistent asthma (Table 23). [D]
- Evaluation of control in order to adjust treatment. Once asthma treatment has begun, the clinical and therapeutic management of the disease must aim to achieve and maintain control. As such, the

Table 22
Classification of asthma control in adults

	WELL controlled (all of the following)	PARTIALLY controlled (any measure in any week)	POORLY controlled
Daytime symptoms	None or ≤ 2 days a week	> 2 days a week	If ≥ 3 asthma features are partially controlled
Limitation of activities	None	Any activity	
Symptoms at night or on waking	None	Any	
Need for relief (rescue) medication (short-acting β_2 adrenergic agonist)	None or ≤ 2 days a week	> 2 days a week	
Pulmonary function			
FEV_1	> 80% theoretical value	< 80% theoretical value	
PEF	> 80% best personal value	< 80% best personal value	
Validated symptom questionnaires			
ACT	≥ 20	16-19	≤ 15
ACQ	≤ 0.75	≥ 1.5	not applicable
Exacerbations	None	≥ 1/year	≥ 1 in any week

FEV_1: forced expiratory volume in the first second; PEF: peak expiratory flow; ACT: asthma control test; ACQ: asthma control questionnaire.

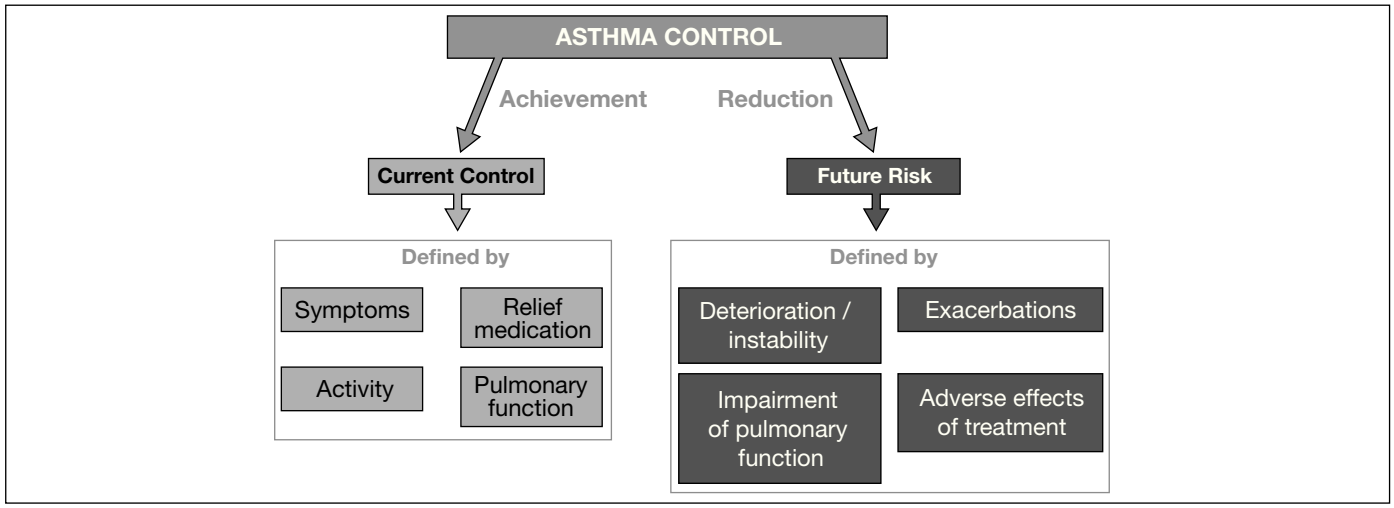


Figure 3. Terms that define and determine level of control.

Table 23
Classification of asthma severity when it is well controlled by treatment (distributed into stages)

Severity	Intermittent	Persistent		
		Mild	Moderate	Severe
Minimum treatment requirements to achieve control	Stage 1	Stage 2	Stage 3 or stage 4	Stage 5 or stage 6

Table 24
Recommendations

Asthma severity must be established at the onset, when the patient is not receiving treatment. If the patient is already being treated, severity must be determined in accordance with the minimum maintenance treatment requirements needed to achieve control.	R2
Control must be evaluated regularly and treatment must be adjusted to achieve and maintain control. Control has two basic components: current control and future risk.	R2
It is advisable to determine the level of asthma control by means of regular medical follow-up visits, which consist of taking well structured and extensive medical notes, a detailed physical examination and a forced spirometry test.	R2
The level of control can be assessed objectively by means of validated symptom questionnaires (ACT and ACQ) and, in individualized cases, by measuring inflammatory biomarkers.	R2

level of control will determine decisions about maintenance treatment and dose adjustment, in accordance with the therapeutic steps or stages shown in the corresponding section. [D]

Methods for measuring control

According to our definition of control, a combination of tests need to be used for its evaluation[77]. The basic tool for assessing the control of the process is the ongoing medical follow-up visit. At these visits the presence of symptoms is evaluated, as well as the signs of disease activity, the presence of exacerbations and visits to ED departments, the influence of the disease on the patient's daily life and activity, the presence of possible side effects and, finally, and of crucial importance, therapeutic adherence, which includes reminding the patient about his self-care plan and the steps to be taken when there is decompensation, always trying to reinforce the relationship between medical personnel and the patient at each visit. [C]

In order to facilitate and standardize the evaluation of control there are various questionnaires that are simple and easy for the patient to complete. The Asthma Control Test (ACT)[78,79] and the Asthma Control Questionnaire (ACQ)[80,81] have been validated and culturally adapted for use in Spain. The ACT has a more detailed validation so it can be used in daily clinical practice, given that it has well defined cut-off points. A score equivalent to or higher than 19 is very consistent with well controlled asthma, scores from 19 to 16 with asthma that is partially or not well controlled and scores lower than 15 with poorly controlled asthma[78-79]. [C]

There are specific tools validated and adapted to provide Spanish versions for measuring the quality of life of adults[82] and children with asthma[83]. However, currently their use is considered more appropriate for research purposes than for clinical practice. Moreover, their application is usually quite time-consuming, despite the availability of abbreviated versions[84]. For both reasons their use is not recommended in daily clinical practice[3]. [C]

The second tool for controlling the disease is forced spirometry. FEV_1 measurements are capable of adjusting what we have defined as current control more accurately[78-79] and also provides data for estimating the future risk of exacerbations[85]. It is a good way of quantifying the progressive and irreversible loss of pulmonary function. [C]

The usefulness of so-called non-invasive markers of inflammatory activity for measuring asthma control continues to be a matter of debate and the subject of intense research, especially the determination of FE_{NO}. Recent studies, including a meta-analysis, have demonstrated that their measurement does not add any benefits to traditional monitoring defined by guidelines[86-87]. Nevertheless, these markers are useful in certain groups of patients. The cytological analysis of sputum samples may have a role to play in assessing the control of adult patients with severe asthma characterized by multiple exacerbations, thus significantly reducing the incidence of exacerbations[88]. [C]

Classification of childhood asthma

Asthma severity

Traditional classifications based on adult asthma are difficult to apply to children, especially when they are very small. Childhood asthma is essentially episodic, sometimes involving serious attacks, but with few symptoms in the interludes between exacerbations. The level of severity depends on the symptoms (number of attacks and the situation between attacks: basically, tolerance of exercise and nocturnal symptoms), the need for a rescue bronchodilator and

Table 25
Classification of the severity of asthma in children

	Occasional Episodic	Frequent Episodic	Moderate persistent	Severe persistent
Episodes	Lasting a few hours or days < one every 10-12 weeks Maximum 4-5 attacks/year	< one every 5-6 weeks Maximum 6-8 crises/year	> one every 4-5 weeks	Frequent
Inter-crisis symptoms	No symptoms with good tolerance of exercise	No symptoms	Mild	Frequent
Wheezing	–	With intense effort	With moderate effort	With minimum effort
Nocturnal symptoms	–	–	≤ 2 nights a week	> 2 nights a week
Relief medication (short-acting β_2 adrenergic agonist)	–	–	≤ 3 days a week	> 3 days a week
Pulmonary Function				
FEV_1	> 80%	< 80%	> 70% - < 80%	< 70%
PEF Variability	< 20%	< 20%	> 20% - < 30%	> 30%

FEV_1: forced expiratory volume in the first second; PEF: peak expiratory flow.

respiratory function test values. In young children, in whom it is not possible to perform a pulmonary function test, severity is classified exclusively in accordance with symptomatology. [D]

Two major patterns have been defined in children: episodic and persistent asthma. Episodic asthma may be occasional or frequent, depending on the number of attacks. Persistent childhood asthma cannot be treated as if it were a mild disease, but rather as at least moderate or severe[29] (Table 25). [D]

Childhood asthma is a disease that is highly variable over time. It can even vary throughout the year, which makes classification difficult. Most young children only have asthma during viral infections and, consequently, they may have moderate or severe asthma in the winter and have no symptoms in the spring and summer. [D]

Other patients, for example children who are allergic to pollen, will only have asthma in the spring (this occurs most often in regions with a continental climate). To classify a case correctly, it is necessary to specify asthma trigger factors in a particular patient and its level of control, as well as its severity. [D]

The disease must be classified when the patient is not receiving any treatment. Once asthma is controlled, the medication required to ensure a child is symptom-free will be a better indication than his symptoms of how severe the condition is. [D]

Control

There are various questionnaires that estimate the extent to which asthma is controlled in children, but the only one that has been validated in Spanish is the CAN (Childhood Asthma Control) questionnaire (Table 26). There is a version for children from 9 to 14 years of age and another for parents (children from 2 to 8 years), which evaluates nine questions about clinical symptoms in the preceding four weeks and scores the results from 0 (good control) to 36 (poor control). A patient's asthma is regarded as poorly controlled when his score is 8 or higher[89]. In addition to clinical control, which is evaluated by means of the CAN questionnaire, it is important to assess lung function by spirometry and probably to control inflammation by measuring FE_{NO}.

Table 26
Childhood Asthma Control Questionnaire (CAN)[89]

1. During the last four weeks, how often have you coughed during the day without having a cold?
   4. More than once a day.
   3. Once a day.
   2. 3 to 6 times a week.
   1. Once or twice a week.
   0. Not at all.
2. During the last four weeks, how often have you coughed at night without having a cold?
   4. More than once a night.
   3. Once a night.
   2. 3 to 6 times a week.
   1. Once or twice a week.
   0. Not at all.
3. During the last four weeks, how often have you had whistling sounds in your chest or wheezing symptoms during the daytime?
   4. More than once a day.
   3. Once a day.
   2. 3 to 6 times a week.
   1. Once or twice a week.
   0. Not at all.
4. During the last four weeks, how often have you had whistling sounds in your chest or wheezing symptoms at night?
   4. More than once a night.
   3. Once a night.
   2. 3 to 6 times a week.
   1. Once or twice a week.
   0. Not at all.
5. During the last four weeks, how often has it been difficult for you to breathe during the daytime?
   4. More than once a day.
   3. Once a day.
   2. 3 to 6 times a week.
   1. Once or twice a week.
   0. Not at all.
6. During the last four weeks, how often has it been difficult for you to breathe at night?
   4. More than once a night.
   3. Once a night.
   2. 3 to 6 times a week.
   1. Once or twice a week.
   0. Not at all.
7. When the child does exercise (plays, runs, etc.) or laughs a lot, does he have a cough or whistling sounds in his/her chest/wheezing symptoms?
   4. Always.
   3. Nearly always.
   2. Sometimes.
   1. Very seldom.
   0. Never.
8. During the last four weeks, how many times has he/she had to go to the ED department because of his/her asthma?
   4. More than 3 times.
   3. Three times.
   2. Twice.
   1. Once.
   0. Not at all.
9. During the last four weeks, how many times has the child been admitted to hospital because of his/her asthma?
   4. More than three times.
   3. Three times.
   2. Twice.
   1. Once.
   0. Not at all.

Maintenance Treatment

Targets

The main aim of asthma treatment is to achieve and maintain control of the disease as soon as possible, as well as to preventing exacerbations and chronic airflow obstruction, and to reduce mortality. Treatment targets (Table 28), both in terms of controlling daily symptoms (current control) and preventing exacerbations and the progressive loss of pulmonary function (future risk), can be achieved in the vast majority of patients if they receive suitable treatment.

To achieve these objectives a comprehensive strategy, which is individualized in the long term and based on optimal adjusted pharmacological treatment and supervision measures, environmental

Table 27
Recommendations

Childhood asthma should be classified when the child is receiving no treatment.	R2
With the aim of classifying asthma correctly, as well as its severity, in children it is important to identify its trigger factors and to establish the level of control.	R2

Table 28
Asthma treatment targets

Current control
– Prevention of symptoms in the daytime, at night and during physical exercise.
– Use of a short-acting β_2 agonist no more than two days a week.
– Maintenance of normal or virtually normal lung function.
– No restrictions on daily life and physical exercise.
– Fulfilment of the expectations of patients and their families.
Future risk
– Prevention of exacerbations and mortality.
– Minimization of the progressive loss of lung function.
– Avoidance of the adverse effects of treatment.

Table 29
Characteristics of inhaled β_2 adrenergic agonists

Drug	Quantity inhaled (μg)		Time required to take effect (minutes)		
	Pressurized Inhaler	Dry Powder	Onset	Maximum	Duration
Short-acting drugs					
Salbutamol	100	100	3-5	60-90	180-360
Terbutaline	–	500	3-5	60-90	180-360
Long-acting drugs					
Formoterol	12	4.5-9-12	3-5	60-90	660-720
Salmeterol	25	50	20-45	120-240	660-720

control and asthma education, must be followed[90]. Pharmacological treatment must be adjusted in accordance with the level of patient control, without forgetting the most effective therapeutic options, safety and the cost of the various alternatives, taking into account the patient's satisfaction with the level of control achieved. Regular patient assessment is required to determine whether targets are being met. There are validated questionnaires that estimate objectively the level of control of the disease. [C]

Prevention of exacerbations and control of asthma

Asthma treatment must follow a comprehensive plan, agreed upon by the doctor and the patient (and eventually his/her family), in which the targets, the means to achieve them and the procedures for their modification or adaptation to the changing circumstances of the disease must be clearly defined. The distinction between the terms current control and future risk as different aspects of control is important, because it has been reported that they may respond differently to treatment[91]. For example, some patients may achieve good daily control of asthma and yet they suffer exacerbations. [C]

Treatment must be continually adjusted so that the patient is always controlled. This cyclical way of adjusting treatment implies that asthma control must be assessed objectively (Table 22), and that the patient must be treated to achieve control and have regular check-ups to maintain control. In other words, if asthma is not well controlled, the treatment must progress through as many therapeutic stages as necessary in order to ensure control is achieved. [D]

If asthma has been controlled for at least three months, maintenance treatment can gradually be reduced to determine the minimal therapeutic needs required to maintain control[92]. [C]

Drugs for treating asthma are classified as control or maintenance and relief medications, the latter also being called "rescue" drugs. Control or maintenance medications, which must be administered every day for prolonged periods, include inhaled or systemic glucocorticoids, leukotriene antagonists, prolonged-action β_2 adrenergic agonists, slow-release theophylline and monoclonal anti-IgE antibodies (omalizumab). Chromones have fallen into disuse, due to their lower efficacy.

Relief medications are used as needed to rapidly treat or prevent bronchoconstriction and they include (selected) inhaled short-acting β_2 adrenergic agonists (Table 29) and inhaled anticholinergics (ipratropium bromide).

The six therapeutic stages (Fig. 4) for achieving asthma control are:

Stages

Stage 1. The first step consists of using inhaled short-acting β_2 adrenergic agonists (salbutamol or terbutaline) exclusively as needed. Stage 1 is only for patients with occasional and mild daytime symptoms (a maximum of two days a week and short-lived episodes), no nocturnal symptoms and asthma that well controlled. The patient should be asymptomatic between episodes and maintain normal pulmonary function, although he is not exempt from the risk of suffering exacerbations. For the vast majority of patients the treatment indicated for fast symptomatic relief is an inhaled short-acting β_2 adrenergic agonist[93]. [A]

The use of an inhaled short-acting β_2 adrenergic agonist as required more than two days a week to treat symptoms (except when it is used preventively before exercise) indicates inadequate control of asthma and requires maintenance therapy to be initiated or increased[93]. Inhaled short-acting β_2 adrenergic agonists administered 10-15 minutes in advance are the drugs of choice for preventing bronchoconstriction induced by exercise[94]. [A]

An inhaled anticholinergic is only recommended as relief medication in rare cases of intolerance to inhaled short-acting β_2 adrenergic agonist[2]. [D]

Stage 2. The treatment of choice at this level is an inhaled glucocorticoid (beclomethasone, budesonide, fluticasone or mometasone) taken regularly at low doses[95-98]. This is usually the first stage for the majority of patients with persistent asthma who have not received previous treatment. [A]

The usual dose ranges from 200 to 400 mg/day of budesonide or its equivalent. The equipotent dose for the most widely used glucocorticoids is shown in Table 3[2].

Inhaled glucocorticoids constitute the most effective maintenance treatment for persistent asthma, both for controlling daily symptoms and for reducing the risk of exacerbations[98]. The possibility of using glucocorticoids intermittently is controversial and the same level of control of daily symptoms as with regular treatment is not achieved[99]. [A]

At this level leukotriene receptor antagonists or antileukotrienes (montelukast and zafirlukast) can also be used as an alternative form of treatment[100-101], although for long-term treatment inhaled glucocorticoids are more effective[100]. Patients who are well controlled on a low dose of inhaled glucocorticoids fail to maintain the same level of control with montelukast[102]. [A]

Antileukotrienes are specially indicated as an alternative in patients who cannot or do not wish to receive inhaled glucocorticoids, experience side effects from them, have difficulties with the inhalation technique or have concomitant allergic rhinitis[103-104]. [B]

There is no evidence that the addition of a long-acting β_2 adrenergic agonist affords any significant benefit at this level[105]. There are other options, but they are not recommended as the first line of treatment. Slow-release theophyllines show a certain efficacy as bronchodilator and anti-inflammatory agents[106,107] [B] but they can cause side effects that may be mild or even serious. Chromones (disodium cromoglycate and nedocromil sodium) demonstrate a comparatively lower efficacy, although they are well tolerated[108]. [A]

Stage 3. The treatment of choice at this level is a combination of a low-dose glucocorticoid with a long-acting β_2 adrenergic agonist (salmeterol or formoterol), both of which are inhaled[77,109-113] and can be administered preferably using the same device or separately. With this combination the symptoms subside, pulmonary function

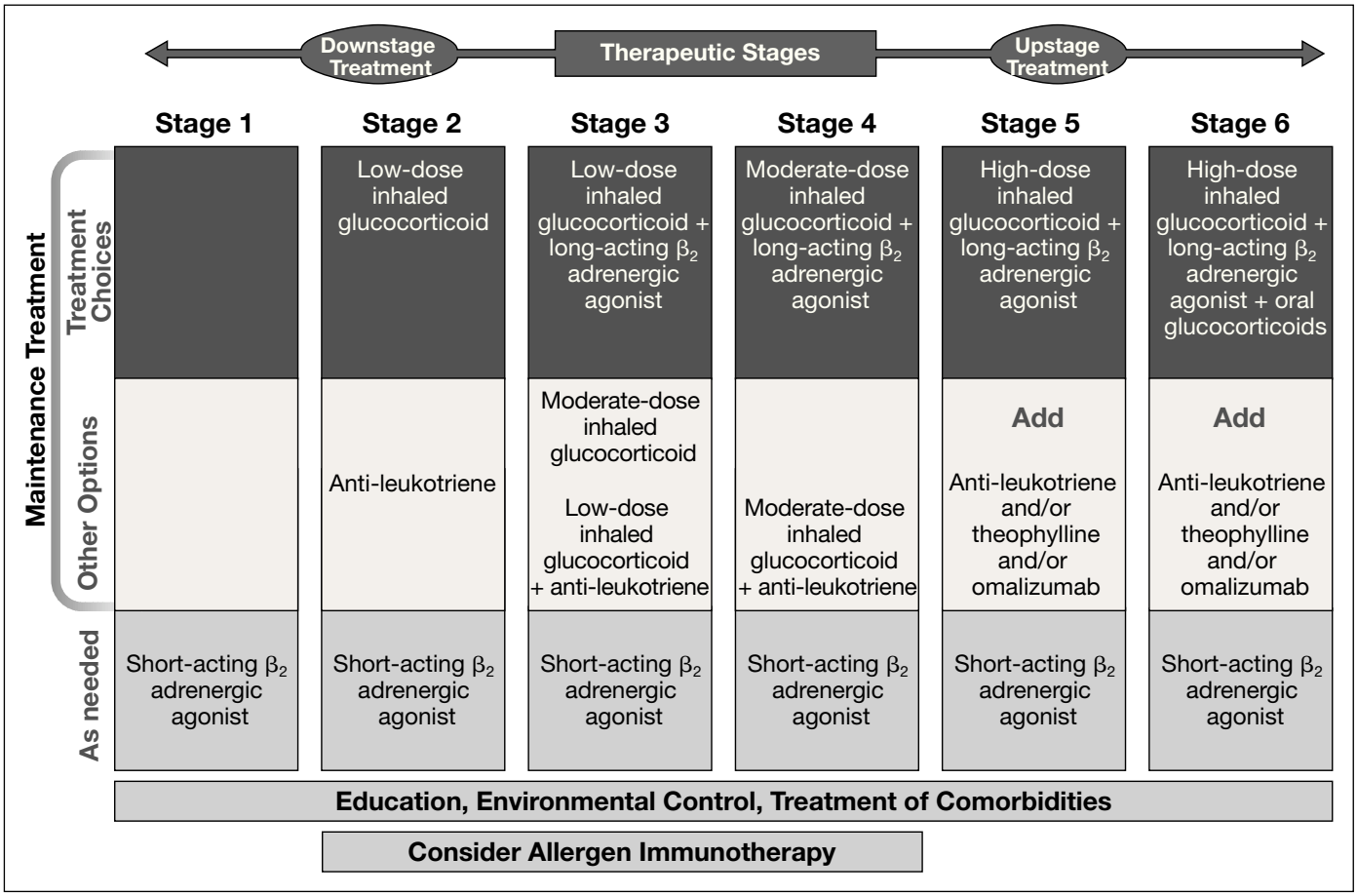


Figure 4. Therapeutic stages of adult asthma maintenance treatment.

Table 30
Equipotent doses of inhaled glucocorticoids

Drug	Low Dose (μg/day)	Average Dose (μg/day)	High Dose (μg/day)
Beclomethasone dipropionate	200-500	501-1,000	1,001-2,000
Budesonide	200-400	401-800	801-1,600
Fluticasone	100-250	251-500	501-1,000
Ciclesonide	80-160	161-320	321-1,280
Mometasone furoate	200-400	401-800	801-1,200

improves and exacerbations and the use of relief medication are reduced more noticeably than when the dose of glucocorticoids is increased [A]. However, it is necessary to conduct a proper individualized risk/benefit assessment with both strategies. The combinations marketed in Spain are: fluticasone with salmeterol, budesonide with formoterol and beclomethasone with formoterol. Long-acting β_2 adrenergic agonists must never be used as monotherapy.

Formoterol is a long-acting β_2 adrenergic agonist, but the onset of its action is rapid. This is why, if the budesonide/formoterol combination is chosen, it can be used both as a maintenance and relief treatment (SMART). This strategy ensures a reduction in exacerbations and better asthma control, despite requiring a smaller amount of glucocorticoids[114-120]. [A]

Another option at this level would be to increase the dose of glucocorticoids to moderate doses[110,121,122]. Alternatively, low doses of an inhaled glucocorticoid combined with an antileukotriene, which has shown itself to be better than glucocorticoid monotherapy, can be used. Although it is not as effective as the glucocorticoid-long-acting β_2 adrenergic agonist combination, it offers excellent safety levels[123-125]. [A]

Stage 4. At this level the treatment of choice is the combination of moderate doses of an inhaled glucocorticoid and a long-acting β_2 adrenergic agonist[77,110,126]. [B]

As an alternative, the combination of moderate doses of an inhaled glucocorticoid and an antileukotriene can be used, although the addition of a long-acting β_2 adrenergic agonist to a glucocorticoid is more effective in preventing exacerbations, controlling daily symptoms and improving pulmonary function[124]. [B]

Stage 5. This step consists of increasing the amount of inhaled glucocorticoids to a high dose and combining it with a long-acting β_2 adrenergic agonist[77,110,126]. [B] At moderate and high doses inhaled glucocorticoids are usually administered twice a day, but with budesonide, therapeutic efficacy can be improved by increasing the frequency of administration to up to four times a day[127].

Other maintenance drugs can be added; a subgroup of patients may respond to the addition of antileukotrienes[128] and delayed-release theophyllines[129]. [C]

In cases of allergic asthma that is poorly controlled with high doses of glucocorticoids and a long-acting β_2 adrenergic agonist, the monoclonal anti-IgE antibody (omalizumab), which improves daily symptoms[130] and exacerbations[131-133], can be added subcutaneously, increasing overall control of the disease.

Stage 6. In patients whose asthma continues to be poorly controlled, despite the use of high doses of inhaled glucocorticoids

Table 31
Recommendations

In patients with asthma symptoms at any therapeutic stage, the use of a short-acting β_2 adrenergic agonist as needed is recommended for rapid relief.	R1
Short-acting β_2 adrenergic agonists, administered 10-15 minutes in advance, are the medication of choice for preventing bronchoconstriction induced by physical exercise.	R1
The administration of an inhaled short-acting β_2 adrenergic agonist as needed is recommended for the treatment of intermittent asthma (stage 1).	R1
The treatment of choice in mild persistent asthma (stage 2) is an inhaled glucocorticoid taken regularly at low doses. Leukotriene receptor antagonists can be considered as an alternative treatment.	R1
In moderate persistent asthma the combination of an inhaled glucocorticoid at low (stage 3) or moderate doses (stage 4) with an inhaled long-acting β_2 adrenergic agonist is recommended as the treatment of choice.	R1
In moderate persistent asthma an inhaled glucocorticoid at low (stage 3) or moderate doses (stage 4) in conjunction with a leukotriene receptor antagonist can be considered as an alternative.	R1
The budesonide/formoterol combination can be employed as maintenance and as needed treatment. With this form of treatment a reduction of exacerbations and an improvement in daily symptoms are achieved, even when the dose of glucocorticoids is reduced.	R1
In severe persistent asthma (stage 5) an inhaled glucocorticoid at high doses and combined with a long-acting β_2 adrenergic agonist is recommended.	R1
In patients with poorly controlled severe allergic asthma the use of omalizumab should be considered.	R1
In severe asthma that is poorly controlled, despite using high doses of inhaled glucocorticoids and a long-acting β_2 adrenergic agonist (stage 6), with or without other maintenance drugs, the addition of oral glucocorticoids will need to be considered.	R2
Inhalation is the route of choice for the treatment of asthma. The use of spacers avoids the problem of coordinating actuation and inspiration, and improves the distribution and the amount of drug reaching bronchial tree.	R2

combined with a long-acting β_2 adrenergic agonist, with or without other maintenance drugs (antileukotrienes, theophylline, omalizumab), and who are limited in their daily activities and have frequent exacerbations, the addition of oral glucocorticoids should be considered (always at the lowest effective dose and for as short a time as possible)[134,135], although this treatment is associated with side effects, that are sometimes serious. [D]

Inhalers and nebulizers

Asthma drugs can be administered in different ways (oral, inhaled and intravenous delivery), but the advantages of inhalation make it the route of choice[136,137]. [C] The most common inhalation devices are the pressurized inhaler, which can be used with or without a spacing chamber (Volumatic®, Aerochamber®, Aeroscopic®, Babyhaler®, Nebuchamber®, Inhalventus®, Prochamber®, Optichamber® and Ildor®), the pressurized inhaler with a solution of extrafine particles (Modulite®), powder inhalers (Turbuhaler®, Accuhaler®, Aerolizer®, Novolizer®, Handihaler®, Easyhaler® and Twisthaler®) and (jet or ultrasonic) nebulizers, each with different characteristics that need to be considered when they are prescribed[138,139]. The age and ability to use a particular inhaler are the most important factors when choosing the most suitable inhaler in each case. The use of hydrofluoroalkanes (HFA) as a propellant in pressurized inhalers increases pulmonary deposits[140], so their use can affect the dose, which should be adjusted in accordance with the indications of the manufacturer.

The main disadvantage of this route is the difficulty of the inhalation technique for different inhalation devices, especially pressurized inhalers, because of the need to coordinate actuation and inhalation. The use of spacers avoids this problem, improves the distribution and the amount of drug which reaches the bronchial tree, reduces the deposition of particles in the oropharynx, decreases coughing and the possibility of oral candidiasis (which may be associated with the use of inhaled glucocorticoids), and reduces systemic bioavailability and, consequently, the risk of deleterious systemic effects[141-143]. In the case of powder inhalers the inhalation technique is easier, although pulmonary deposition depends on the inspiratory flow, which needs to be relatively high (> 60 l/minute)[139]. A fundamental aspect of the use of inhalation devices is that the patient must be trained to use them[138,144,145]. Therefore, once the device has been chosen, its characteristics and the appropriate inhalation technique must be explained to the patient and he must be shown how to use it. He would be asked to demonstrate how the device is used (with a placebo inhaler) and errors must be corrected. The inhalation technique must be checked at all successive visits.

Nebulizers are not the devices of choice for routine maintenance treatment and should only be used in special situations[139].

Other treatments

Environmental control

Asthma patients who smoke have more severe symptoms, a poorer response to glucocorticoid treatment and an accelerated loss of pulmonary function[146,147]. The proportion of asthma patients who smoke is high and similar to that of the general population, which is why the first aim of environmental control is to get the patient to stop smoking. In order to accomplish this the patient must be informed about suitable methods to help him deal with his addiction[148]. Exposure to environmental pollutants and passive smoking have a negative effect on the course of the disease and, in addition, they are a risk factor for developing asthma in childhood[30]. [C]

In allergic asthma, specific recommendations must be taken into consideration, once the sensitivity of each patient to different allergens has been confirmed. The most effective measures, such as those which can be applied in many cases of occupational asthma (change of job) or asthma caused by exposure to epithelia (removal of animals from the home)[149-152], are those which enable exposure levels to be drastically reduced and that ensure the introduction of such interventions at an early stage in the development of the disease (see occupational asthma). [C]

Isolated individual measures, such us the use of mattress covers or acaricides, are not effective, not even in reducing levels of exposure[153-155]. However, with the application of specific combined interventions a significant reduction in the level of allergenic exposure and, consequently, clinical efficacy is achieved[149,156,157].

A randomized trial, involving 937 patients with uncontrolled moderate-severe asthma and sensitized to at least one domestic allergen, in which a series of measures were applied (impermeable mattress covers, vacuum cleaners and air purifiers in bedrooms [both devices with HEPA filters], cockroach disinfection plans), together with a year-long general educational programme, led to a significant reduction in symptoms and unscheduled medical visits[149]. [B]

On the other hand, two systematic reviews with a meta-analysis concluded that the efficacy of environmental control measures against mites is minimal in rhinitis patients[158] and totally ineffective in asthma patients[155]. Nevertheless, this meta-analysis has been questioned, due to the inappropriate selection of the studies it includes[159]. [B]

Various factors, such as climatic conditions, building types, furniture and bed clothing, or lifestyle habits, can have a marked influence on the efficacy of these measures. Consequently, the generalization of the results of a particular program may be questionable.

Some asthma patients, especially those who develop naso-sinusal polyps, may have asthma attacks when they are given aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). Many of these reactions are serious or an even fatal[160], so patients must be correctly diagnosed, either on the basis of an obvious clinical history (various reactions to different NSAIDs) or and oral challenge, which can be substituted in serious cases by bronchial or nasal inhalatory challenge[161,162]. The best alternative analgesic agent in these patients

Table 32
Painkillers and anti-inflammatory agents which can be used in NSAID-intolerant patients

Painkillers
– Paracetamol taken in ≤ 650 mg doses
– Opiates: tramadol, codeine, dextropropoxyphene
Anti-inflammatory drugs
– Glucocorticoids
– Selective COX_2 inhibitors : meloxicam
– Specific COX_2 inhibitors : celecoxib, etoricoxib

(Table 32) is paracetamol administered at less than 650 mg per individual dose, given that some patients may have bronchospastic crises and these occur more often if high doses are used. Opiates, such as tramadol or codeine, are also regarded as safe alternative painkillers. Glucocorticoids can be employed as anti-inflammatory drugs. Selective (meloxicam) or specific (celecoxib, etoricoxib) COX-2 inhibitors could be another alternative, although, before recommending them, it is advisable to confirm patient tolerance[163]. This type of test should be conducted in centers with experience in this field. [C]

Allergen immunotherapy

Immunotherapy involving subcutaneous administration of allergen vaccines is an effective treatment for well controlled allergic asthma with low or moderate treatment levels (therapeutic stages 2-4), as long as a clinically relevant IgE-mediated sensitization to common aeroallergens has been demonstrated, well characterized and standardized extracts are used[164,165] and the use of complex mixtures is avoided[166]. [A] Immunotherapy must not be prescribed for patients with severe or uncontrolled asthma because it is ineffective and due to the high risk of severe, even fatal, reactions[167,168]. This is why subcutaneous immunotherapy should be prescribed by specialists with experience in using this treatment and administered in centers with basic measures for the immediate treatment of a possible reaction. [B]

The search for safer and more convenient alternatives for patients has stimulated research on the efficacy of sublingual immunotherapy. Two systematic reviews conclude that it is capable of significantly reducing bronchial manifestations in children and adolescents with allergic asthma[169,170]. Most clinical trials that have demonstrated its clinical efficacy have done so with well characterized extracts at much higher doses than those routinely used in subcutaneous immunotherapy. The tolerance profile of sublingual immunotherapy is optimal and fatal reactions have not been reported. [B]

Currently there are no cost-efficacy studies that compare immunotherapy with conventional pharmacotherapy. Nevertheless, immunotherapy has additional advantages, including maintenance of the clinical benefits obtained, even several years after treatment has been withdrawn[171,172]. It also curtails the progression of rhinoconjunctivitis caused by pollen allergies to asthma[172] or the appearance of new sensitizations in monosensitized patients[173]. [B]

Influenza and pneumonia vaccination

Influenza[174-175] and pneumonia vaccinations[176] have shown no efficacy in preventing asthma exacerbations. [A]

Education

Education of asthma patients reduces the risk of suffering an exacerbation, increases quality of life and lowers healthcare costs[77,177], so it is an indispensable part of the overall treatment of the disease[2,4,178-182]. The main aim of education is to provide patients with the knowledge and skills needed to improve self-management and to achieve therapeutic compliance. [A]

From a practical point of view[183], education must address two major aspects: the transmission of knowledge and the acquisition of skills (Table 34). With respect to the information patients should receive about asthma, their needs, previous knowledge, beliefs, age, asthma severity and the degree to which they need to be implicated in self-control and treatment must be taken into account. In relation to the skills to be developed, they must be trained and monitored wherever possible to confirm that they are taking the medication prescribed and to establish his level compliance. It is also necessary to ensure that familiarity with the technique of the inhalation devices used, and to check any exacerbations/attacks and how they deal with them, as well as avoidance of allergenic trigger factors[184,185]. [A]

Table 33
Recommendations

In allergic asthma an evaluation of possible sensitizations to different allergens is recommended.	R1
In allergic asthma due to mites, isolated environmental control measures are not recommended.	R2
In well controlled allergic asthma with low or moderate treatment levels (stages 2-4), as long as a clinically relevant IgE-mediated sensitization to common aeroallergens has been demonstrated and well standardized extracts are used, allergen immunotherapy is recommended.	R1
Allergen immunotherapy should be prescribed by experienced medical specialists and administered at centers wiht basic measures for the immediate treatment of an adverse reaction.	R2

Table 34
Information and basic skills that the asthma patient must learn

Patients must be aware that asthma is a chronic disease and needs continuous treatment, even though it may have no obvious symptoms.
They must know the difference between inflammation and bronchoconstriction.
They must be able to differentiate between drugs which "control" inflammation and drugs which "relieve" obstruction.
They must recognize the symptoms of the disease.
They must use inhalers correctly.
They must identify and avoid trigger factors as much as possible.
They must monitor symptoms and peak expiratory flow (PEF).
They must recognize the signs and symptoms of exacerbations of the disease (loss of control).
They must take action when there is any deterioration in their condition, in order to prevent a crisis or exacerbation.

For education to be effective it is important to establish trust between the medical team and the patient, so that patients can voice any doubts, concerns or fears. Medical personnel will need to use a language that is comprehensible to patients and/or their relatives, clarifying any concepts which have been presented but not fully understood and inviting them to express any doubts or questions. Furthermore, shared objectives must be set with patients, which will always require individualized plans to be drawn up in writing.

The educational program must include the preparation of asthma action plans. Plans consist of a set of written instructions tailored to each patient, taking into account the severity and control of asthma and the usual treatment prescribed. The main aim of asthma action plans is the early detection of exacerbations and the rapid implementation of interventions designed to achieve rapid remission. The level of control, on which the intervention plan will be based, can be assessed either in terms of the severity and frequency of asthma symptoms or on the basis of the daily PEF measurements the patient takes in his own home, depending on the preferences of patients or their doctor[186-189]. This plan should consist of two basic parts[190,192]: the usual treatment for situations of clinical stability and the steps to be taken if the patient's asthma deteriorates (Table 35). It must be reviewed at each appointment, whether the visit is scheduled or not, as well as during any hospital admissions or ED visits. [A]

Since education is a continuous process and not an isolated event, each visit is an opportunity for review, reinforcement and an expansion of patient knowledge and skills, so it is essential for the

Table 35
Action plan

I. USUAL TREATMENT
1. Take on a daily basis _____
2. Before doing exercise, take _____
II. WHEN YOUR TREATMENT MUST BE INCREASED
1. Assessment of the level of control of your asthma:
   Do you have asthma symptoms more than twice a day? Yes No
   Is your activity or physical exercise limited by your asthma? Yes No
   Does your asthma wake you up at night? Yes No
   Do you need to use your bronchodilator more than twice a day? Yes No
   If you use a flow (PEF) meter, are the values lower than _____? Yes No
   If you have replied "Yes" to three or more questions, your asthma is not well controlled and your usual treatment needs to be increased
2. How to increase your treatment:
   Increase your treatment in the following way and assess your improvement daily:
   _____ (write down the increase in your new treatment)
   Maintain this treatment for _____ days (specify the number).
3. When you need to ask your doctor/hospital for help:
   Telephone your doctor/hospital _____ (provide telephone numbers)
   If your asthma fails to improve in _____ days (specify the number)
   _____
   _____ (complementary instructions)
4. Emergency. Serious lack of control of your asthma:
   If you have intense bouts of breathlessness and you can only utter short phrases.
   If you have intense and severe asthma attacks.
   If you have to use your rescue or relief bronchodilator every 4 hours and there is no improvement.
   1. Take 2 to 4 puffs (rescue bronchodilator).
   2. Take _____ mg of _____ (oral glucocorticoids).
   3. Request medical help: go to _____: address _____ Call number _____.
   4. Continue using your _____ (rescue bronchodilator) until you get medical help.

entire team to agree upon and be consistent about[181]. We need to remember that, during the educational process, when the intensity of intervention is reduced, its efficacy also decreases, given that purely informative interventions are not effective[182]. [A] The educational tasks for each visit are described in Table 36[71]. After receiving training, nursing personnel must participate actively in the administration and management of this type of educational program[193,194]. [B]

Asthma exacerbations

Exacerbations (asthma attacks) are acute or subacute episodes, which are characterized by a progressive increase in one or more typical asthma symptoms (dyspnea, coughing, wheezing and tightness of the chest) accompanied by a decrease in expiratory flow (PEF or FEV_1). Depending on the speed with which crises ensue, there are two types: those that are slow to develop (normally over a period of days or weeks) and those that develop quickly (in less than three hours), and they must be identified in accordance with their different causes, pathogenesis and prognosis[160,195]. Exacerbations that are slow to develop (over 80% of the cases seen in ED) are often due to upper respiratory tract infections or to deficient control of the disease, as a result of poor therapeutic adherence; the basic mechanism underlying deterioration is inflammation and the response to treatment is also slow. Meanwhile, exacerbations that develop rapidly are due to inhaled allergens, the ingestion of drugs (NSAIDs or ,-blockers), foods (reactions to additives and preservatives) or emotional stress; the mechanism is bronchospasm and, although initially more serious (with a risk of intubation and death), the response to treatment is better and quicker. The intensity of exacerbations is variable. Sometimes the symptoms are mild and cannot be detected by the patient and other times they are very severe episodes that are life-threatening. There are patients who have a greater risk of suffering life-threatening asthma crises (Table 38)[196-198]. [C]

Table 37
Recommendations

Asthma patients should follow a formal asthma educational program. Actions which are purely informative have not been shown to be effective.	R1
Asthma patients should be provided with a written action plan to ensure the early detection of asthma exacerbations and to enable interventions to achieve rapid remission.	R1

Evaluation of severity

The severity of an exacerbation determines its treatment and, consequently, it is essential to make a quick initial assessment of the patient. The evaluation of an attack is performed in two stages[199]: [D]

- The initial (or static) stage. Its aims are: to identify patients with risk factors (Table 38), to identify life-threatening signs and symptoms (Table 39) and to objectively measure the extent of airflow obstruction by determining FEV_1 or PEF and its repercussion on gaseous exchange. [D]
- The stage following response to treatment (or dynamic evaluation). Its objectives are: to compare the changes obtained in the degree of airflow obstruction with respect to initial values and to estimate the need to perform other diagnostic tests. [D]

A brief initial medical history will give us an idea of the cause of the asthma symptoms, the duration of the attacks and prior treatment. The presence of life-threatening signs or symptoms and the imminence of a cardio-respiratory attack (alteration of sensory perception or consciousness, bradycardia, hypotension, cyanosis, "silent" chest or psychomotor agitation) mean that intensive care units must be contacted. Other signs and symptoms (Table 39) are of little use, due to their poor correlation with the level of obstruction and wide variations in their interpretation[200]. [C]

Table 36
Educational tasks for every visit

	Communication	Information	Instruction
Initial visit	Investigate expectations. Agree on targets. Discuss compliance.	Basic asthma concepts and treatment.	Inhalation technique. Self-monitoring.
Second visit	Evaluate achievements in terms of targets and expectations. Discuss compliance.	Reinforce the information received at the first visit. Inform the patient about environmental avoidance measures.	Reinforce inhalation technique. How to avoid trigger factors. Interpretation of readings. Action plan.
Check-ups	Evaluate achievements in terms of targets and expectations. Discuss therapeutic compliance and environmental avoidance measures.	Reinforce all information.	Review and reinforce the inhalation technique. Review and reinforce self-monitoring and the self-management plan.

Table 38
Pre-disposing factors for patients life-threatening asthma

Previous ICU admissions or intubation/mechanical ventilation.
Frequent hospitalizations during the previous year.
Multiple visits to Accident and Emergency Services in the last year.
Psychological traits (alexythimia) and disorders (attitudes of negation) or psychiatric diseases (depression) that make treatment adherence difficult.
Cardiovascular comorbidity.
Short-acting β_2 adrenergic agonist abuse.
Abrupt crisis onset.
Patients with no regular control of their disease.

ICU: Intensive Care Unit.

Table 39
Assessment of the severity of asthmatic exacerbations

	Mild Crisis	Moderate-severe Crisis	Imminent Respiratory Failure
Dyspnea	Mild	Moderate-intense	Very intense
Speech	Paragraphs	Phrases-words	
Respiratory rate (x')	Increased	> 20-30	
Heart rate (x')	< 100	> 100-120	Bradycardia
Use of accessory muscles	Absent	Present	Paradoxical thoracic-abdominal movement
Wheezing	Present	Present	Auscultatory silence
Consciousness	Normal	Normal	Impaired
Paradoxical pulse	Absent	> 10-25 mmHg	Absent (muscular fatigue)
FEV_1 or PEF (reference values)	> 70%	< 70%	
SaO_2 (%)	> 95%	90-95%	< 90%
PaO_2 mmHg	Normal	80-60	< 60
$PaCO_2$ mmHg	< 40	> 40	> 40

FEV_1: forced expiratory volume during the first second; PEF: peak expiratory flow; x': per minute; SaO_2: oxyhaemoglobin saturation; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure.

The objective appraisal of the level of airflow obstruction using a spirometer (FEV_1) or a PEF meter permits initial severity and response to treatment to be determined. Depending on the values obtained, an exacerbation will be considered mild if the FEV_1 or PEF value is equivalent to or 70% higher than its theoretical or best previous personal value respectively, moderate if the FEV_1 or PEF measurement is between 70% to 50% and serious if these values are lower than 50%. It is estimated that the functional response to treatment is satisfactory when FEV_1 or PEF values are higher than 45% of the predetermined value and PEF increases at least 50 l/min 30 minutes after treatment is initiated[201]. The initial therapeutic airflow obstruction response is the key prognostic factor for assessing an attack. [C]

The measurement of oxygen saturation by pulsioximetry is required in all patients with a FEV_1 or PEF reading of less than 50% of its theoretical value in order to rule out hypoxemia. Arterial gasometry is useful in patients whose saturation cannot be maintained above 90% despite oxygenotherapy[202]. [D]

Other complementary tests may be performed at the outset, such as chest X-rays and ECG. They are usually performed when the presence of symptoms including fever, pain or intense dyspnea, suggest the possibility of complications, such as pneumothorax or an infection of the lower respiratory tract, or when the therapeutic response as measured by means of objective parameters, is inappropriate[203]. [D]

Treatment

The immediate aim of attacks treatment is to preserve the life of the patient by reversing airflow obstruction and hypoxemia, if it is present, as fast as possible and then to instate or revise the therapeutic plan to prevent new attacks. Figure 5 and Table 40 show the pharmacological treatment that must be employed, depending on severity, and the normally recommended doses.

Mild exacerbations

In addition to the hospital ED, milder crises can be treated at home by the patient and at Primary Care Centers, as long as a proper clinical assessment of PEF is made and there is a response to treatment in the first two hours. [D]

Patients with written action plans for treating mild attacks, who record their PEF at home, are using the best strategy for managing mild exacerbations since they can apply it early in an attack[204]. They need to be trained to recognize early indicators of an exacerbation and to act immediately in accordance with the action plan designed for them and that must include the measures that need to be taken depending on the response to treatment. [C]

The treatment regimen to be followed does not depend on the place where the patient receives treatment. Basically, it must include the administration of fast-acting β_2 adrenergic agonist bronchodilators (salbutamol or terbutaline), oral glucocorticoids and oxygen (if necessary). Inhaled short-acting β_2 adrenergic agonists are the fastest and more effective bronchodilator drugs for the treatment of asthma exacerbations. Salbutamol (or terbutaline) is employed at 200 to 400 μg doses and is administered using an inhalation chamber (2 to 4 inhalations) every 20 minutes during the first hour[205-206]. A lack of response, in cases of outpatient management, means that patients must be transferred to a hospital ED. When the response is good, salbutamol at a dose of two inhalations every 3-4 hours must be continued until the attacks remits. [A]

If the patient progresses favorably in the first two hours of treatment (disappearance of symptoms, PEF higher than 80% of its theoretical value or best personal value) and this improvement is maintained for 3-4 hours, no further treatment is necessary.

The use of systemic glucocorticoids accelerates the resolution of exacerbations. Except in very mild attacks, they should always be administered[207], especially if: a) a reversal of airway obstruction is not achieved with inhaled fast-acting β_2 adrenergic agonists; b) the patient was already taking oral glucocorticoids; c) the patient has already treated his previous loss of control with other therapeutic options without success; d) there is a history of previous exacerbations requiring oral glucocorticoids. The daily dose is 0.5 to 1 mg of prednisone/kg (or the equivalent amount of other steroids) of the patient's ideal weight, maintaining the same dose for 5 to 10 days (without requiring progressive dose reduction) in order to achieve faster improvement and to avoid early relapses[208-210]. [A]

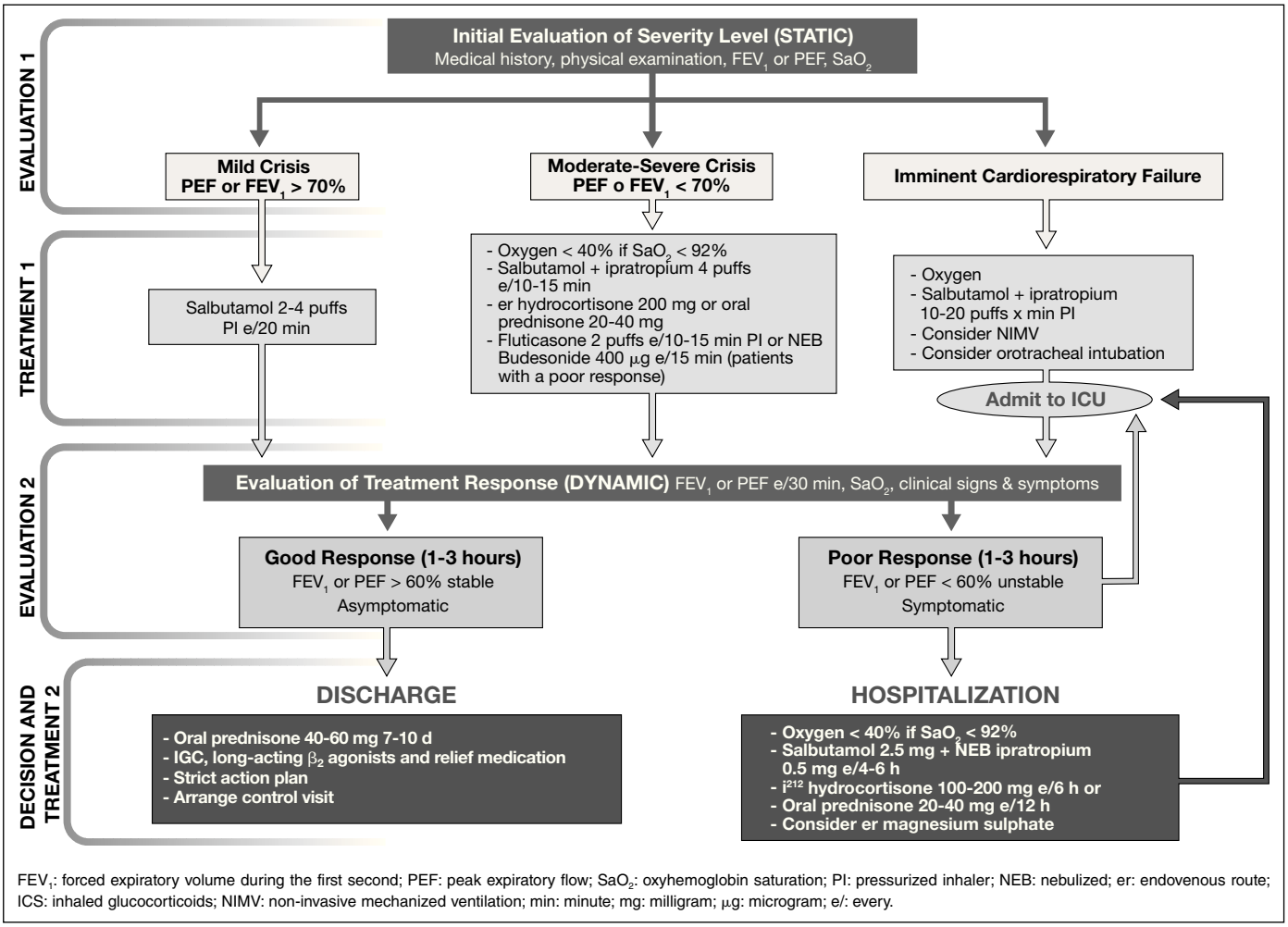
When the response to the first doses of inhaled bronchodilator treatment is satisfactory, hospital referral is not necessary. The patient needs to be instructed about how to follow subsequent treatment properly and about changes in his therapeutic maintenance plan, or his asthma educational program must be reviewed[211]. [D]

Moderate-severe exacerbations

The first line of action consists of administering oxygen in order to maintain a SaO_2 level higher than 90%, avoiding the administration of high concentrations that can lead to hypercapnic respiratory failure[212], especially in patients with more severe obstruction. [C]

After that, it is advisable to administer a short-acting β_2 adrenergic agonist. Repeated administration at regular intervals and evaluating the treatment response, has been shown to be effective in eliciting a bronchodilator response in asthma attacks[213]. Depending on the system used, up to three consecutive nebulizations of salbutamol (2.5 mg) can be administered every 30 minutes or 12 puffs (4 every 10 minutes) if they are delivered with a pressurized inhaler and an inhalation chamber. In serious cases continuous nebulization can also be used at a rate of 10 mg/h[214]. [A]

Salbutamol must only be administered intravenously or subcutaneously in patients who are ventilated or who fail to respond



FEV_1: forced expiratory volume during the first second; PEF: peak expiratory flow; SaO_2: oxyhemoglobin saturation; PI: pressurized inhaler; NEB: nebulized; er: endovenous route; ICS: inhaled glucocorticoids; NIMV: non-invasive mechanized ventilation; min: minute; mg: milligram; μg: microgram; e/: every.

Figure 5. Diagnostic and therapeutic management of adult asthma exacerbations (from the ALERTA 2008 Guide[199]).

to inhaled treatment, as there is no difference in its efficacy and it has more side effects[215]. [C]

Table 40
Drugs and doses for the treatment of asthma exacerbations

Therapeutic Groups	Drugs	Dose
Inhaled β_2 adrenergic agonists	Salbutamol or terbutaline	– 4-8 puffs (100 μg/puff) e/10-15 min (PI + spacing chamber) – 2.5-5.0 mg e/20 min (intermittent NEB) – 10-15 mg/h (continuous NEB)
	Formoterol	– 24-36 μg (Turbuhaler)
Systemic β_2 adrenergic agonists	Salbutamol	– 200 μg iv in 20 min followed by 0.1-0.2 μg/kg/min.
Anticholinergics	Ipratropium bromate	– 4-8 puffs (18 μg /puff) e/10-15 min (PI + spacing chamber) – 0.5 mg e/20 min (intermittent NEB)
Systemic Glucocorticoids	Prednisone	– 20-40 mg e/12 h (or)
	Hydrocortisone	– 100-200 mg e/6 h (er)
Inhaled Glucocorticoids	Fluticasone Budesonide	– 2 puffs (250 μg/puff) e/10-15 min (PI + spacing chamber) – 800 μg e/20 min (NEB)
Systemic magnesium sulphate		– 2 g to be taken in 20 min (er)
Inhaled magnesium sulphate		– 145-384 mg in isotonic solution (NEB)
Aminophylline		– 6 mg/kg to be taken in 30 min followed by 0.5-0.9 mg/kg/h

PI: pressurized inhaler; NEB: nebulized; or: oral route; er: endovenous route; ICS: inhaled glucocorticoids; kg: kilogram; min: minute; mg: milligram; μg: microgram; e/: every; h: hour.

Formoterol (a long-acting and rapid-onset β_2 adrenergic agonist), administered using a powder system, is equivalent to salbutamol in patients with moderate or severe attacks[216]. [B]

The use of nebulized ipratropium bromate (0.5 mg) during the initial phase of asthma crises in patients with severe asthma or with a poor initial response to β_2 adrenergic agonists provides a significant increase in bronchodilation[217]. [A]

Systemic glucocorticoids must be administered at an early stage (during the first hour of treatment in ED) in all patients who have moderate or severe exacerbations or who fail to respond to initial treatment. A systematic review demonstrated that prompt administration of steroids lowers the rate of readmissions and hospitalizations in patients with asthma exacerbations[218]. The recommended dose of steroids is 100-200 mg of hydrocortisone or 40-60 mg of methylprednisolone when initiating treatment. The studies available do not show differences between high and low doses or between intravenous and oral administration[207]. [A]

The repeated administration of inhaled glucocorticoids in conjunction with bronchodilators, at intervals no longer than 30 minutes and during the first 90 minutes of treatment, elicits a significant improvement in lung function and a reduction in the number of hospitalizations[219]. [B]

The nebulization of salbutamol in an isotonic magnesium sulphate solution produces no additional benefits, except in a subgroup of patients with a FEV_1 value lower than 30%[220]. In the case of patients with very severe attacks and a poor response to treatment,

intravenous magnesium sulphate can be used as a single 1-2 g dose administered over a period of 20 minutes[221]. [B]

With respect to other drugs, such as aminophylline[222], heliox,[223] antibiotics and leukotriene receptor antagonists, there is no data to support their use in the treatment of moderate-severe asthma exacerbations.

Failure to respond to treatment[224]

Should refractory respiratory failure or symptoms or signs of severe exacerbation persist despite treatment, there is still the possibility of using non-invasive mechanical ventilation (NIMV) or transferring the patient to the ICU for orotracheal intubation and mechanical ventilation [D]. Few studies using NIMV have been carried out to date. The decision to perform intubation is a matter of clinical judgement, when there is progressive deterioration or failure of the respiratory muscles. Permissive hypercapnic ventilation has demonstrated better results than the usual ventilation methods[224]. [C]

Hospitalization criteria

Various studies have shown that, once the peak bronchodilator response plateau has been reached, further administration of medication is not synonymous with greater clinical improvement[213,225]. [C] This explains why it is usually recommended that decisions about hospital admissions should be made three hours after initiating treatment. Patients who have received adequate treatment during that time and continue to show symptoms, who require oxygenotherapy to maintain a SaO_2 level higher than 90% and demonstrate a persistent reduction in pulmonary function (FEV_1 or PEF below 40%) must be hospitalized[226]. [D]

In all cases in which the criteria for hospitalization are not met, it is recommended that the patient be kept under observation for 60 minutes to confirm his clinical and functional stability before discharge.

Hospital discharge criteria

Patients who have been admitted to the hospital for an asthma exacerbation, can be discharged if they comply with the following criteria: disappearance or significant improvement in asthma symptoms; PEF higher than 70% of the patient's best personal value in a stable situation; daily PEF variability less than 20%; short-acting 2 adrenergic agonists need to be used as needed less than three times a day, absence of significant dyspnoea on walking and the patient has already started to receive inhaled glucocorticoids[227,228].

Treatment of asthma in children

Maintenance treatment

Drugs

Inhaled Glucocorticoids. Persistent wheezing in children under the age of three can be controlled with inhaled glucocorticoids, but the treatment does not appear to modify the progression of the disease[229]. [B] Pre-school children with intermittent wheezing episodes related to viral infections show a poor response to treatment[230]. Intermittent treatment with inhaled glucocorticoids does not improve control or progression of the disease[231]. Infants with risk factors for developing persistent asthma (Asthma Predictive Index or API)[31] also demonstrate a better response to glucocorticoid treatment[229,232]. [A] In children over the age of three, the efficacy of inhaled glucocorticoids has been sufficiently demonstrated. Due to improvements in clinical, functional and bronchial inflammation parameters, so glucocorticoids constitute the first line of treatment[95-96]. [A]

Equipotential doses of inhaled glucocorticoids for children are shown in Table 42.

Table 41
Recommendations

The evaluation of any asthma exacerbation must include the identification of signs and any history of life-threatening risk and the use of objective measurements (PEF or spirometry) to quantify the degree of airflow obstruction (static assessment).	R2
In patients with an asthma attacks we recommend considering the initial therapeutic response to airflow obstruction in order to decide how to proceed (dynamic assessment).	R2
In asthma attacks, treatment with inhaled β_2 adrenergic agonists is recommended.	R1
In moderate-severe exacerbations prompt administration of systemic glucocorticoids and oxygen at the minimum concentration that will permit a SaO_2 > 90% is recommended.	R1

Leukotriene Receptor Antagonists. Their efficacy in controlling childhood asthma has been demonstrated, although they have less anti-inflammatory capacity and clinical efficacy than inhaled glucocorticoids[233]. [A] Their use in conjunction with glucocorticoids improves the control of symptoms[234,235] and they may reduce the number of exacerbations induced by viruses in children with intermittent asthma[236]. [B] In a study involving atopic children under 3 years of age with clinical symptoms of recurrent wheezing, leukotriene receptor agonist have been shown to be effective in reducing the number of asthma episodes, improving pulmonary function and decreasing the amount of exhaled nitric oxide exhaled[237]. [C]

Chromones. Their long-term efficacy is no greater than for placebo, so they are not used in children[238]. [A]

Long-acting β_2 Adrenergic Agonists and Inhaled Glucocorticoid Combinations. Their use is authorized for patients over 4 years of age, but their efficacy in children has not been as well demonstrated in comparative studies as it has been in adults[239]. One study demonstrated a reduction in exacerbations and in the need for systemic glucocorticoids in children receiving formoterol/budesonide administered in a single inhaler, both as maintenance and relief treatment (SMART strategy)[240]. [B] Long-acting β_2 adrenergic agonists are safe as long as they are administered together with an inhaled glucocorticoid and never as rescue medication[126,241]. [B]

Theophyllines. As maintenance monotherapy, they are less effective than inhaled glucocorticoids, although their anti-inflammatory effect means they can be used in association with an inhaled glucocorticoid in cases of severe persistent asthma[242]. [B]

Monoclonal Anti-IgE Antibodies. Various studies have demonstrated their therapeutic efficacy in children over 12 years of age with moderate persistent or severe atopic asthma[243]. [B]

Immunotherapy. When biologically standardized extracts are used in properly selected sensitized patients, this treatment has been shown to reduce symptoms, rescue and maintenance medication and (specific and non-specific) bronchial hyperresponse[165]. [A]

Treatment in accordance with level of severity

The classification of asthma according to severity (Table 25) must be done when the patient is not receiving treatment and is useful for choosing initial maintenance treatment. After that, modifications must be made in stages, depending on the level of control obtained for children under 3 years of age (Fig. 6) and (Fig. 7) for older children. [D]

Children with occasional episodic asthma must start their treatment at stage 1: in other words, using bronchodilators as needed and with

Table 42
Equipotential doses of inhaled glucocorticoids in children (μg per day)

	Low Doses	Moderate Doses	High Doses
Budesonide	≤ 200	200-400	> 400
Fluticasone	≤ 100	100-250	> 250

	Treatment Stage	Control Medication	Rescue Medication
Assessment of compliance and inhalatory technique	1	No control medication	Fast-acting bronchodilator as needed
	2	Low-dose ICS or LTRA	
	3	Moderate-dose ICS or low-dose ICS + LTRA	
	4	Moderate-dose ICS + LTRA	
Environmental control	5	High-dose ICS + LTRA If control is not achieved add: LAβ_2AA*	
	6	Oral GC	

ICS: inhaled glucocorticoids; LTRA: leukotriene receptor antagonist; LAβ_2AA: long-acting β_2 adrenergic agonist; GC: glucocorticoids. The treatment alternatives included in each stage are listed in order of preference.

Figure 6. Stages of asthma treatment depending on the level of control in children under 3 years of age.

		Treatment Stage	Control Medication	Rescue Medication
Assessment of compliance and inhalatory technique	Consider Immunotherapy	1	No control medication	Fast-acting bronchodilator as needed
		2	Low-dose ICS or LTRA	
		3	Moderate-dose ICS or low-dose ICS + LAβ_2AA or low-dose ICS + LTRA	
Environmental control		4	Moderate-dose ICS + LAβ_2AA or moderate-dose ICS + LTRA	
		5	High-dose ICS + LAβ_2AA If control is not achieved add: LTRA, theophylline	
		6	Oral GC Omalizumab	

ICS: inhaled glucocorticoids; LTRA: leukotriene receptor antagonist; LAβ_2AA: long-acting β_2 adrenergic agonist; GC: glucocorticoids. The treatment alternatives included in each stage are listed in order of preference.

Figure 7. Stages of asthma treatment depending on the level of control in children over 3 years of age.

no maintenance treatment. Children with frequent episodic asthma should start their treatment at stage 2 and, if control is not achieved, their treatment must be upstaged until it is controlled. Children with moderate persistent asthma must start receiving treatment at stage 3. For children with severe asthma it is preferable to start at stage 5 and to stage treatment down as soon as control is achieved, always aiming to find the minimum effective dose[244-246]. [B]

Assessment and treatment of exacerbations

General considerations

Therapeutic approaches to exacerbations will depend on their severity. Drug doses and administration times must be modified in accordance with the severity of attacks and their response to treatment. [D]

Moreover, how long a particular attacks has taken to develop, the treatment previously administered, the maintenance treatment the patient is receiving, and concomitant diseases and risk factors (prior intubation, hospitalization in the previous year, use of oral glucocorticoids, etc.) must be considered. [D]

Mild and moderate attacks can be treated at Primary Care centers. When attacks are severe and/or complications are suspected, or

Table 43
Recommendations

The use of inhaled glucocorticoids is recommended as the first line of treatment for controlling persistent asthma in children of any age.	R1
Long-acting β_2 adrenergic agonists are a form of treatment that should be considered for children if they are used in association with an inhaled glucocorticoid.	R1
Long-acting β_2 adrenergic agonists must never be administered as monotherapy.	R1
Children with moderate persistent asthma should initiate treatment with moderate doses of inhaled glucocorticoids until control is achieved and then the dose should be reduced. As an alternative, treatment can begin with a combination of inhaled glucocorticoids at low doses and an anti-leukotriene in children under 4 years of age or a long-acting β_2 adrenergic agonist in older children.	R1
For treatment of children with allergic asthma, immunotherapy treatment should be considered, as long as biologically standardized extracts are used and patients are carefully selected.	R1

there is a history of high-risk attacks or failure to respond to treatment, patients must be referred to a hospital ED.

Assessment of severity

Assessment is essentially based on clinical criteria (respiratory rate, presence of wheezing and retractions of the sternocleidomastoid muscles), variables included in the *Pulmonary Score* (Table 44)[247]. This stage is simple and applicable to all ages. The symptoms, together with the oxygen saturation level determined by pulsioximetry (SaO_2), enable estimation of the severity of an episode (Table 45). [C]

An SaO_2 level below 92% following initial inhaled bronchodilator treatment identifies the most serious patients and they must be hospitalized to commence intensive treatment[248]. [C]

Drugs

Short-acting β_2 Adrenergic Agonists. These are the first line of treatment. Inhalation is the route of choice, due to its greater effectiveness and fewer side effects[249]. The pressurized inhaler system with a spacing chamber is at least as effective as nebulizers for the treatment of acute asthma episodes[206,250,251]. [A]

The recommended doses will depend on the severity of the crisis and the response to initial doses. The most widely used drug is salbutamol, which is available as a nebulizer solution, pressurized inhaler or dry powder. Terbutaline in dry powder form can be used for the treatment of attacks in older children who use the Turbuhaler® system correctly. The bronchodilator must be administered in series of 2-10 100 μg puffs of salbutamol until a response is achieved. In mild crises a single series of 2-4 puffs may be sufficient, and in severe attacks it may be necessary to administer up to ten puffs. [A]

The use of nebulized β_2 adrenergic agonists must be limited exclusively to cases in which the patient requires oxygen in order to normalize his SaO_2. Continuous nebulization does not offer great advantages with respect to intermittent nebulization, when the same total doses are administered[252]. [B]

Ipratropium bromide. Add frequent doses of ipratropium bromide, which it has shown itself to be effective and safe, during the first two hours in cases of severe asthma crisis or in moderate crises that fail to respond to initial treatment with β2 adrenergic agonists[217,253]. [A]

The nebulized dose is 250 μg/4-6 hours in patients who weigh less than 30 kg and 500 μg/4-6 hours in patients weighing more than 30 kg. The dose delivered using an inhalation chamber is 40-80 μg (2-4 puffs). Repeated doses must be administered every 20 or 30 minutes. The maximum effect, which is not maintained, is elicited by the initial doses, so it should only be used in the first 24-48 hours.

In infants its use in combination with inhaled, 2 adrenergic agonists has been shown to be effective in the treatment of more severe attacks[254]. [B]

Systemic Glucocorticoids. These have shown a beneficial effect when they are used at an early stage[209,218] [B], with the oral route preferable to the intravenous route[255,256].[B] They must be administered during all moderate and severe attacks, and in mild attacks if an improvement is not maintained by the administration of bronchodilators (short-acting β2 adrenergic agonists are needed within 4 hours) or if the child has a history of severe attacks. The recommended dose is 1-2 mg/kg/day (maximum 60 mg) over a period of 3-5 days or until the attacks relents. [B]

Inhaled Glucocorticoids. Although there are various studies that do not support the use of inhaled glucocorticoids in asthma attacks in children[257-259], a meta-analysis that included 470 adults, and 663 children and adolescents, suggested that high and multiple doses of inhaled glucocorticoids (500 μg of nebulized fluticasone every 15 minutes, or 800 μg of nebulized budesonide every 15 minutes, or alternatively 500 μg of budesonide every 10 minutes using a pressurized inhaler with a spacing chamber or 400 mg of budesonide every 30 minutes using a spacing chamber) administered at intervals of 30 minutes or less over a period of at least 90 minutes has a rapid and additive effect to that of oral glucocorticoids[219]. [B] Inhaled glucocorticoids should not serve as a substitute for systemic glucocorticoids.

Table 44
Pulmonary score for the clinical assessment of asthma attacks in children*[247]

Score	Respiratory Rate		Wheezing	Use of sternocleidomastoid muscle
	< 6 years	≥ 6 years		
0	< 30	< 20	No	No
1	31-45	21-35	Final expiration	Slight increase
2	46-60	36-50	During entire expiration (stethoscopy)	Increased
3	> 60	> 50	Inspiration and expiration without stethoscopy**	Maximum activity

*Each section is scored from 0 to 3 (minimum 0, maximum 9). **If there is no wheezing and the activity of the sternocleidomastoid muscle is increased, assign the "wheezing" section a score of 3.

Table 45
General assessment of the severity of asthma exacerbations in children including the pulmonary score and oxygen saturation

	Pulmonary Score	SaO_2
Mild	0-3	> 94%
Moderate	4-6	91-94%
Severe	7-9	< 91%

SaO_2: oxyhemoglobin saturation. If there is a difference between the clinical score and the oxygen saturation level, the value which indicates greater severity should be used.

Therapeutic regimens

The treatment of an asthma attacks will depend on its severity and must follow the steps in the flow chart provided in Figure 8. In all cases in which oxygen saturation is lower than 94% oxygen must be administered[260]. [C]

Short-acting β_2 adrenergic agonists must be used as needed, preferably using a pressurized inhaler and a spacer device[249,261]. [A] The doses and frequency of administration will depend on the severity of the attacks. In moderate and severe crises, a short cycle (3-5 days) of oral glucocorticoids must be added[262]. [A]

Severe attacks must be referred to a hospital in a medically equipped ambulance, administering oxygen, bronchodilators and systemic glucocorticoids on the way. [D]

Rhinitis

Definition

The term "rhinitis" defines an inflammatory process affecting the nasal mucosa that is characterized by the following clinical symptoms: anterior or posterior rhinorrhea, sneezing, blocked nose or nasal congestion and/or pruritis/itching of the nose. These symptoms must be present for two or more days in a row and for more than an hour on most days[263]. [D]

Sinusitis is always accompanied by rhinitis, which is why inflammation of the paranasal sinuses is known as "rhinosinusitis", and it is characterized by the presence of two or more of the following symptoms: blocked nose/congestion/ obstruction, anterior or posterior rhinorrhea, facial pain/pressure and/or impairment/loss of sense of smell; the presence of one of the first two symptoms is required[264]. [C]

In the report from the nomenclature review committee of the World Allergy Organization (WAO), allergic rhinitis (AR) was defined

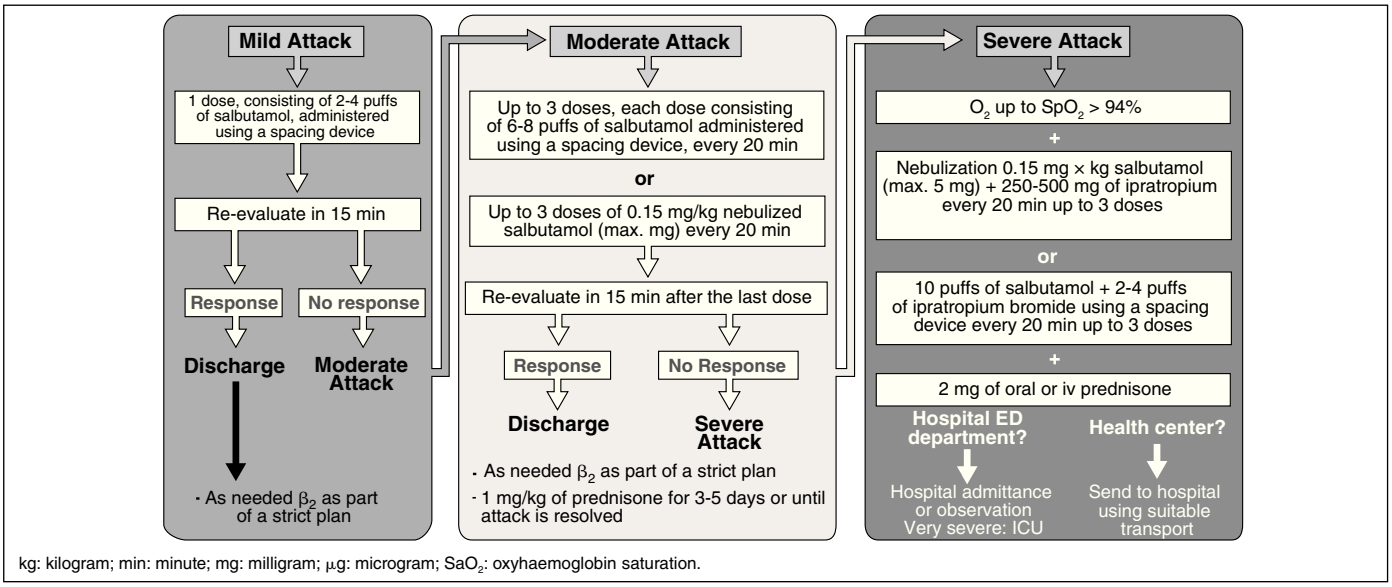


Figure 8. Treatment of asthma attacks in children.

Table 46
Recommendations

Short-acting β_2 adrenergic agonists at high doses, administered at an early stage and repeated, are recommended as the first line of treatment for an asthma crisis.	R1
It is advisable to tailor drug doses according to the severity of the attack and its response to treatment.	R1
The use of a pressurized inhaler with a spacer device system is recommended in the treatment of mild-moderate asthma attack.	R1
In moderate-severe attacks the early use of a systemic glucocorticoid is recommended.	R1

as "clinical signs and symptoms of a hypersensitivity reaction which is immunologically mediated (IgE) and affects the nose"[265]. [D]

Classification

There are numerous classifications of rhinitis, which have been made by various groups and panels of experts. Many of these classifications are of little use in clinical practice, as they mix pathogenic and aetiological criteria. A clinical classification of rhinitis, supported by a broad international consensus, has been proposed in the recently reviewed ARIA *(Allergic Rhinitis and its Impact on Asthma)* document[266] (Table 47). [D]

Infectious rhinitis is the most common form and it is classified as the common cold or acute viral rhinosinusitis (symptoms last less than ten days), acute non-viral rhinosinusitis (the symptoms get worse after the first five days or are maintained longer than ten days) or chronic rhinosinusitis with or without polyps (symptoms last longer than 12 weeks)[264]. [D]

AR is the most common form of non-infectious rhinitis[266] and the most closely related to asthma. The classification of AR changed after the publication of the ARIA document[267] because the classical classification into seasonal, perennial and occupational asthma did not reflect the clinical reality of patients[268]. The current classification proposed by ARIA has been validated[269], although criteria to differentiate moderate and severe rhinitis have been proposed[270] (Table 48). [C]

Epidemiology

The most common form of rhinitis is infectious rhinitis. Its incidence in adults is from 2 to 5 episodes of the common cold a year and in children is from 7 to 10 episodes a year[264]. [C]

The prevalence of AR in the general Spanish population has been estimated to be about 21.5% (average age 31.3 years), of which 21-64% of cases are persistent, 36-79% intermittent, 48.5-63% perennial and 37-51.5% seasonal[271,272]. 82% of intermittent cases are mild (18% moderate/severe) and 44% of persistent cases are mild (56% moderate/severe). [C]

Table 47
Classification of rhinitis

Infectious Rhinitis		
– Viral	– Bacterial	– Other Infectious Agents
Allergic, depending on		
– The allergen responsible: perennial, seasonal, work-related		
– Duration: intermittent, persistent		
– Severity: mild, moderate-severe		
Occupational		
– Duration: intermittent, persistent		– Severity: mild, moderate-severe
Drug-induced		
– Aspirin	– Other medications	
Hormonal		
Other causes		
– NARES (non-allergic rhinitis with eosinophilia syndrome).		– Caused by irritants
– Food-related	– Emotional	– Atrophic
Idiopathic		

Classification of rhinitis adapted from the ARIA document (Bousquet[266]).

Table 48
Classification of Allergic Rhinitis (AR)

According to duration
INTERMITTENT means that symptoms are present:
– 4 days a week
– or during ≤ 4 consecutive weeks
PERSISTENT means that symptoms are present:
– > 4 days a week
– and > 4 consecutive weeks
According to severity
MILD means that none of the following items are present:
– Sleep disturbances
– Daily, leisure and/or sports activities are affected
– School or work activities are affected
– The symptoms cause discomfort
MODERATE means that one, two or three of the above items are present
SEVERE means that all four items are present

Classification of AR according to the ARIA document (modified by Valero[270]).

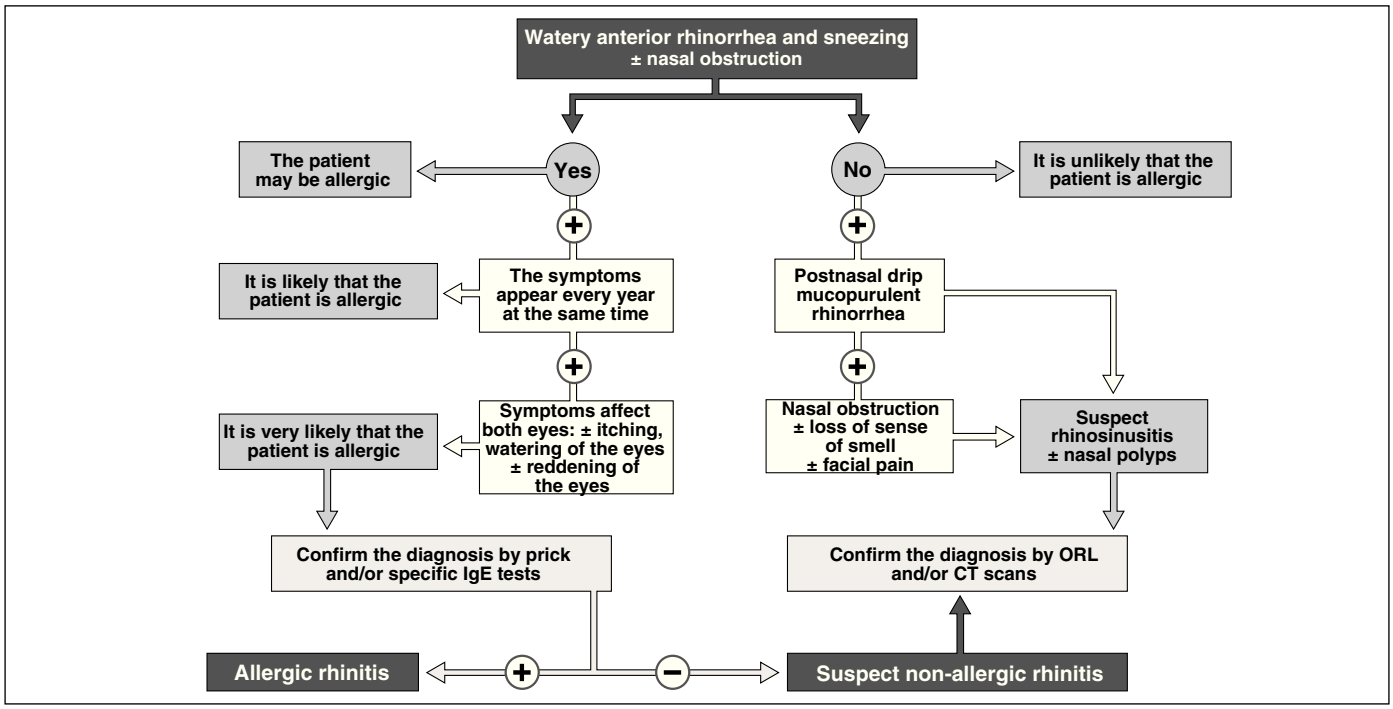


Figure 9. Differential diagnosis algorithm for rhinitis (modified by Bousquet[266]).

A study conducted in Spain found that rhinitis was the most common reason for consultations at Allergology departments (55.5% of total visits). Of all of these consultations an allergic aetiology was confirmed in 72% of patients. 51.9% were sensitized to pollen and 40.2% to mites, and polysensitization was frequent (31.2%). 37.3% of the rhinitis patients were diagnosed with asthma[273]. [C]

In the ISAAC study, a prevalence of rhinoconjunctivitis symptoms of 7.9% was recently confirmed in Spanish children aged 6-7 years (an annual increase of 0.33%) and a prevalence of 15% in children aged 13-14 years (an annual increase of 0.10%)[274].

Diagnosis

The diagnosis of rhinitis is essentially clinical. [D]

A family history of allergy, seasonal variation of symptoms, the fact that ocular and nasal symptoms coincide and a link to exposure to epithelia, pollen and dust are clinical data that are diagnostically highly predictive when AR is suspected[275]. In the aetiological diagnosis of allergic rhinitis the most cost-effective analyses are prick and/or in vitro specific serum IgE tests[276]. In cases with any doubt, the specific nasal challenge test must be performed using the suspected allergen[277]. However, positive prick or specific IgE test results to certain allergens may be irrelevant from a clinical point of view. Other complementary tests include the objective evaluation of nasal obstruction (acoustic rhinometry, active anterior rhinomanometry, measurement of peak nasal inspiratory flow) and the assessment of the sense of smell by olfactometry (Fig. 9). [C]

Rhinitis and asthma

Numerous epidemiological, physiopathological and therapeutic studies have demonstrated a link between rhinitis and asthma[266,278]. [C]

In asthma patients the prevalence of rhinitis is very high, much higher than in the general population[279]. In this country two recent studies showed a prevalence of rhinitis in asthma patients of 71% and 89.5%[280,281]. In a study conducted in Spain and Portugal, 49% of the AR patients had asthma[272]. A parallel increase in the prevalence of asthma and rhinitis has also been demonstrated in Spain[282]. There is a temporal link between AR and asthma onset, and AR usuallly precedes the development of asthma[283]. It has been demonstrated that AR and non-allergic rhinitis are risk factors for developing asthma[279,284]. Rhinitis also aggravates asthma and increases the consumption of healthcare resources[285-287]. [C]

Inflammatory changes have been demonstrated in the bronchial mucosa of non-asthmatic patients with AR[288], as occurs with eosinophilic nasal inflammation in asthma patients with no clinical nasal symptoms[289].

The treatment of AR can improve some aspects of asthma (Table 49); nevertheless, a systematic review failed to confirm that this improvement was statistically significant[290]. [A]

Treatment

The therapeutic strategy for AR includes: patient education, avoidance of allergens and pollutants, and pharmacotherapy and allergen-specific immunotherapy[266,291,292]. When choosing pharmacological treatment, the efficacy, safety and cost-effectiveness of drugs, patients preferences, disease severity and the presence of comorbidities must be assessed. The pharmacological treatment of AR must include clear recommendations graded into different stages, depending on the level of severity (Table 50); (Fig. 10).

In both adults and children oral H_1 antihistamines improve rhinitis symptoms[293], including rhinorrhea, sneezing, nasal and eye symptoms[294,295], although they are less effective against nasal obstruction[296]. Second-generation H_1 antihistamines have fewer side effects (cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mequitazine, mizolastine and rupatadine)[297] and mild anti-inflammatory effects[298]. Topical H_1 antihistamines (azelastine, emedastine, ketotifen, levocabastine and olopatadine) have also shown themselves to be effective in cases of rhinitis and allergic conjunctivitis[299]. [A]

Glucocorticoids (beclomethasone, budesonide, fluticasone, mometasone, triamcinolone) are the most potent and effective anti-inflammatory drugs for treating AR and non-allergic rhinitis[300,301], in

Table 49
Studies on the effects of treating concomitant rhinitis on asthma

Study Authors	Location	N	Type	Variable	Comments
Adams, 2002	USA	13844	Retrospective cohort	RR 0.7 (ED visits)	Patients receiving nasal glucocorticoids
Crystal-Peters, 2002	USA	4944	Retrospective cohort	RR 0.5 (ED visits / hospitalizations)	
Corren, 2004	USA		Cases / controls	RR 0.56 (hospitalizations)	Patients receiving nasal glucocorticoids
Moller, 2002	Europe	205	RCT	RR 0.40 (of developing asthma)	IT 3 years
Greembiale, 2000	United Kingdom	44	RCT	BHR ↓ MIT	IT 2 years
Polosa, 2003b	Italy	30	RCT	BHR ↓ AMP but not for MIT	IT 3 years
Dahl, 2005b	Europe	262	RCT	Tendency to improve not statistically significant	Nasal fluticasone
Lombardi, 2001	Italy	51	Non-randomized CT	BHR ↓ MIT	IT 3 years
Taramarcaz, 2003	Multiple (Cochrane review)	425	Systematic RCT review	Tendency to improve not statistically significant	11 RCTs to evaluate the efficacy of nasal glucocorticoids

RR: relative risk; BHR: bronchial hyperresponse; MIT: methacholine inhalation test; RCT: randomized clinical trial; CT: clinical trial; IT: immunotherapy; N: population.

Table 50
Levels of recommendation for the drugs used in the treatment of allergic rhinitis (partly based on Bousquet)[266]

	Seasonal Rhinitis Adults	Seasonal Rhinitis Children	Perennial Rhinitis Adults	Perennial Rhinitis Children	Persistent Rhinitis
Oral H_1 antihistamines	R1	R1	R1	R1	R1
Nasal H_1 antihistamines	R1	R1	R1	R1	No data
Nasal glucocorticoids	R1	R1	R1	R1	No data
Oral glucocorticoids	R1	R1	R1	R1	No data
Antileukotrienes	R1	R1 (> 6 years)	–	–	No data
Nasal chromones	R1	R1	R1	R1	No data
Nasal decongestants	R2	R2	R2	R2	No data
Nasal anticholinergics	–	–	R1	R1	No data
Subcutaneous immunotherapy	R1	R1	R1	R1	No data
Sublingual immunotherapy	R1	R1	R1	R1	No data
Anti-IgE	R1	R1 (> 12 years)	R1 (> 12 years)	R1	No data
Allergenic avoidance	R2	R2	R2	R2	No data

Table 51
Recommendations

The classification of allergic rhinitis will depend on: duration, the disease being classified as intermittent or persistent, and severity, which is considered mild, moderate or severe.	R2
It is recommended that the diagnosis of rhinitis be based on clinical criteria (symptoms).	R2
To confirm a diagnosis of allergic rhinitis it is advisable to perform prick tests and/or determine of specific serum IgE.	R2
When asthma has been confirmed, it is advisable to investigate the presence or not of rhinitis in order to devise a combined diagnostic and treatment strategy.	R2
The use of oral and topical nasal antihistamines, together with topical nasal glucocorticoids, is recommended for the pharmacological treatment of allergic rhinitis.	R1
In appropriately selected allergic patients (adults and children) allergen-specific immunotherapy is recommended.	R1

both adults and children. The topical application of glucocorticoids delivers a high drug concentration to the nasal mucosa with a minimal risk of systemic side effects. Their efficacy in improving the symptoms of AR, including nasal obstruction and ocular symptoms, has been well documented. They constitute the first line of treatment for persistent moderate-severe AR. [A]

Oral glucocorticoid regimens lasting for short periods of time are used in cases of severe rhinitis that fails to respond to other treatments[266]. [D]

Intranasal decongestants (oxymetazoline and xylometazoline) can be used for a short period of time in patients with substantial nasal obstruction[302]. Prolonged use can trigger drug-induced rhinitis. Although they are effective, oral decongestants (phenylephrine and pseudoephedrine), used alone or in association with oral antihistamines, are not exempt from systemic side effects. [A]

Leukotriene receptor antagonists (montelukast and zafirlukast) are effective in the treatment of allergic rhinitis and conjunctivitis in both adults and children. These drugs have shown themselves to be as effective as antihistamines, but less than topical nasal glucocorticoids[303]. [A]

Topical anticholinergics (ipratropium bromide) are effective and are recommended for the treatment of rhinorrea that is refractory to other treatments, and for AR and non-allergic rhinitis[304]. [A]

Topical chromones (sodium cromoglycate) have demonstrated moderate efficacy in the treatment of rhinitis and allergic conjunctivitis[305]. [A]

Omalizumab (anti-IgE) has proved effective in the treatment of AR in adults and children over 12 years of age[306]. However, in Spain its use has not been approved for this purpose. [A]

Specific allergen immunotherapy, using either subcutaneous or oral (sublingual) administration, is effective for treating AR caused by pollen and mites in adults and children. A correct allergological diagnosis is required for its indication. It can alter the natural course of allergic respiratory disease, reducing the frequency of asthma episodes and preventing new sensitizations[165,307,308]. [A]

Measures designed to ensure avoidance of indoor allergens (mites) have demonstrated a reduction in exposure levels, but no improvement in the symptoms or progression of the disease[309]. [D]

The principles which underlie the treatment of rhinitis in children are the same as in adults, but special care needs to be taken with adverse effects. The right doses must be used and in some cases the age of the patient needs to be taken into consideration when prescribing certain drugs[266]. [D]

Special Circumstances

Asthma and pregnancy

Some 4-7% of pregnant women suffer from asthma, which is the most common respiratory disease during pregnancy. Up to 20% of pregnant women with asthma experience exacerbations of the disease and 6% have to be admitted to the hospital because of severe attacks[310]. These figures are worse in patients with severe persistent asthma, up to 50% of whom may suffer an exacerbation[311]. The most

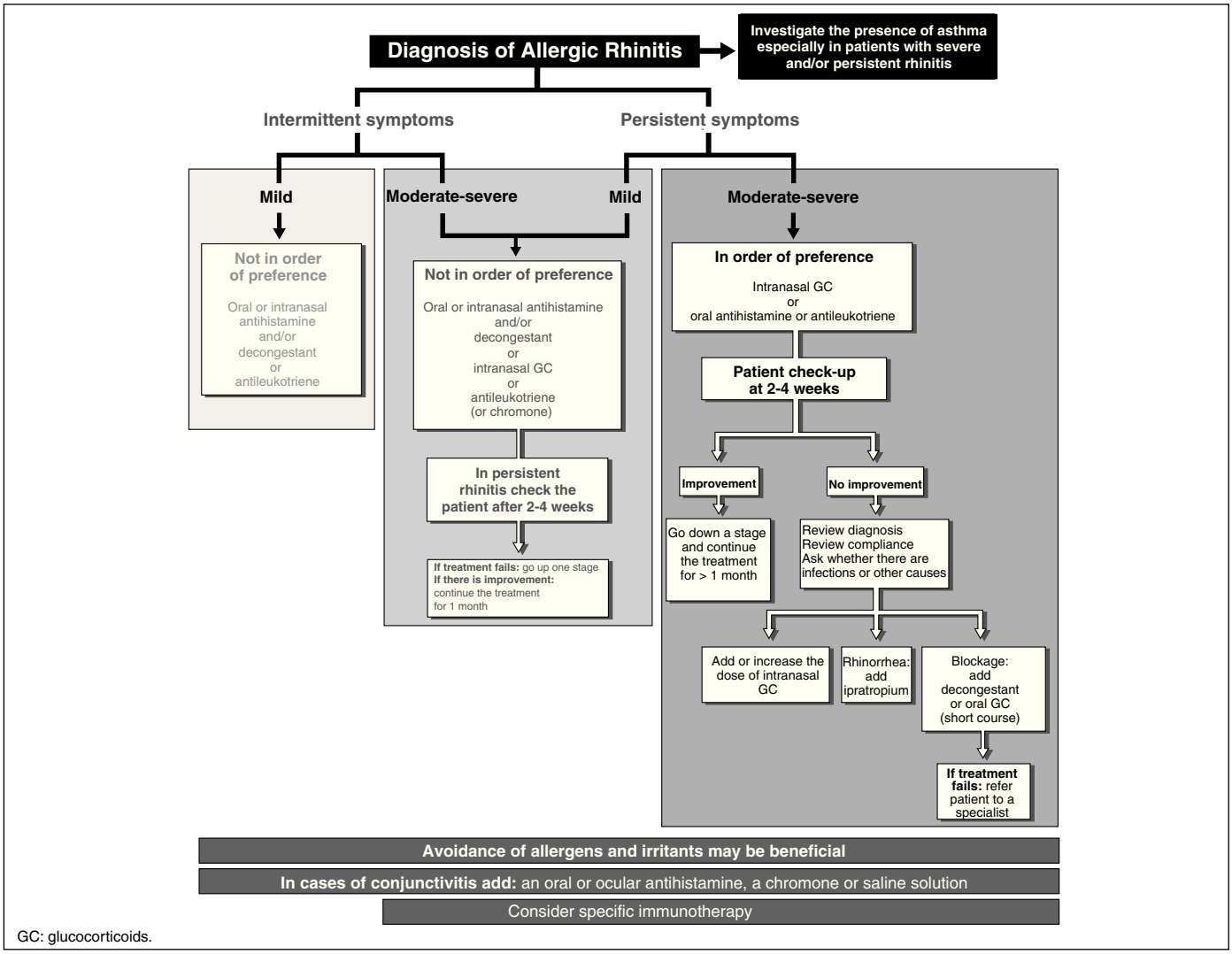


Figure 10. Algorithm for treating allergic rhinitis in accordance with ARIA International Guidelines[266].

common trigger factors are viruses. Exacerbations in pregnancy are associated with poor compliance or adherence to inhaled glucocorticoid maintenance treatment[310,312]. [B]

Effects of asthma on pregnancy

Pregnant asthma patients have a higher incidence of complications, particularly hemorrhages, eclampsia, hypertension, placental presentation, the need for caesarean delivery, low birth weight and/or premature delivery[313]. In poorly controlled asthma, hypoxemia caused by an exacerbation is the main risk factor for premature delivery, intrauterine growth retardation and low birth weight[314]. [C]

The results of some recent studies suggest that in pregnant asthma patients, in whom the foetus is female, there is a deterioration of their asthma with a greater number of exacerbations and hospitalizations during gestation as a result of their disease[315].

Treatment of asthma during pregnancy

Practically all medications employed in the treatment of asthma cross the placental barrier; however, few have repercussions on the foetus. Poor control of maternal asthma poses a greater risk to the foetus than the possible teratogenic effects of the drugs habitually used in asthma treatment[316-318]. The drugs from used to treat asthma during pregnancy are not substantially different to those employed with any other woman with asthma of a similar level of severity, including for exacerbations[318-320]. [C]

A study involving 2,014 newborns, whose mothers were treated with inhaled budesonide during the period of gestation, did not identify a higher incidence of teratogenesis (3.8%) in comparison with the general population (3.5%)[321]. [C]

Clinical studies that compared the safety of short-acting β2 adrenergic agonists (chiefly salbutamol) did not detect a greater risk of side effects[319,322]. No information is available on long-acting β2 adrenergic agonists. [B]

Nor did trials that evaluated the safety of theophyllines (risk category C according to the FDA) during pregnancy demonstrate a higher risk of side effects. [B]

With respect to the use of oral glucocorticoids (risk category B according to the FDA), although in the past they were associated with a greater risk of foetal deformities (particularly when they were taken during the last three months of pregnancy[323]), the evidence currently available is not conclusive. Our opinion is that it can be administered during pregnancy[324], as long as its use is justified. [B]

There are no conclusive studies about the safety of antileukotrienes in pregnancy[325]. [B]

Difficult to control asthma

It is accepted that 5% of asthma patients have asthma that is difficult to control (DCA).[326] Although a universally accepted definition is lacking, SEPAR has proposed a diagnostic approach

Table 52
Recommendations

Given that poor asthma control during pregnancy entails an increase in maternal and fetal morbi-mortality because of the risk of suffering a severe asthma exacerbation, it is advisable to monitor the level of asthma control closely throughout gestation.	R2
The drugs usually employed (β_2 adrenergic agonists and inhaled glucocorticoids) are recommended for the maintenance treatment of asthma in pregnant women.	R1

Table 53
Summary of levels of evidence for the general and therapeutic management of pregnant women with asthma[319,320]

Recommendations for asthma during pregnancy	Level of evidence
The effect of asthma on pregnancy and vice versa is not a contraindication for gestation.	B
It is safer for the patient and the fetus to receive treatment that controls asthma symptoms.	B
Assessment must include clinical evaluations, spirometry and the occasional measurement of inflammatory parameters.	B
To assess pulmonary function it is preferable to use spirometry rather than peak expiratory flow measurement, although the latter may be sufficient.	C
Routine evaluation of pulmonary function (spirometry) is recommended in pregnant patients with persistent asthma, as pulmonary function and asthma severity may vary during gestation.	C
Inhaled glucocorticoids are the first choice for control therapy in persistent asthma.	B
Budesonide is the glucocorticoid of choice.	B
Inhaled salbutamol is the relief therapy of choice.	B
Salmeterol and formoterol can be used in selected cases, but considering the findings of a risk-benefit analysis.	C
Montelukast, zafirlukast and nedocromil sodium can continue to be used in pregnant women with difficulties controlling asthma who have previously responded to these drugs.	C
Immunotherapy can be continued in patients who are receiving maintenance doses and who obtain a demonstrated therapeutic benefit.	B
Breastfeeding is not contraindicated in the case of: prednisone, theophylline, antihistamines, inhaled glucocorticoids, β_2 adrenergic agonists or sodium cromoglycate.	B
The need for medication is reduced if maternal trigger factors are identified, controlled and avoided (obesity, allergens, irritants and tobacco smoke).	B
Application of the asthma education program: monitorinf of symptoms and daily variability of lung function (peak expiratory flow meter), review of correct inhalatory technique, implementation and regular review of the action plan.	C

based on major and minor criteria[327]. DCA includes all asthma patients whose disease is characterized as particularly aggressive and insufficiently or poorly controlled, although the patients follow an appropriate therapeutic strategy adjusted to their level of clinical severity[327]. Synonyms for DCA include: refractory asthma, asthma which is resistant to treatment, glucocorticoid-resistant asthma, corticoid-dependent and difficult asthma. [D]

Diagnosis and associated factors

The final diagnosis of DCA must comply with three previous conditions: confirmation that the anti-asthma treatment is appropriate and that it is being followed correctly, that other diseases resembling asthma have been ruled out (Table 54) and that factors that aggravate the disease are controlled (Table 55) (Fig. 11). The diagnosis is confirmed in only 55% of patients who are initially suspected of having DCA[328]. [C] Hospital admission may be necessary to determine whether a conventional but supervised treatment achieves better results. Ten percent of DCA cases have major psychiatric problems[328,329]. Clinically, as long as there is reason to suspect DCA, all the diagnostic techniques described in Table 56 must be attempted. [D]

Table 54
Diseases that resemble or are often associated with asthma

Other Diseases	
– Chronic obstructive pulmonary disease	– Bullous emphysema or emphysema due to alpha-1 antitrypsin deficiency
– Cystic fibrosis and bronchiectasis	
– Bronchiolitis	– Tracheal or central airway obstruction
– Left ventricle failure	– Hyperventilation
	– Neuromuscular disease
Asthma-related Diseases	
– Rhinosinusitis	– Gastroesophageal reflux
– Allergic bronchopulmonary aspergillosis	– Vocal cord dysfunction
	– Churg-Strauss syndrome
– Psychiatric disorders	– Eosinophilic pneumonia
– Carcinoid syndrome	– Obstructive sleep apnea syndrome
– Hyperthyroidism	

Table 55
Factors that aggravate asthma

Continued exposure to allergens or irritants	
– Pets	– Domestic dust mites
– Environmental fungi	– Tobacco smoke
– Inhalation of cocaine	– Occupational exposure
Drugs	
– Aspirin and anti-inflammatory COX-1 inhibitors	– Angiotensin converting enzyme inhibitors
– β-blockers	
Other factors	
– Stress, anxiety, depression, panic attacks	– Premenstrual syndrome

Table 56
Diagnostic techniques and attitudes recommended for the evaluation of difficult to control asthma

Confirm asthma diagnosis	
– Spirometry with a bronchodilator test	
– Bronchoconstriction test (methacholine, histamine and other agents)	
– Daily variability of peak expiratory flow	
Confirm good therapeutic compliance	
– Hospital admission with supervised treatment	
– Morning levels of plasma cortisol (patients receiving oral glucocorticoid treatment)	
Evaluation of other respiratory diseases	
– Lung volumes	– Alveolar-capillary diffusion
– CT of sinuses and upper respiratory tract	– High resolution chest CT
– Exhaled nitric oxide (FE_{NO})	– Laryngoscopy
– Bronchoscopy	– Sputum inflammatory cell count
Evaluation of aggravating factors	
– Allergological assessment using prick tests/ IgE analysis	– Oesophageal pH-metry
– Psychiatric assessment	– Evaluation of work-related respiratory risk
Complete diagnosis with the DCA phenotype	

CT = computerized tomography; GC = glucocorticoids; DCA: difficult to control asthma.

Treatment

Despite their side effects, oral glucocorticoids continue to be the drug of choice. Their administration must be adjusted as to deliver the minimum dose that will ensure the patient has few symptoms and exacerbations as possible. Total control of the disease is not always the ultimate goal of treatment. This is why relatively frequent use of rescue medication is accepted and it is best to reach a compromise with the patient as to what level of symptoms is tolerable [D]. A limitation in the use of oral glucocorticoids has been the main aim of a series of drugs (immunomodulators) that are specifically used for DCA. The reduction in glucocorticoids as a result of the use of these drugs has been very modest and their role in the treatment of DCA is not entirely clear. The most recent approach is treatment using an alpha tumoral necrosis factor (TNFα) antagonist (etanercept), but, after an initially promising publication[330], its efficacy has not been confirmed in a recent clinical trial[331]. [B]

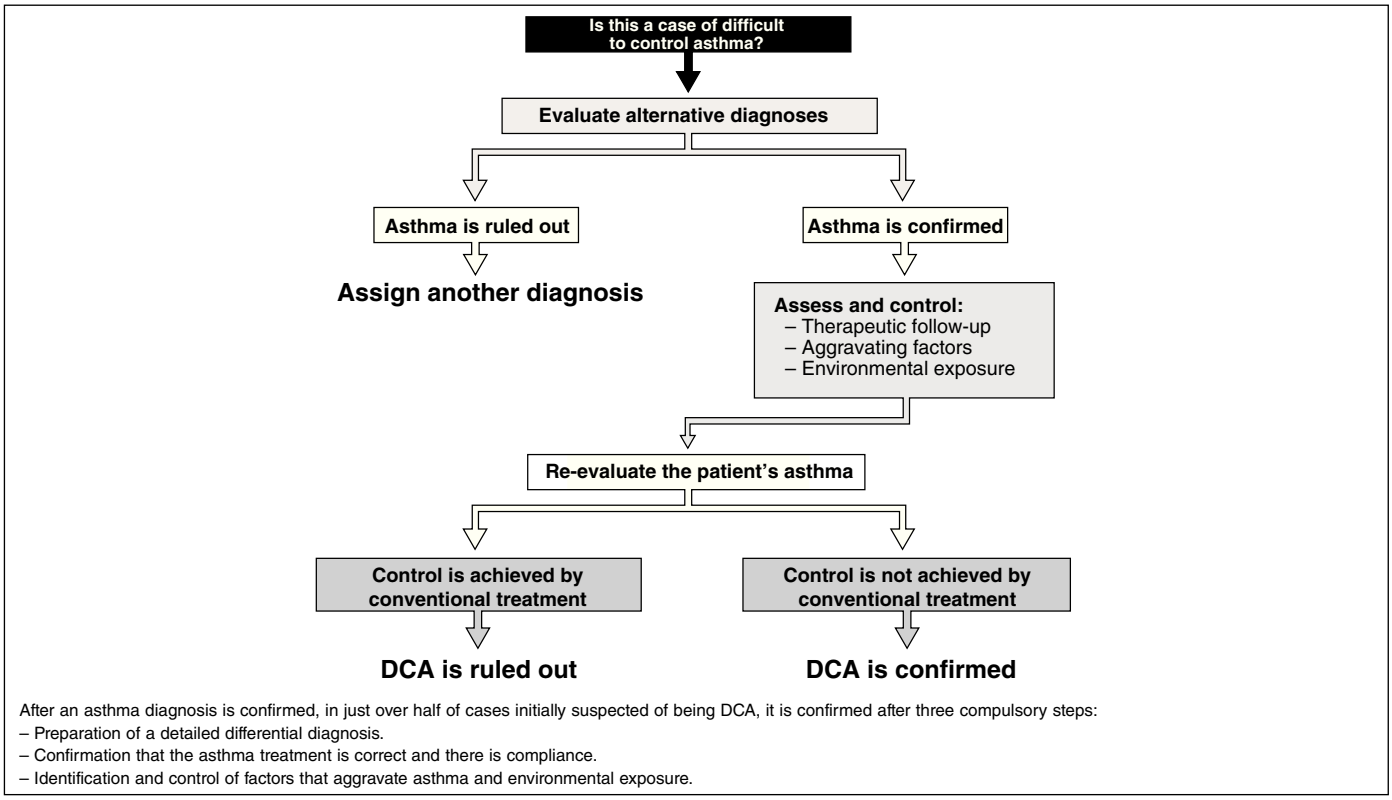


Figure 11. Algorithm for the diagnosis of difficult to control asthma (DCA).

Some patients with DCA may benefit from theophylline treatment if serum levels are adjusted so that they fall within the right therapeutic range[332]. [C]

Recognition of the patient's phenotype may contribute therapeutic advantages[333]. Thus, in cases of asthma associated with atopia and with high levels of IgE, omalizumab reduces the number of hospitalizations and visits to the ED[334]. [B] In addition, in asthma associated with nasal polyposis and aspirin intolerance, anti-leukotriene agents may be useful[332]. Another group of asthma patients with severe and sudden-onset crises (type II brittle asthma) may benefit from self-administration of epinephrine using pre-loaded syringes (Altellus®)[326]. [D]

Table 57
Recommendations

Patients with difficult to control asthma (DCA) should normally be controlled at specialized hospital centers by experienced medical personnel.	R2
In diagnostic and therapeutic approaches to DCA it is advisable to follow a protocol framework based on decision algorithms, which establish the steps and drugs that must be used rationally, progressing in stages from less to more aggressive measures.	R2
Recognition of the DCA phenotype may confer therapeutic advantages.	R1
DCA treatment should not pursue the absolute control of symptoms, so it is advisable to reach an agreement with the patient as to what constitutes a maximum tolerable level of control of asthma symptoms.	R2

Work-related asthma

The inhalation of certain agents (Table 58) in the workplace may cause asthma or make it. The former is known as "occupational asthma" (OA) and the latter as "work-aggravated asthma" (WAA).

Occupational asthma

OA is a disease characterized by a varying degree of airflow limitation and/or bronchial hyperresponse and/or inflammation of the respiratory tract due to causes and conditions that can be attributed to a specific work environment and not to stimuli found outside the workplace[335]. It is the most common occupational respiratory disease and can account for as much as 25% of all cases of asthma onset in adults[337]. [C] Depending on its mechanism of action and whether or not there is a period of latency, we can distinguish between:

Immunological occupational asthma or asthma with a latency period. The immunological mechanism by which certain agents cause OA may or may not be mediated by IgE. In general, it is accepted that high molecular weight particles (proteins) generate an IgE-mediated response. It is possible to demonstrate sensitization to these agents by means of prick or in vitro tests, which involve determining specific IgE levels using ELISA and immunoblotting methods[68]. People who are atopic have a higher risk of developing OA[338, 339]. [C]

Often there is an association with rhinitis[340], and having occupational rhinitis increases the risk of suffering OA[341]. In general, when low molecular weight agents induce asthma by an immunological mechanism, they usually do so via a route that is not IgE-dependent, although sometimes some of them (isocyanates, persulfates or metals) can cause asthma by an IgE-mediated mechanism[342]. [C]

The diagnosis of this disease entity is based on a detailed clinical and occupational history, the demonstration of sensitization when the mechanism is IgE-mediated, confirmation of asthma and finally proof that the asthma is work-related[343]. When and how to use the different diagnostic methods at our disposal is summarized in Figure 12. [C]

The specific bronchial provocation test is considered the gold standard for confirming a diagnosis of OA[344]. [C]

Various studies have shown that when exposure to the occupational agent causing OA is curtailed, there is significant clinical improvement[345]. [C]

Table 58
Agents that cause occupational asthma[152,336]

Type	Agent	Industry/exposure
Immunological or with a latency period		
High molecular weight		
Enzymes	Alcalase, amylase, other enzymes	Soaps, breadmaking, food industry
Cereals and Flour	Wheat, barley, rye, oats, corn, sunflower seeds, soy, etc.	Baking industry, breadmaking, cakemaking, milling, transport, agriculture
Animals	Rats, guinea pigs, cows, crustaceans, etc.	Laboratory personnel, vets, farmers, seafood processors
Latex	Latex	Healthcare personnel
Low molecular weight		
Diisocyanates	Toluene diisocyanate (TDI), methylene diisocyanate (MDI) and hexamethylene diisocyanate (HDI)	Polyurethane, plastic varnishes, insulation materials, spray painting
Acid anhydrides	Phthalic, trimethyl, hexahydrophthalic and tetrachlorophthalic acid, pyromellitic dianhydride	Plastics and resins, adhesives, chemical industry, flame retardants
Metals	Platinum salts, cobalt sulphate, chromium sulphate and other chromium salts, potassium dichromate	Platinum refineries, polishers, chrome and silver paint, tanners, ground glass
Antibiotics	Penicillin, spiramycin, tetracycline	Pharmaceutical industry
Amines	Piperazine, ethanolamine, dimethylpropylamine, ethylendiamine, aliphatic amines, aminoethanolamine, hexamethylenetetramine	Chemical industry, aerosol paint, ski manufacturing, lacquers, photography, rubber, soldering, cables
Wood	Red cedar, colophony	Timber, electronic welding
Miscellaneous	Glutaraldehyde, persulfate salts, cyanoacrylate, methyl methacrylate, polyethylene, chloramine	Nursing/endoscopy, hairdressing, orthopaedics, glue, paper packaging, plastic bags, sterilizing equipment
Non-immunological or with no latency period		
Bleach / hydrochloric acid	Chlorine and ammonium	Cleaning
Smoke	Smoke	Fire service, accidents, etc.
Gases	NOx, SO_2, ozone	Metallurgy, agriculture, etc.
Other	Resins, acetic acid, caustic soda, etc.	Chemical industry, healthcare personnel, etc.

Table 59
Recommendations

In adult onset asthma, occupational origin must be ruled out.	R2
The standard test for diagnosing immunological occupational asthma is the specific bronchial provocation test.	R2
For the diagnosis of WAA in a person who has previously been diagnosed with asthma, the demonstration of work-related deterioration in lung function is recommended.	R2
In the treatment of immunological occupational asthma, total cessation of exposure to the causal agent is recommended.	R2
In reactive airway dysfunction syndrome (RADS), if asthma control is achieved with or without medical treatment, it is not necessary for the patient to change his job.	R2

Table 60
Recommendations

Vocal cord dysfunction must be diagnosed by fibroscopic video rhino-laryngoscopy.	R2
For the treatment of vocal cord dysfunction, the use of speech rehabilitation and vocal cord relaxation techniques is recommended.	R2

The symptoms and changes in pulmonary function may persist for years after the last exposure to the causal agent[346]. [C]

The reduction of environmental levels of the causal agent minimizes the number of individuals who become sensitized and may therefore develop OA[347]. [C]

Non-immunological occupational asthma or asthma without a latency period. The inhalation of high concentrations of irritant agents can cause non-immunological OA or reactive airway dysfunction syndrome (RADS)[348]. The diagnosis is made on the basis of clinical criteria[152]. If the patient recovers or his asthma is controlled by his usual treatment, a change of post is not strictly necessary[349]. It is uncertain whether chronic exposure to low doses of irritants can cause OA[350]. [C]

Work-aggravated asthma

WAA is a situation in which the aggravation of a patient's asthma is due to circumstances that can be attributed to the workplace.

Diagnosis is based on clinical suspicion, when the patient complains of work-related clinical deterioration of asthma that existed before he joined his post, if work-related changes in pulmonary function are demonstrated and if occupational asthma is ruled out[351]. [D]

In addition to appropriate pharmacological treatment, therapy is based on improving environmental conditions in the workplace and on the use of protection systems. The patient will only need to abandon his post in severe cases[352].

Vocal acord dysfunction

Vocal cord dysfunction is defined as a "paradoxical adduction of the vocal cords during inspiration, which can simulate an asthma attack"[353]. It may take the form of laryngeal stridor, dyspnea, dysphonia, a dry cough, muscular retraction and/or superficial respiration, and it may be accompanied by wheezing in the upper thoracic region[354]. It is more common in adolescent women[355] and has been linked to physical exercise[356] and psychiatric factors (anxiety and personality disorders)[354]. [B] The diagnosis is confirmed by identifying paradoxical movements and adduction of the vocal cords by fibroscopic video rhino-laryngoscopy[354]. [D] Spirometry can show interruptions of the inspiratory loop and an increase in the forced expiratory flow/ forced inspiratory flow ratio to 50% of vital capacity[357]. The proposed treatments are rehabilitation techniques based on speech therapy and relaxation, inhaled anticholinergic agents, helium inhalation or the use of a facial mask that affords inspiratory resistance[358]. [C]

Declaration of conflict of interests

The editors of this guide declare that in the last five years they have received payment for their participation in meetings, congresses or research studies organized by the following pharmaceutical industries: ALK-Abelló, Almirall, Alter, AstraZeneca, Boheringer-Ingelheim, Chiesi, Faes Farma, Laboratorios Dr. Esteve, GlaxoSmithKline, MSD, Novartis, Pfizer and Stallergens.

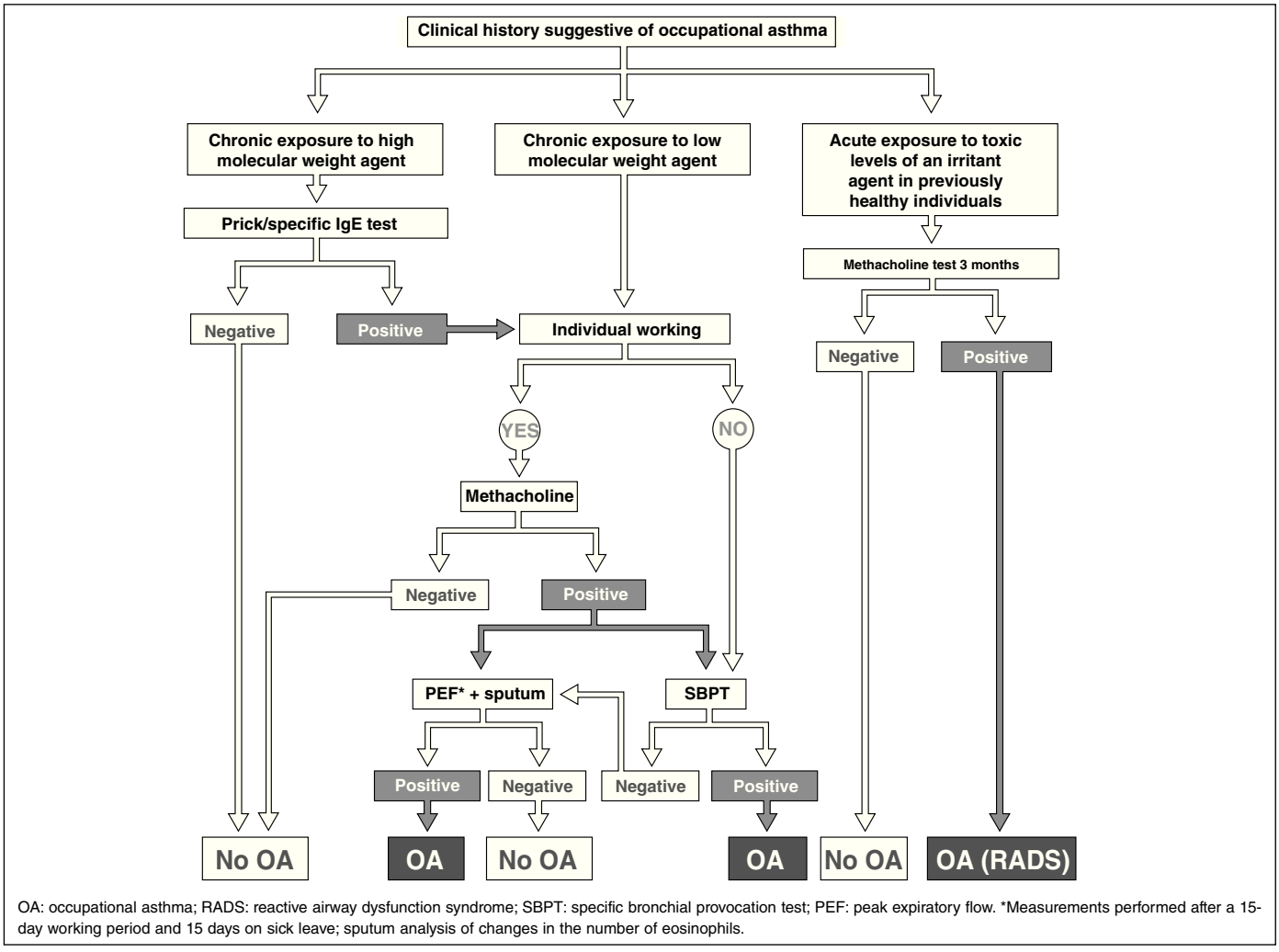


Figure 12. Algorithm for the diagnosis of occupational asthma.

References

1. Grupo de trabajo sobre GPC. Elaboracion de Guias de Practica Clinica en el Sistema Nacional de Salud. Manual Metodologico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragones de Ciencias de la Salud-I+CS; 2007. Guias de Practica Clinica en el SNS: I+CS N.o 2006/0I.
2. GINA 2006. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report. 2006. http://www.ginasthma.com.
3. NAEPP-EP3 2007. Nacional Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute, 2007.
4. BTS 2007. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. 2007. http://www.sign.ac.uk/guidelines. Thorax. 2008; 63(Suppl 4): iv1-121.
5. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650): 924-6.
6. ECRHHS. The European Community Respiratory Health Survey II. Eur Respir J. 2002; 20: 1071-9.
7. ISAAC. ISAAC STEERING COMMITE. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir. 1996; 9:687-95.
8. Grupo Español del Estudio Europeo en Asma. Estudio europeo del asma Prevalencia de hiperreactividad bronquial y asma en jovenes en 5 regiones de Espana. Grupo español del estudio europeo del asma. Med Clin (Barc). 1996; 106: 761-7.
9. Martinez Moratalla J, Alma E, Sunyer J, Ramos J, Pereira A, Payo F, et al. Grupo Español de Estudio Europeo del Asma. Identifi cacion y tratamiento de individuos con criterios epidemiologicos de asma en adultos jovenes de cinco areas españolas. Arch Bronconeumol. 1999; 35: 223-8.
10. Sobradillo V, Miravitlles M, Jimenez CA, Gabriel R, Viejo JL, Masa JF, et al. Estudio IBERPOC en Espana: prevalencia de sintomas respiratorios habituales y de limitacion cronica al fl ujo aereo. Arch bronconeumol. 1999; 35: 159-66.
11. ISAAC, Carvajal-Urena I, Garcia-Marcos L, Busquets-Monge R, Morales Sanchez-Varela M, Garcia De Andoain N, et al. Variaciones geografi cas de la prevalencia de sintomas de asma en los ninos y adolescentes españoles. International Study of Asthma and Allergies in Childhood (ISAAC) Fase III Espana. Arch Bronconeumol. 2005; 41: 659-66.
12. Cohn L, Elias JA, Chupp GL. Asthma mechanisms of disease persistence and progression. Annu Rev Innunol. 2004; 22: 789-815.
13. Douwes J, Gibson P, Pekkanen J, Pearce N. Non eosinophilic asthma: importance and possible mechanisms. Thorax. 2002: 57; 643-8.
14. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. Lancet. 2006; 368: 754-62.
15. Hirst SJ, Martin JG, Bonacci JV, Chan V, Fixman ED, Hamid QA, et al. Proliferative aspects of airway smooth muscle. J Allergy Clin Immunol. 2004; 114(Suppl 2): S2-17.
16. Hoshino M, Nakamura Y, Hamid Q. Gene expresion of vascular endothelial growth factor and its receptors and angiogenesis in bronchial asthma. J Allergy Clin Immunol. 2001; 107: 1034-8.
17. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mastcell infi ltration of airway smooth muscle in asthma. N Engl J Med. 2002; 346(22): 1699-705.
18. Gleich GJ. Mechanisms of eosinophilassociated infl ammation. J Allergy Clin Immunol. 2000; 105: 651-63.
19. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic infl ammation in sputum from subjects with asthma exacerbation. J Allergy Clin Immunol. 1995; 95(4): 843-52.
20. Peters-Golden M. The alveolar macrophage: the forgotten cell in asthma. Am J Respir Cell Mol Biol. 2004; 31(1): 3-7.
21. Polito AJ, Proud D. Epithelia cells as regulators of airway infl ammation. J Allergy Clin Immunol. 1998; 102(5): 714-8.

22. Groneberg DA, Quarcoo D, Frossard N, Fischer A. Neurogenic mechanisms in bronchial infl ammatory diseases. Allergy. 2004; 59: 1139-52.
23. Murray CS. Can inhaled corticosteroids infl uence the natural history of asthma? Curr Opin Allergy Clin Immunol. 2008; 8(1): 77-8.
24. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet. 2006; 368(9537): 780-93.
25. O'Byrne PM, Inman MD. Airway hyperresponsiveness. Chest. 2003; 123: 411S-6S.
26. Holloway JW, Keith TP, Davies DE, Powell R, Haitchi HM, Holgate ST. The discovery and role of ADAM 33, a new candidate gene for asthma. Expert Rev Mol Med. 2004; 6: 1-12.
27. Brusasco V, Crimi E, Pellegrino R. Airway hyperresponsiveness in asthma: not just a matter of airway infl ammation. Thorax. 1998; 53: 992-8.
28. Warner JO, Naspitz CK. Third International Pediatric Consensus statement on the management of childhood asthma. International Pediatric Asthma Consensus Group. Pediatr Pulmonol. 1998; 25: 1-17.
29. Castillo Laita JA, De Benito Fernandez J, Escribano Montaner A, Fernandez Benitez M, Garcia de la Rubia S, Garde Garde J, et al. Consenso sobre tratamiento del asma en pediatria. An Pediatr (Barc). 2007; 67(3): 253-73.
30. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the fi rst six years of life. The Group Health Medical Associates. N Engl J Med. 1995; 332: 133-8.
31. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir. Crit Care Med. 2000; 162: 1403-6.
32. Gilbert TW, Morgan WJ, Zeiger RS. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol. 2004; 114: 1282-7.
33. BTS 2004. British guideline on the management of asthma. A national clinic guideline. Revised edition. 2004; Edinburg.
34. Buke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family historyas a predictor of asthma risk. Am J Prev Med. 2003; 24(2): 160-9.
35. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26(5): 948-68.
36. Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, et al. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow up. Chest. 2004; 126: 1875-82.
37. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airfl ow obstruction. Thorax. 1992; 47:162-6.
38. Phillips K, Oborne J, Lewis S, Harrison TW, Tattersfi eld AE. Time course of action of two inhaled corticosteroids, fl uticasone propionate and budesonide. Thorax. 2004; 59: 26-30.
39. Reddel HK, Salome CM, Peat JK, Woolcock AJ. Which index of peak expiratory flow is most useful in the management of stable asthma? Am J Respir Crit Care Med. 1995; 151: 1320-5.
40. Boezen HM, Schouten JP, Postma DS, Rijcken B. Distribution of peak expiratory flow variability by age, gender and smoking habits in a random population sample aged 20-70 yrs. Eur Respir J. 1994; 7: 1814-20.
41. Cockcroft DW. Bronchoprovocation methods: direct challenges. Clin Rev Allergy Immunol. 2003; 24: 19-26.
42. Van den Berge M, Meijer RJ, Kerstjens HA, de Reus DM, Koeter GH, Kauffman HF, Postma DS. PC20 adenosine 5'– monophosphate is more closely associated with airway infl ammation in asthma than PC20 methacholine. Am J Respir Crit Care Med. 2001; 163: 1546-50.
43. Anderson SD, Brannan J, Spring J, et al. A new method for bronchialprovocation testing in asthmatic subjects using a dry powder of mannitol. Am J Respir Crit Care Med. 1997; 156: 758-65.
44. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing. Am J Respir Crit Care Med. 2000; 161: 309-29.
45. Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol. 1992; 89: 23-30.
46. ATS/ERS2005. American Thoracic Society/European Respiratory Society. Recommendations for standardized procedures for the online and offl ine measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. Am J Respir Crit Care Med. 2005; 171: 912-30.
47. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. Thorax. 2006; 61: 817-27.
48. Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. Chest. 2003; 123: 751-6.
49. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med. 2004; 169: 473-8.
50. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Sorkness CA. Classifying Asthma Severity in Children: Mismatch Between Symptoms, Medication Use, and Lung Function. Am J Respir Crit Care Med. 2004; 170(4): 426-32.
51. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A. ATS/ERS TASK force: standardisation of lung function testing. Standardisation of spirometry. Eur Respir J. 2005; 26: 319-38.
52. Ownby D, Peterson E, Johnson C. Factors Related to Methacholine Airway Responsiveness in Children. Am J Respir Crit Care Med. 2000; 161(5): 1578-83.
53. Parker AL, Abu-Hijleh M, McCool FD. Ratio Between Forced Expiratory Flow Between 25% and 75% of Vital Capacity and FVC Is a Determinant of Airway Reactivity and Sensitivity to Methacholine. Chest. 2003; 124(1): 63-9.
54. Faul JL, Demers EA, Burke CM, Poulter LW. The reproducibility of repeat measures of airway infl ammation in stable atopic asthma. Am J Respir Crit Care Med. 1999; 160: 1457-61.
55. Asensio de la Cruz O, Cordon Martinez A, Elorz Lambarri J, Moreno Galdo A, Villa Asensi JR, Grupo de Tecnicas de la Sociedad Española de Neumologia Pediatrica. Estudio de la funcion pulmonar en el paciente colaborador. Parte II. An Pediatr (Barc.). 2007; 66(5): 518-30.
56. Perez-Yarza EG, Villa JR, Cobos N, Navarro M, Salcedo A, Martin C, et al. Espirometria forzada en preescolares sanos bajo las recomendaciones de la ATS/ERS: estudio CANDELA. An Pediatr (Barc). 2009; 70(1): 3-11.
57. Stanojevic S, Wade A, Lum S, Stocks J. Reference equations for pulmonary function tests in preschool children: A review. Pediatric Pulmonology. 2007; 42(10): 962-72.
58. Beydon N, Davis SD, Lombardi E, Allen JL, Arets H, Aurora P, et al. On behalf of the American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. An Offi cial American Thoracic Society/European Respiratory Society Statement: Pulmonary Function Testing in Preschool Children. Am J Respir Crit Care Med. 2007; 175: 1304-45.
59. Cobos Barroso N, Perez-Yarza EG, Sardon Prado O, Reverte Bover C, Gartner S, Korta Murua J. Oxido nitrico exhalado en ninos: un indicador no invasivo de la inflamacion de las vias aereas. Arch Bronconeumol. 2008; 44(1): 41-51.
60. Warke TJ, Fitch PS, Brown V, Taylor R, Lyons JD, Ennis M, et al. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. Thorax. 2002; 57: 383-7.
61. Pijnenburg MW, Hofhuis W, Hop WC, De Jonste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. Thorax. 2005; 60: 215-8.
62. Heinzerling L, Frew AJ, Bindslev-Jensen C, Bonini S, Bousquet J, Bresciani M, et al. Standard skin prick testing and sensitization to inhalant allergens across Europe – a survey from GA2LEN network. Allergy. 2005; 60: 1287-300.
63. Chan EY, Dundas I, Bridge PD, Healy MJ, McKenzie SA. Skin-prick testing as a diagnostic aid for childhood asthma. Pediatr Pulmonol. 2005; 39: 558-62.
64. Oppenheimer J, Nelson HS. Skin testing. Ann Allergy Asthma Immunol. 2006; 96: S6-12.
65. Choi IS, Koh YI, Koh JS, Lee MG. Sensitivity of the skin prick test and specifi city of the serum-specifi c IgE test for airway responsiveness to house dust mites in asthma. J Asthma. 2005; 42: 197-202.
66. Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantifi cation and the probability of wheeze in preschool children. J Allergy Clin Immunol. 2005; 116: 744-9.
67. Tschopp JM, Sistek D, Schindler C, Leuenberger P, Perruchoud AP, Wuthrich B, et al. Current allergic asthma and rhinitis: diagnostic effi ciency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on Air Pollution and Lung Diseases in Adults. Allergy. 1998; 53: 608-13.
68. Beach J, Russell K, Blitz S, Hooton N, Spooner C, Lemiere C, et al. A systematic review of the diagnosis of occupational asthma. Chest. 2007; 131: 569-78.
69. GINA 2002. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: NHLBI/WHO Report. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute, 2002. Publication 02-3659.
70. NAEPP 2002. Nacional Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma: Expert Panel Report 2. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute, 2002. Publication 97-4051.
71. Plaza V, Alvarez FJ, Casan P, Cobos N, Lopez Vina A, et al. En calidad de Comite Ejecutivo de la GEMA y en representacion del grupo de redactores. Guia Española para el Manejo del Asma (GEMA 2003). Arch Bronconeumol. 2003; 39(Suppl 5): 1-42.
72. Bateman ED. Severity and control of severe asthma. J Allergy Clin Immunol. 2006; 117: 519-21.
73. Stoloff SW, Boushey HA. Severity, control, and responsiveness in asthma. J Allergy Clin Immunol. 2006; 117: 544-8.
74. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. J Allergy Clin Immunol. 1996; 98: 1016-8.
75. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008; 32: 545-54.
76. Osborne ML, Vollmer WM, Pedula KL, Wilkins J, Buist AS, O'Hollaren M. Lack of correlation of symptoms with specialist-assessed long-term asthma severity. Chest. 1999; 115: 85-91.
77. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guidelinedefi ned asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med. 2004; 170: 836-44.
78. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control test. J allergy Clin Immunol. 2004; 113: 59-65.
79. Vega JM, Badia X, Badiola C, Lopez-Vina A, Olaguibel JM, Picado C, et al. Covalair Investigator Group. Validation of the Spanish version of the Asthma Control Test (ACT). J Asthma. 2007; 44:867-72.
80. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999; 14: 902-7.
81. Picado C, Badiola C, Perulero N, Sastre J, Olaguibel JM, Lopez Vina A, Vega JM; Covalair Investigator Group. Validation of the Spanish version of the Asthma Control Questionnaire. Clin Ther 2008; 30: 1918-31.
82. Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationshipbetween quality of life and clinical status in asthma: a factor analysis. Eur Respir J. 2004; 23(2): 287-91.

83. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffi th LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res. 1996; 5(1): 35-46.
84. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999; 14(1): 32-8.
85. Fuhlbrigge AL, Kitch BT, Paltiel AD, et al. FEV1 is associated with risk of asthma attacks in a pediatric population. J Allergy Clin Immunol. 2001; 107: 61-7.
86. Petsky HL, Cates CJ, Li AM, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev. 2008(2): CD006340.
87. Szefl er SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guidelinebased treatment for innercity adolescents and young adults: a randomised controlled trial. Lancet. 2008; 372(9643): 1065-72.
88. Petsky H, Kynaston J, Turner C, Li A, Cates C, Lasserson T, et al. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev. 2007(2): CD005603.
89. Perez-Yarza EG, Badia X, Badiola C, Cobos N, Garde J, Ibero M, et al. On behalf of the CAN Investigator Group. Development and validation of a questionnaire to assess asthma control in pediatrics. Pediatr Pulmonol. 2009; 44: 54-63.
90. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P, on behalf of the Canadian Asthma Consensus Group. Sumary of recommendations from the Canadians Asthma Consensus report. CMAJ. 1999; 161(Suppl 11): S1-S12.
91. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance longacting betaagonist and inhaled corticosteroid on asthma control and asthma exacerbations. J Allergy Clin Immunol. 2007; 119: 344-50.
92. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fl uticasone propionate/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006; 117(3): 563-70.
93. Cockcroft DW. As-needed inhaled beta2-adrenoceptor agonists in moderate-to-severe asthma: current recommendations. Treat Respir Med. 2005; 4: 169-74.
94. Tan RA, Spector SL. Exerciseinduced asthma: diagnosis and management. Ann Allergy Asthma Immunol. 2002; 89: 226-35.
95. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev. 2005; (1): CD002738.
96. Adams NP, Bestall JC, Lasserson TJ, Jones PW, Cates C. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev. 2005; (4): CD003135.
97. Koh MS, Irving LB. Evidence-based pharmacologic treatment for mild asthma. Int J Clin Pract. 2007; 61: 1375-9.
98. Reddel HK, Belousova EG, Marks GB, Jenkins CR. Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A doubleblind randomised controlled trial. Prim Care Respir J. 2008; 17: 39-45.
99. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, et al. Daily versus asneeded corticosteroids for mild persistent asthma. N Engl J Med. 2005; 352: 1519-28.
100. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. Am J Med. 2005; 118: 649-57.
101. Barnes NC, Miller CJ. Effect of leukotriene receptor antagonist therapy on the risk of asthma exacerbations in patients with mild to moderate asthma: an integrated analysis of zafi rlukast trials. Thorax. 2000; 55: 478-83.
102. Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, et al. ALA. American Lung Association Asthma Clinical Research Centers, Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med. 2007; 356: 2027-39.
103. Busse WW, Casale TB, Dykewicz MS, Meltzer EO, Bird SR, Hustad CM, et al. Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity. Ann Allergy Asthma Immunol. 2006; 96: 60-8.
104. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. Allergy. 2006; 61: 737-42.
105. O'Byrne PM, Barnes PJ, Rodriguez Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med. 2001; 164: 1392-7.
106. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. Respir Med. 2002; 96: 432-8.
107. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Antiinfl ammatory effects of low-dose oral theophylline in atopic asthma. Lancet. 1994; 343(8904): 1006-8.
108. Dudley T, Parker S, Baldwin R. Clinical inquiries. Is nedocromil effective in preventing asthmatic attacks in patients with asthma? J Fam Pract. 2004; 53: 927-8.
109. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med. 1996; 153: 1481-8.
110. Pauwels RA, Lofdahl CG, Postma DS, Tattersfi eld AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997; 337: 1405-11.
111. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000; 320: 1368-73.
112. Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database Syst Rev. 2005; (4): CD005533.
113. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax. 2005; 60: 730-4.
114. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004; 20: 1403-18.
115. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budsonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005; 171: 129-36.
116. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study. Lancet. 2006; 368(9537): 744-53.
117. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006; 129: 246-56.
118. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J. 2005; 26: 819-28.
119. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fl uticasone. Respir Med. 2007; 101: 2437-46.
120. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007; 61: 725-36.
121. Szefl er SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002; 109: 410-8.
122. Powell H, Gibson PG. Initial starting dose of inhaled corticosteroids in adults with asthma: a systematic review. Thorax. 2004; 59: 1041-5.
123. Pieters WR, Wilson KK, Smith HC, Tamminga JJ, Sondhi S. Salmeterol/fluticasone propionate versus fl uticasone propionate plus montelukast: a cost-effective comparison for asthma. Treat Respir Med. 2005; 4: 129-38.
124. Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax. 2008; 63: 453-62.
125. Ram FS, Cates CJ, Ducharme FM. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev. 2005; 25(1): CD003137. Update in: Cochrane Database Syst Rev. 2006; (4): CD003137.
126. Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev. 2005; (4):CD005535.
127. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Infl uence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. J Allergy Clin Immunol. 1982; 70: 288-98.
128. Tonelli M, Zingoni M, Bacci E, Dente FL, Di Franco A, Giannini D, et al. Short-term effect of the addition of leukotriene receptor antagonists to the current therapy in severe asthmatics. Pulm Pharmacol Ther. 2003; 16: 237-40.
129. Inoue H, Komori M, Matsumoto T, Fukuyama S, Matsumura M, Nakano T, et al. Effects of salmeterol in patients with persistent asthma receiving inhaled corticosteroid plus theophylline. Respiration. 2007; 74: 611-6.
130. Humbert M, Berger W, Rapatz G, Turk F. Add-on omalizumab improves day-today symptoms in inadequately controlled severe persistent allergic asthma. Allergy. 2008; 63: 592-6.
131. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005; 60: 309-16.
132. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001; 108(2): 184-90.
133. Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis. Curr Med Res Opin. 2007; 23: 2379-86.
134. Mash B, Bheekie A, Jones PW. Inhaled vs oral steroids for adults with chronic asthma. Cochrane Database Syst Rev. 2000. p. 2.
135. Polosa R. An overview of chronic severe asthma. Intern Med J. 2008; 38: 190-8.
136. Newman SP, Clarke SW. Therapeutic aerosols 1–physical and practical considerations. Thorax. 1983; 38: 881-6.
137. Clarke SW, Newman SP. Therapeutic aerosols 2–Drugs available by the inhaled route. Thorax. 1984; 39: 1-7.
138. Giner J, Basualdo LV, Casan P, Hernandez C, Macian V, Martinez I, et al. Normativa sobre la utilizacion de farmacos inhalados. Recomendaciones SEPAR. Arch Bronconeumol. 2000; 36: 34-43.
139. Hess DR. Aerosol delivery devices in the treatment of asthma. Respir Care. 2008; 53: 699-723.
140. Cheng YS, Fu CS, Yazzie D, Zhou Y. Respiratory deposition patterns of salbutamol pMDI with CFC and HFA-134a formulations in a human airway replica. J Aerosol Med. 2001; 14: 255-66.

141. Brown PH, Greening AP, Crompton GK. Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitaryadrenalaxis function. Thorax. 1993; 48: 233-8.
142. Newman SP, Newhouse MT. Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. J Aerosol Med. 1996; 9: 55-70.
143. Newman SP. Spacer devices for metered dose inhalers. Clin Pharmacokinet. 2004; 43: 349-60.
144. Plaza V, Sanchis J. Medical personnel and patient skill in the use of metered dose inhalers: a multicentric study. CESEA Group. Respiration. 1998; 65: 195-8.
145. Giner J, Macian V, Hernandez C, Grupo EDEN, et al. Multicenter prospective study of respiratory patient education and instruction in the use of inhalers (EDEN study). Arch Bronconeumol. 2002; 38: 300-5.
146. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year followup study of ventilatory function in adults with asthma. N Engl J Med. 1998; 339: 1194-200.
147. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. Am J Respir Crit Care Med. 2005; 171:109-14.
148. Jimenez Ruiz CA, Barrueco M, Solano S, Torrecilla M, Dominguez M, Diaz-Maroto, et al. Recomendaciones en el abordaje diagnostico y terapeutico del tabaquismo. Documento de consenso. Arch Bronconeumol. 2003; 39: 35-41.
149. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med. 2004; 351: 1068-80.
150. Phipatanakul W, Cronin B, Wood RA, Eggleston PA, Shih MC, Song L, et al. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. Ann Allergy Asthma Immunol. 2004; 92: 420-5.
151. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. Chest. 2005; 127: 1565-71.
152. Orriols R, Abu K, Alday E, Cruz MJ, Galdiz JB, Isidro I, et al. Normativa del asma ocupacional. Arch Bronconeumol. 2006; 42(9): 457-74.
153. Luczynska C, Tredwell E, Smeeton N, Burney P. A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics. Clin Exp Allergy. 2003; 33: 1648-53.
154. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. N Engl J Med. 2003; 349: 225-36.
155. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. Allergy. 2008; 63:646-59.
156. Htut T, Higenbottam TW, Gill GW, Darwin R, Anderson PB, Syed N. Eradication of house dust mite from homes of atopic asthmatic subjects: a double-blind trial. J Allergy Clin Immunol. 2001; 107: 55-60.
157. Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. J Allergy Clin Immunol. 2003; 111: 169-76.
158. Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database of Systematic Reviews. 2007, Issue 1.
159. Platts-Mills TAE. Allergen avoidance in the treatment of asthma: Problems with the meta-analyses. J Allergy Clin Immunol. 2008; 122: 694-6.
160. Plaza V, Serrano J, Picado C, Sanchis J. High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J. 2002; 19: 846-52.
161. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyfska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. Allergy. 2007; 62: 1111-8.
162. Casadevall J, Ventura PJ, Mullol J, Picado C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. Thorax. 2000; 55: 921-4.
163. Valero A, Baltasar M, Enrique E, Pau L, Dordal MT, Cistero A, et al. C. NSAID-sensitive patients tolerate rofecoxib. Allergy. 2002; 57: 1214-5.
164. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med. 1995; 151: 969-74.
165. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. Cochrane Database Syst Rev. 2003; (4): CD001186.
166. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med. 1997; 336: 324-31.
167. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol. 2004; 113: 1129-36.
168. Moreno C, Cuesta Herranz J, Fernandez Tavora L, Alvarez Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy. 2004; 34: 527-31.
169. Olaguibel JM, Alvarez Puebla MJ. Effi cacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one metaanalysis. J Investig Allergol Clin Immunol. 2005; 15: 9-16.
170. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, et al. Metaanalysis of the effi cacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest. 2008; 133: 599-609.
171. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Longterm clinical effi cacy of grasspollen immunotherapy. N Engl J Med. 1999; 341: 468-75.
172. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. The PAT investigator group. Specifi c immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007; 62: 943-8.
173. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A sixyear follow-up study. Clin Exp Allergy. 2001; 31: 1392-7.
174. Abadoglu O, Mungan D, Pasaoglu G, Celik G, Misirligil Z. Infl uenza vaccination in patients with asthma: effect on the frequency of upper respiratory tract infections and exacerbations. J Asthma. 2004; 41: 279-83.
175. Christy C, Aligne CA, Auinger P, Pulcino T, Weitzman M. Effectiveness of influenza vaccine for the prevention of asthma exacerbations. Arch Dis Child. 2004; 89: 734-5.
176. Sheikh A, Alves A, Dhami S. Pneumococcal vaccine for asthma. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. N.o: CD002165. DOI: 10.1002/14651858. CD002165.
177. Johnston NW, Sears MR. Asthma exacerbations. Epidemiology. Thorax. 2006; 61: 722-8.
178. Hughes DM, McLeod M, Garner B, Goldbloom RB. Controlled trial of a home and ambulatory program for asthmatic children. Pediatrics. 1991; 87: 54-61.
179. Colland VT. Learning to cope with asthma: a behavioural selfmanagement program for children. Patient Educ Couns. 1993; 22: 141-52.
180. Van der Palen J, Klein JJ, Zielhuis GA, van Herwaarden CL, Seydel ER. Behavioural effect of self-treatment guidelines in a self-management program for adults with asthma. Patient Educ Couns. 2001; 43: 161-9.
181. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood Bauman A, et al. Educacion para el autocuidado y examen medico regular para adultos con asma (Revision Cochrane traducida). En: La Biblioteca Cochrane Plus, 2008 Numero 1. Oxford: Update Software Ltd. Disponible en: http://www.updatesoftware.com.
182. Powell H, Gibson PG. Opciones para la educacion sobre el autocuidado para los adultos con asma (Revision Cochrane traducida). En: La Biblioteca Cochrane Plus, 2008, Numero 1. Oxford: Update.
183. Partridge MR. Patient education. En: O'Byrne P, Thomsen NC, editores. Manual of asthma management. WB Saunders. 1995. p. 378-92.
184. Haynes RB, McDonald H, Garg AX et al. Interventions for helping patients to follow prescriptions for medications (Cochrane Review). 2001; 3. Oxford: Update Software.
185. Creer TL. Medication compliance and childhood asthma. En: Krasnegor NA, Epstein L, Johnson SB, Yaffe SJ, editores. Developmental aspects of health compliance behavior. Hittsdale, NS: Lawrence Associate. 1993; 303-33.
186. Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2000; (2):CD001117. Cochrane Database Syst Rev. 2003; (1): CD001117.
187. Abramson MJ, Bailey MJ, Couper FJ, Drivers JS, Drummer OH, Forbes AB, eta l. Are asthma medications and management related to deaths from asthma? Am J Respir Crit Care Med. 2001; 163: 12-8.
188. Douglass J, Aroni R, Goeman D, Stewart K, Sawyer S, Thien F, et al. A qualitative study of action plans for asthma. BMJ. 2002; 324: 1003-5.
189. Reddel HK, Marks GB, Jenkins CR. When can personal best peak fl ow be determined for asthma action plans? Thorax. 2004; 59: 922-4.
190. Lahdensuo A. Guided self management of asthma-how to do it. BMJ. 1999; 319: 759-60.
191. Cote J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. Am J Respir Crit Care Med. 2001; 163: 1415-9.
192. Gibson PG, Powell H. Written action plans for asthma: an evidencebased review of the key components. Thorax. 2004; 59: 94-9.
193. Castro M, Zimmermann NA, Crocker S, Bradley J, Leven C, Schechtman KB. Asthma intervention program prevents readmissions in high healthcare users. Am J Respir Crit Care Med. 2003; 168(9): 1095-9.
194. Borgmeyer A, Gyr PM, Jamerson PA, Henry LD. Evaluation of the role of the pediatric nurse practitioner in an inpatient asthma program. J Pediatr Health Care. 2008; 22(5): 273-81.
195. Woodruff PG, Emond SD, Singh AK, Camargo CA Jr. Sudden-onset severe acute asthma: clinical features and response to therapy. Acad Emerg Med. 1998; 5: 695-701.
196. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A casecontrol study in hospitalized patients with asthma. Am J Respir Crit Care Med. 1998; 157: 1804-9.
197. Mitchell I, Tough SC, Semple LK, Green FH, Hessel PA. Near-fatal asthma: a population-based study of risk factors. Chest. 2002; 121: 1407-13.
198. Serrano J, Plaza V, Sureda B, De Pablo J, Picado C, Bardagi S, et al. Alexithymia: a relevant psychological variable in near-fatal asthma. Eur Respir J. 2006; 28: 296-302.
199. ALERTA 2008. Guia ALAT-SEPAR ALERTA. America Latina y Espana: Recomendaciones para la Prevencion y el Tratamiento de la Exacerbacion Asmatica. Barcelona: Ed. Mayo. 2008.
200. McFadden ER, Kisser R, De Groot WJ, Acute bronchial Asthma: relations between clinical and physiological manifestations. Engl J Med. 1973; 288:221-5.
201. Rodrigo G, Rodrigo C. Early prediction of poor response in acute asthma patients in the emergency department. Chest. 1998; 114: 1016-21.
202. Carruthers DM, Harrisson BD. Arterial Blood gas analysis or oxygen saturation in the assessment of acute asthma? Thorax. 1995; 50: 186-8.
203. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults. A review. Chest. 2004; 125: 1081-2.

204. Cowre RI, Revitt SG, Underwood MF. The effect of peak-fl ow based action plan in the prevention of exacerbation of asthma. Chest. 1997; 112: 1534-8.
205. Reisner C, Kotch A, Dworkin G. Continuous versus frequent intermittent nebulization of albuterol in acute asthma: a randomized, prospective study. Ann Allergy Asthma Immunol. 1995; 75: 41-7.
206. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database of Systematic Reviews. 2006; 2: CD000052. DOI: 10.1002/14651858.CD000052.pub2.
207. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database Syst Rev. 2000. p. 2.
208. Hasegawa T, Ishihara K, Takakura S, Fujii H, Nishimura T, Okazaki M, et al. Duration of systemic corticosteroids in the treatment of asthma exacerbation: a randomized study. Intern Med. 2000; 39(10): 794-7.
209. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbation of asthma (Cochrane Review). London: John Wiley & Sons Ltd. The Cochrane Library. 2001; 3.
210. Rowe BH, Spooner CH, Ducharme FM, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database of Systematic Reviews. 2007; 3: CD000195. DOI: 10.1002/14651858.CD000195.
211. Osman LM, Calder C, Godden DJ, Friend JA, McKenzie L, Legge JS, et al. A randomised trial of self-management planning for adult patients admitted to hospital with acute asthma. Thorax. 2002; 57: 869-74.
212. Rodrigo GJ, Rodriguez-Verde M, Peregalli V, Rodrigo C. effects of shortterm 28% and 100% oxygen in paCO2 and peak expiratory fl ow rate in acute Asthma. A randomized trial. Chest. 2003; 124: 1312-7.
213. Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. Chest. 1998; 113: 593-8.
214. Camargo CA, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. Cochrane Database of Systematic Reviews. 2003; 4: CD001115. DOI: 10.1002/14651858.CD001115.
215. Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. Cochrane Database of Systematic Reviews. 2001; 1: CD002988. DOI: 10.1002/14651858. CD002988.
216. Rubinfeld AR, Scicchitanow R, Hunt A, Thompson PJ, van Nooten A, Selroos O. Formoterol Turbuhaler as reliever medication in patients with acute asthma. Eur Respir J. 2006; 27:735-41.
217. Rodrigo GJ, Castro Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis Thorax. 2005; 60: 740-6.
218. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews. 2001; 1: CD002178. DOI: 10.1002/14651858. CD002178.
219. Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma. An evidencebased evaluation. Chest. 2006; 130: 1301-11.
220. Rodrigo GJ, Nannini LJ. Is there a place for nebulized magnesium sulfate in the treatment of acute asthma? A systematic review. Curr Ther. 2006; 1: 181-5.
221. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2000, Issue 1. Art. N.o: CD001490. DOI: 10.1002/14651858.CD001490.
222. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database of Systematic Reviews. 2000; 4: CD002742. DOI: 10. 1002/14651858. CD002742.
223. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for nonintubated acute asthma patients. Cochrane Database of Systematic Reviews. 2006; 4: CD002884. DOI: 10.1002/14651858.CD002884.pub2.
224. Tuxen DV. Permissive hypercapnic ventilation. Am J Respir Crit Care Med. 1994; 150: 870-4.
225. Strauss L, Hejal R, Galan G, Dixon L, McFadden ER. Observations of the effects of aerosolized albuterol in acute asthma. Am J Respir Crit Care Med. 1997; 155: 545-8.
226. Grunfeld A, Fitzgerald JM. Discharge considerations in acute asthma. Can Respir J. 1996; 3: 322-4.
227. Udwadia ZF, Harrison BD. An attempt to determine the optimal duration of hospital stay following a severe attack of asthma. J R Coll Physicians Lond. 1990; 24: 112-4.
228. Pearson MG, Ryland I, Harrison BD. National audit of acute severe asthma in adults admitted to hospital. Standards of Care Committee, British Thoracic Society. Qual Health Care. 1995; 4: 24-30.
229. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefl er SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N. Engl. J Med. 2006; 354: 1985-97.
230. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. Cochrane Database Syst Rev. 2000; 1: CD001107.
231. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med. 2006; 354: 1998-2005.
232. Teper AM, Kofman CD, Szulman GA, Vidaurreta SM, Maffey AF. Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. Am. J Respir Crit Care Med. 2005; 171: 587-90.
233. Szefl er SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005; 115: 233-42.
234. Ducharme FM. Anti-leukotrienes as add-on therapy to inhaled glucocorticoids in patients with asthma: systematic review of current evidence. BMJ. 2002; 324: 1545.
235. Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, doubleblind, crossover study. J Pediatr. 2001; 138: 694-8.
236. Bisgaard H, Zielen S, Garcia Garcia ML, Johnston SL, Gilles L, Menten J, et al. Montelukast reduces asthma exacerbations in 2– to 5-year-old children with intermittent asthma. Am J respir Crit Care Med. 2005; 171: 315-22.
237. Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. Eur Respir J. 2005; 25: 289-94.
238. Van der Wouden JC, Tasche MJ, Bernsen RM, Uijen JH, De Jongste JC, Ducharme FM. Inhaled sodium cromoglycate for asthma in children. Cochrane Database Syst Rev. 2003; CD002173.
239. Bisgaard H. Effect of long-acting beta2 agonists on exacerbation rates of asthma in children. Pediatr. Pulmonol. 2003; 36: 391-8.
240. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist, C. Budesonide/Formoterol Maintenance Plus Reliever Therapy. A new strategy in pediatric asthma. Chest. 2006; 130: 1733-43.
241. Rodrigo GJ, Plaza V, Garcia-Marcos L, Castro Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma: a systematic review with meta-analysis. Pulmonary Pharmacology and Therapeutics. 2009; 22: 9-19.
242. Seddon P, Bara A, Ducharme FM, Lasserson TJ. Oral xanthines as maintenance treatment for asthma in children. Cochrane Database Syst Rev. 2006; CD002885.
243. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti– IgE for chronic asthma in adults and children. Cochrane Database Syst Rev. 2006; CD003559.
244. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane Database of Systematic Reviews. 2003; 4: CD004109. DOI: 10.1002/14651858.CD004109.pub2.
245. Ni Chroinin M, Greenstone IIG, Ducharme F. Addition of inhaled longacting beta2-agonists to inhaled steroids as fi rst line therapy for persistent asthma in steroid-naive adults. Cochrane Database of Systematic Reviews. 2004; 4: CD005307. DOI: 10.1002/14651858.CD005307.pub2.
246. Ducharme F, di Salvio F. Antileukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database of Systematic Reviews. 2004; 1: CD002314. DOI: 10.1002/14651858.CD002314.pub2.
247. Smith SR, Baty JD, Hodge D. Validation of the pulmonary score: An asthma severity score for children. Acad Emerg Med. 2002; 9: 99-104.
248. Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre– and postreatment pulse oximetry in acute childhood asthma. Acad Emerg Med. 1997; 4(2): 114-7.
249. Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr. 1985; 106(4): 672-4.
250. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonist through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: A systematic review with meta-analysis. J Ped. 2004; 145: 172-7.
251. Rubilar L, Castro-Rodriquez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. Pediatr Pulmonol. 2000; 29(4): 264-9.
252. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. Acad Emerg Med. 1996; 3(11): 1019-24.
253. Plotnick LH, Ducharme FM. Combined inhaled anticholinergic agents and beta-2 agonists for initial treatment of acute asthma in children (Cochrane Review). London: John Wiley & Sons Ltd. The Cochrane Library. 2001; 3.
254. Everard ML, Bara A, Kurian M, Elliot TM, Ducharme F. Anticholinergic drugs for wheeze in children under the age of two years (Cochrane Review). London: John Wiley & Sons Ltd. The Cochrane Library. 2001; 3.
255. Becker JM, Arora A, Scarfone RJ, Spector ND, Fontana-Penn ME, Gracely E, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. J Allergy Clin Immunol. 1999; 103: 586-90.
256. Barnett PL, Caputo GL, Bassin M, Kuppermann N. Intravenous versus oral corticosteroids in the management of acute asthma in children. Ann Emerg Med. 1997; 29: 212-7.
257. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arsenault R, et al. A comparison of inhaled fl uticasone and oral prednisone for children with severe acute asthma. N Engl J Med. 2000; 343: 689-94.
258. Schuh S, Dick PT, Stephens D, Hartley M, Khaikin S, Rodriguez L, et al. High-dose inhaled fl uticasone does not replace oral prednisolone in children with mild to moderate acute asthma. Pediatrics. 2006; 118: 644-50.
259. Nakanishi AK, Klasner AK, Rubin BK. A randomized controlled trial of inhaled flunisolide in the management of acute asthma in children. Chest. 2003; 124: 790-4.
260. Geelhoed GC, Landau LI, Le Souef PN. Evaluation of SaO_2 as a predictor of outcome in 280 children presenting with acute asthma. Ann Emerg Med. 1994; 23(6): 1236-41.
261. Bradding P, Rushby I, Scullion J, Morgan MD. As-required versus regular nebulized salbutamol for the treatment of acute severe asthma. Eur Respir J. 1999; 13(2): 290-4.
262. Kayani S, Shannon DC. Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. Chest. 2002; 122(2): 624-8.
263. InternationalRhinitisManagement-WorkingGroup. International Consensus Report on Diagnosis and Management of Rhinitis. Allergy. 1994; 49(19): 1-34.
264. Fokkens W, Lund V, Mullol J, EPPo. R. a. N. P. Group. European Position Paper on Rhinosinusitis and Nasal Polyps 2007. Rhinology. 2008; (Suppl 20): 1-111.

265. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004; 113(5): 832-6.
266. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN* and AllerGen**). Allergy. 2008; 63(86): 8-160.
267. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001; 108(Suppl 5): S147-334.
268. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallestrini E, et al. Seasonal and perennial allergic rhinitis: is this classifi cation adherent to real life? Allergy. 2005; 60(7): 882-7.
269. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005; 60(3): 350-3.
270. Valero A, Ferrer M, Sastre J, Navarro AM, Monclus L, Marti-Guadano E, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. J Allergy Clin Immunol. 2007; 120: 359-65.
271. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004; 24(5): 758-64.
272. Pereira C, Valero A, Loureiro C, Davila I, Martinez-Cocera C, Murio C, et al. Iberian study of aeroallergens sensitisation in allergic rhinitis. Eur Ann Allergy Clin Immunol. 2006; 38(6): 186-94.
273. Navarro, A. Rinitis. Alergologica 2005. Factores epidemiologicos, clinicos y socioeconomicos de las enfermedades alergicas en Espana. Madrid: Luzan 5 S.A. de ediciones. 2006. p. 107-32.
274. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. Pediatr Allergy Immunol. 2008; 19(2): 110-24.
275. Gendo K, Larson EB. Evidencebased diagnostic strategies for evaluating suspected allergic rhinitis. Ann Intern Med. 2004; 140(4): 278-89.
276. Crobach MJ, Hermans J, Kaptein AA, Ridderikhoff J, Petri H, Mulder JD. The diagnosis of allergic rhinitis: how to combine the medical history with the results of radioallergosorbent tests and skin prick tests. Scand J Prim Health Care. 1998; 16(1): 30-6.
277. Malm L, Gerth van Wijk R, Bachert C. Guidelines for nasal provocations with aspects on nasal patency, airfl ow, and airfl ow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. Rhinology. 2000; 38(1): 1-6.
278. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol. 2003; 111(6): 1171-83; quiz 1184.
279. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004; 113(1): 86-93.
280. Castillo JA, Mullol J. Comorbilidad de rinitis y asma en Espana. Arch Bronconeumol. 2008; 44: 593-9.
281. Navarro AM, Valero A, Julia B, Quirze S. Coexistence of asthma and allergic rhinitis in adult patients attending clinics: ONEAIR Study. J Investig Allergol Clin Immunol. 2008; 18(4): 233-8.
282. Arnedo-Pena A, Garcia-Marcos L, Garcia Hernandez G, Aguinagua Ontoso I, Gonzalez Diaz C, Morales Suarez-Varela M, et al. Time trends and geographical variations in the prevalence of symptoms of allergic rhinitis in 6-7-year-old children from eight areas of Spain according to the ISAAC. An Pediatr (Barc.) 2005; 62(3): 229-36.
283. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, et al. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. Allergy. 2002; 57(11): 1048-52.
284. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol. 2002; 109(3): 419-25.
285. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy [corrected]. Clin Exp Allergy. 2005; 35(6): 723-7.
286. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthmarelated health care use by adults. Clin Exp Allergy. 2005; 35(3): 282-7.
287. Sazonov Kocevar V, Thomas J, Jonsson L, Valovirta E, Kristensen F, Yin DD, et al. Association between allergic rhinitis and hospital resource use among asthmatic children in Norway. Allergy. 2005; 60(3): 338-42.
288. Boulay ME, Boulet LP. Lower airway infl ammatory responses to repeated very low-dose allergen challenge in allergic rhinitis and asthma. Clin Exp Allergy. 2002; 32(10):1441-7.
289. Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S, et al. Eosinophils are a feature of upper and lower airway pathology in nonatopic asthma, irrespective of the presence of rhinitis. Clin Exp Allergy. 2000; 30(5): 663-9.
290. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. Cochrane Database Syst Rev. 2003; (4): CD003570.
291. Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, Baena-Cagnani CE, Bouchard J, et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA2LEN). Allergy. 2006; 61(9): 1086-96.
292. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. J Allergy Clin Immunol. 2007; 119(4): 881-91.
293. Simons FE. H1-antihistamines in children. Clin Allergy Immunol. 2002; 17: 437-64.
294. Pasquali M, Baiardini I, Rogkakou A, Riccio AM, Gamalero C, Descalzi D, et al. Canonica. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and infl ammatory parameters. Clin Exp Allergy. 2006; 36(9): 1161-7.
295. Canonica GW, Tarantini F, Compalati E, Penagos M. Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. Allergy. 2007; 62(4): 359-66.
296. Hore I, Georgalas C, Scadding G. Oral antihistamines for the symptom of nasal obstruction in persistent allergic rhinitis–a systematic review of randomized controlled trials. Clin Exp Allergy. 2005; 35(2): 207-12.
297. Simons FE. Advances in H1– antihistamines. N Engl J Med. 2004; 351(21): 2203-17.
298. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, antiinflammatory actions and cardiac effects. Clin Exp Allergy. 2002; 32(4): 489-98.
299. Owen CG, Shahm A, Henshaw K, Smeeth L, Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of effi cacy and effectiveness. Br J Gen Pract. 2004; 54(503): 451-6.
300. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ. 1998; 317(7173): 1624-9.
301. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with metaanalysis. Ann Allergy Asthma Immunol. 2002; 89(5): 479-84.
302. Barnes ML, Biallosterski BT, Gray RD, Fardon TC, Lipworth BJ. Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis. Rhinology. 2005; 43(4): 291-5.
303. Rodrigo GJ, Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol. 2006; 96(6): 779-86.
304. Borum P, Mygind N, Schultz Larsen F. Intranasal ipratropium: a new treatment for perennial rhinitis. Clin Otolaryngol Allied Sci. 1979; 4(6): 407-11.
305. Schuller DE, Selcow JE, Joos TH, Hannaway PJ, Hirsch SR, Schwartz HJ, et al. A multicenter trial of nedocromil sodium, 1% nasal solution, compared with cromolyn sodium and placebo in ragweed seasonal allergic rhinitis. J Allergy Clin Immunol. 1990; 86(4 Pt 1): 554-61.
306. Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2003; 91(2): 160-7.
307. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and metaanalysis. Allergy. 2005; 60(1): 4-12.
308. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007: CD001936.
309. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2) LEN). Allergy. 2005; 60(9): 1112-5.
310. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax. 2006; 61(2): 169-76.
V. Plaza et al / Arch Bronconeumol. 2009;45(Supl 2):2-35 35
311. Clifton V. Maternal asthma during pregnancy and fetal outcomes: potential mechanisms and possible solutions. Curr Opin Allergy Clin Immunol. 2006; 6(5): 307-11.
312. Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. Ann Allergy Asthma Immunol. 2002; 89(5): 437-8.
313. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med. 1998; 158(4): 1091-5.
314. Clifton VL, Giles WB, Smith R, Bisits AT, Hempenstall PA, Kessell CG, et al. Alterations of placental vascular function in asthmatic pregnancies. Am J Respir Crit Care Med. 2001; 164(4): 546-53.
315. Bakhireva LN, Schatz M, Jones KL, Tucker CM, Slymen DJ, Klonoff-Cohen HS, et al. OTIS Collaborative Research Group. Fetal sex and maternal asthma control in pregnancy. J Asthma. 2008; 45(5): 403-7.
316. Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med. 1995; 151(4): 1170-4.
317. Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. Am J Obstet Gynecol. 1996; 175(1): 150-4.
318. Schatz M, Zeiger RS, Harden K. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Irnmunology. 1997; 100: 301-6.
319. NAEPP 2004. National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. J Allergy Clin Immunol. 2005; 115(1): 31-3.
320. Asthma in pregnancy. ACOG Practice Bulletin No. 90. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2008; 111: 457-64.
321. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonid in early pregnancy. Obstet. Gynecol. 1999; 93: 392-5.

322. Rayburn WF, Atkinson BD, Gilbert K. Short term effects of inhaled albuterol on maternal and fetal circulations. Am J Obstet Gynecolog. 1994; 170: 770-3.
323. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and metaanalysis of epidemiological studies. Teratology. 2000; 62: 385-92
324. Czeizel AE, Rockembauer M. Population based case-control study of teratogenic potential of corticosteroids. Teratology. 1997; 56:335-40.
325. Rey E, Boulet LP. Asthma in pregnancy. BMJ. 2007; 334: 582-5.
326. Barnes PJ, Woolcock AJ. Diffi cult asthma. Eur Respir J. 1998; 12: 1209-18.
327. Lopez Vina A, Aguero Balbin R, Aller Alvarez JL, Bazus Gonzalez T, Cosio BG, de Diego Damia A, et al. Normativa para el asma de control dificil. Arch Bronconeumol. 2005; 41: 513-23.
328. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Asthma and Allergy Research Group of the National Heart and Lung Institute. Systematic assessment of diffi cult-to-treat asthma. Eur Respir J. 2003; 22: 478-83.
329. Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. Allergy. 2007; 62: 554-60.
330. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med. 2006; 354: 697-708.
331. Morjaria JB, Chauhan AJ, Babu KS, Polosa R, Davies DE, Holgate ST. The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. Thorax. 2008; 63: 584-91.
332. Wenzel S. Severe asthma in adults. Am J Respir Crit Care Med. 2005; 172: 149-60.
333. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic infl ammation. J Allergy Clin Immunol. 2004; 113: 101-8.
334. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy. 2005; 60:302-8.
335. Bernstein IL, Bernstein DI, Chan-Yeung M, Malo JL. Defi nitions and classification of asthma in the workplace. En: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editores. Asthma in the worplace. 3.a ed. New York: Marcel Dekker. 2006. p. 1-8.
336. Malo JL, Chan-Yeung M. J Allergy Clin Immunol. 2008. p. 23. Epub ahead of print.
337. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective populationbased study (ECRHS-II). Lancet. 2007; 28; 370: 336-41.
338. Malo JL. Prevention of occupational asthma. Proceedings of the fi rst Jack Pepys occupational asthma symposium. Am j Respir Crit Care Med. 2003; 167: 463-4.
339. Jeal H, Draper A, Jones M, Harris J, Welsh K, Taylor AN, et al. HLA associations with occupational sensitization to rat lipocalin allergens: a model for other animal allergies? J Allergy Clin Immunol. 2003; 111: 795-9.
340. Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjuntivitis in subjects with occupational asthma. Eur Respir J. 1997; 10: 1513-5.
341. Karjalainen A, Mortikainen R, Khukka T, Saarinen K, Uitt T. Risk of asthma among Finnish patients with occupational rhinitis. Chest. 2003; 123: 283-88.
342. Pronk A, Preller L, Raulf-Heimsoth M, Jonkers IC, Lammers JW, Wouters IM, et al. Respiratory symptoms,sensitization, and exposure response relationships in spray painters exposed to isocyanates. Am J Respir Crit Care Med. 2007; 176(11): 1090-7.
343. Chan-Yeung M, Malo JL. Occupational asthma. N Engl J Med. 1995; 333: 107-12.
344. Vandenplas O, Cartier A, Malo JL. Occupational challenge test. En: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, editores. Asthma in the workplace. 3.a ed. New York: Marcel Dekker; 2006. p. 227-52.
345. Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman-Taylor A, Cullinan P. The outcome of occupational asthma after cessation of exposure: a systematic review. Thorax. 2007; 62: 147-52.
346. Padoan M, Pozzato V, Simoni M, Zedda L, Milan G, Bononi L, et al. Longterm follow-up of toluene diisocyanateinduced asthma. Eur Respir J. 2003; 21: 637-40.
347. Cullinan P, Tarlo S, Nemery B. The prevention of occupational asthma. Eur Respir J. 2003; 22: 853-60.
348. Brooks SM, Weiss MR, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. Chest. 1985; 88: 376-84.
349. Tarlo SM, Boulet LP, Cartier A, Cockcroft D, Cote J, Hargreave FE, et al. Canadian Thoracic Society guidelines for occupational asthma. Can Respir J. 1998; 5: 289-300.
350. Brooks SM, Hammad Y, Richards I, Giovinco-Barbas J, Jenkins K. The spectrum of irritant-induced asthma. Sudden and not-so-sudden onset and the role of allergy. Chest. 1998; 113: 42-9.
351. Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of workrelated asthma: American College Of Chest Physicians Consensus Statement. Chest. 2008; 134(Suppl 3): 1S-41S.
352. Henneberger PK. Workexacerbated asthma. Curr Opin Allergy Clin Immunol. 2007; 7: 146-51.
353. Christopher KL, Wood RP, Eckert RC, Blager FB, Raney RA, Souhrada JF. Vocalcord dysfunction presenting as asthma. N Engl J Med. 1983: 308(26): 1566-70.
354. Wood RP, Milgrom H. Vocal cord dysfunction. J Allergy Clin Immunol. 1996; 98(3): 481-5.
355. Kayani, S, Shannon DC. Vocal cord dysfunction associated with exercise in adolescent girls. Chest. 1998; 113(2): 540-2.
356. McFadden ER, Zawadski DK. Vocal cord dysfunction masquerading as exercise induced asthma. a physiologic cause for "choking" during athletic activities. Am J Respir Crit Care Med. 1996; 153(3): 942-7.
357. Newman, KB, Mason UG, Schmaling KB. Clinical features of vocal card dysfunction. Am J Respir Crit Care Med. 1995; 152: 1382-6.
358. Doshi DR, Weinberger MM. Longterm outcome of vocal cord dysfunction. Ann Allergy Asthma Immunol. 2006; 96(6): 794-9.