1. Introduction

1.1 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.

1.2 Prevalence

Asthma prevalence varies ostensibly worldwide, ranging from 2% in Tartu (Estonia) to 11.9% in Melbourne (Australia). The prevalence of wheezing in the last 12 months varies from 4.1% in Mumbai (India) to 32% in Dublín (Ireland) [6,7].

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 1.1 and 1.2). 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].

1.3 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

Table 1.1. 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 results 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.

Table 1.2. 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 1 night/week	0.8	1.4	0.6	1.3	0.7	1.4
– Wheezing which 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 as percentages.

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asthma phenotypes, although there may be certain differences between patients and at different stages of the disease [13].

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 1.3). The structural cells of the respiratory tract have a vital role in its pathogenesis, as they not only serve as a target, but also play an active part in the inflammatory and repair processes that take place in the respiratory tract (Table 1.4). The cellular interactions that make this inflammatory process possible occur via cell mediators and molecules with a wide range of functions (Table 1.5).

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Often ther is a thickening of the reticular layer of the basal membrane, known as subepithelial fibrosis [14], hypertrophy

Table 1.3. 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].
- **Denditric 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 1.4. 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].

Table 1.5. 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.
- **Citokines:** 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, dentritic cells and eosinophils.

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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].

1.4 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 1.6).

Various trigger factors (Table 1.7) 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 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 1.6).

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A characteristic, although not exclusive, feature of the disease is the phenomenon known as bronchial

Table 1.6. 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 result of an increase in the number of calciform 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 1.7. Trigger factors for asthma exacerbations

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

Table 1.8. 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 contractilly 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.

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

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factors also have an influence [26]. Anti-inflammatory treatment improves asthma control and reduces BHR, but does not eradicate it entirely [27] (Table 1.8).

Table 1.9. The most common asthma processes associated with wheezing in children

Newborns and very young infants (0-3 months)
- Bronchopulmonary dysplasia.
- Congenital anomalies 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
- Gastroesophageal reflux/ aspiration
- Cystic fibrosis
- Cardiac abnormalities

Children over 12 months of age
- Aspiration of a foreign body
- Bronchiolitis obliterans
- Vocal cord dysfunction (adolescents)
- Primary ciliary dyskinesia
- Congenital lung and respiratory tract abnormalities

Table 1.10. Phenotypes or developmental models of children with wheezing symptoms [29]

Early-stage transitory wheezing:
- Onset during the first year of life, remiting 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 to 11 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 1.11. 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 develop asthma by the time they reach school age (6-13 years).

1.5 Differential Characteristics of Childhood Asthma

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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 1.9).

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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 1.10) [29]. The classification of a child into a particular phenotype is useful for establishing treatment and prognosis.

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 1.11).