1. Introduction

1.1 Definition

Asthma is a syndrome that includes various clinical phenotypes that share similar clinical manifestations, probably of different etiologies, which prevents to establish a precise definition of the disorder. The most commonly used definitions of this disease are usually based on the description of its clinical and pathophysiological characteristics. From a pragmatic point of view, asthma may be defined as a chronic inflammatory airway disease, in which different inflammatory cells and mediators are involved, conditioned in part by genetic factors and associated with bronchial hyperresponsiveness (BHR) and variable degree of airflow obstruction that is totally or partially reversible by either the action of drugs or spontaneously.

1.2 Prevalence

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Asthma prevalence is highly variable worldwide, ranging from 2 % in Tartu (Estonia) to 11.9 % in Melbourne (Australia). Similarly, the prevalence of wheezing (over the last 12 months) varies from 4.1 % in Mumbai (India) to 32 % in Dublin (Ireland)[9,10].

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In our country, The European Respiratory Health Study reported prevalence rates of 4.7 % in Albacete, 3.5 % in Barcelona, 1.1 % in Galdakano, 1 % in Huelva and 1.7 % in Oviedo[11]. The prevalence of asthma in Spain has increased over the last few years, most likely due to the industrial development[12]. A number of cross-sectional studies with special attention on air pollutants and in which environmental questionnaires were used showed differences in the prevalence of asthma according to geographical distribution[13,14]. Incidences of 8.2 cases per 1000 person-years[15] in Castellón and 15.6 cases per 1000 person-years in Huelva[16] were observed, although both studies showed substantial differences in some variables, such as age, case definition or risks related to differences in the number of cases lost at follow-up[11] (table 1.1). In another study designed to assess the prevalence of asthma and its relationship with lower respiratory tract infections (considered a risk factor for asthma), prevalence rates of 9.3% for asthma and 16.6% for persistent wheezing at 6 years of age were found[17].

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Finally, in another study carried out in children aged 6 to 7 years and adolescents aged 13 to 14 years in Galicia[18] and conducted according to the methodology of the International Study of Asthma and Allergies in Childhood (ISAAC), prevalence rates of frequent wheezing ranged from 11.4 % in Santiago de Compostela to 15.7 % in Vigo, for younger children, and from 8.8% in Orense to 18.8 % in Vigo for older subjects. With regard to sex, a greater prevalence was reported in boys aged 6-7 years. The estimated overall prevalence in Galicia was 13.6 % for children and 12.2 % for adolescents, with a higher proportion reported in coastal than inland cities. In previous studies, rates of 16.7 % had been found in Cantabria[19].

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In summary, using the ISAAC methodology, the mean prevalence of childhood asthma in Spain is 10%, similar to that reported for the European Union, with higher prevalence rates noted in coastal areas[15,14]. Differences in prevalence have been explained by several authors to genetic factors, the proportion of immigrant population as well as to environmental, organizational and healthcare-related factors in the Healthcare Services of the Autonomous Communities.

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Table 1.1. Prevalence of asthma in Spain

Author	Geographical area	Year	Prevalence	Comments
Bercedo[19]	Cantabria	2004	16.7 %	
García Marcos[15]	Castellón	2004	8.2 %	
Pereira[16]	Huelva	2008	1.5 %	
Puig[17]	Barcelona	2010	9.3 %/16.6 %	6 years/persistent wheezing
López[18]	Galicia	2011	13.6 %/12.2 %	6-7 years/13-14 years

1.3 Risk factors

Risk factors for the development of asthma should be distinguished from triggers of asthma symptoms. The former are those related to the onset of asthmatic disease, whereas triggers of asthma symptoms are defined as those causing symptoms in patients with asthma, which can ultimately lead to an exacerbation episode.

The most widely studied risk factors for asthma development, or those with a higher degree of association, are shown in table 1.2. Many host-related factors are perinatal, while environmental factors vary greatly and can impact on patients of different age groups.

The importance of triggers of asthma symptoms is based on the fact that interventions aimed at avoiding them are crucial in the management of asthma. The most common factors are shown in table 1.3.

Interestingly, it has been shown that some environmental factors known to trigger asthma symptoms also protect against developing of asthma when exposure occurs in childhood.

Genetic factors may contribute to the development of asthma, modulate individual response to other risk factors for developing asthma or influence upon the effect of other precipitating factors.

Table 1.2. Risk factors for asthma development

Risk factors	Category of evidence	Association	Type of study	Reference
Host-related factors				
Atopy	B-C	OR 3.5 (2.3-5.3)	b	Arbes 2007[20]
Early menarche	B-C	OR 2.79 (1.06-7.34)	b	Macsali 2011[21]
	B-C	OR 2.34 (1.19-4.59)	b	Al.Sahab 2011[22]
Obesity	B-C	OR 0.9 (0.7-1.1)[13]	b	Sin 2002[23]
Bronchial hyperresponsiveness	B-C	OR 4.2 (1.92-9.23)	b	Carey 1996[24]
Rhinitis	B-C	OR 3.21 (2.21-4.71)	b	Guerra 2002[25]
	B-C	OR 4.16 (3.57-4.86)	b	Burgess 2007[26]
	B-C	RR 3.53 (2.11-5.91)	b	Shaaban 2008[423]
Chronic rhinosinusitis	B-C	OR 3.48 (3.20-3.76)	b	Jarvis 2012[458]
Perinatal factors				
Prematurity	A-B	OR 2.81 (2.52-3.12)[1]	a	Been 2014[27]
	A-B	OR 1.37 (1.17-1.62)[2]	a	Been 2014[27]
Neonatal jaundice	B-C	OR 1.64 (1.36-1.98)	b	Ku 2012[28]
Lactation	B-C	OR 0.88 (0.82-0.95)[12]	b	Silvers 2012[29]
	A-B	OR 0.70 (0.60-0.81)[12]	a	Gdalevich 2001[30]
Cesarean section	B-C	HR 1.52 (1.42-1.62)	b	Tollanes 2008[31]
Smoking in pregnancy	B-C	OR 1.72 (1.11-2.67)	b	Strachan 1996[32]
	B-C	RR 8.8 (3.2-24)	b	Gilliland 2006[33]
	B-C	OR 1.87 (1.25-2.81)	b	Ehrlich 1996[34]
	B-C	OR 1.65 (1.18-2.31)	b	Neuman 2012[35]
Environmental factors				
Aeroallergens	B-C	OR 0.68 (0.49-0.95)[7,12]	b	Kerkhof 2009[36]
Workplace allergens	B-C	RR 2.2 (1.3-4.0)	b	Kogevinas 2007[619]
Respiratory tract infections	B-C	OR 0.52 (0.29-0.92)[9,12]	b	Illi 2001[37]
Smoking	B-C	RR 3.9 (1.7-8.5)	b	Gilliland 2006[33]
	B-C	OR 2.98 (1.81-4.92)	c	Polosa 2008[38]
Drugs				
Antibiotics	B	OR 1.12 (0.88-1.42)[10,13]	a	Marra 2006[39]
	A	OR 2.82 (2.07-3.85)[11]	a	Marra 2006[39]
	B-C	OR 1.75 (1.40-2.17)	b	Hoskin-Parr 2013[40]

Category of evidence: table 0.1 shows the classification of evidence. Association: odds ratios (OR) with their 95 % confidence intervals in parenthesis are shown. 1 Very premature, 2 Moderately premature, 3 Intake of vitamin E, 4 Intake of zinc, 5 Mediterranean diet, 6 Exposure to dogs, 7 Exposure to cats, 8 Living on a farm, 9 Non-respiratory viral infection, 10 Prospective studies, 11 Retrospective studies, 12 Protecting factor, 13 No association. Types of studies: a: meta-analysis – systematic review, b: large prospective epidemiological study, c: large retrospective epidemiological study.

Table 1.3. Asthma triggers

Environmental factors	Atmospheric	Pollution	- SO_2 - NO_2 - Ozone - CO
		Plants	- Suspended particulates - Grass pollen - Tree pollen - Weed pollen
	Domestic	- Dust mites - Cat dander	- Dog dander - Cockroaches
	Infectious agents	Fungi	- *Alternaria alternata* - *Cladosporium herbarum* - *Penicillium* - *Aspergillus fumigatus*
		Viruses and bacteria	- Rhinovirus - Other respiratory viruses
Work-related factors	Low molecular weight substances	The industry involved	
	Drugs Anhydrides Diisocyanates Woods Metals Other	Pharmaceutical industry Plastic industry Polyurethane, plastic, varnish and enamel industries Sawmills, carpentry work, cabinetmaking Foundries, nickel plating, silver plating, tanning, boiler cleaning industries Cosmetic industry, hairdressing, photograph developing, cooling, dyes	
	High molecular weight substances	The industry involved	
	Substances of plant origin, powder and flours Food Plant enzymes Vegetable gums Fungi and spores Animal enzymes	Farmers, port workers, mills, bakeries, beer industry, soy processing, cacao, coffee and tea industries, textile industry Food industry Food industry, pharmaceutical industry, printer shops, latex industry, sanitary ware Bakeries, farms, farmers Mills, carmine manufacturing	
Systemic factors	Drugs	- Sensitizing antibiotics - Acetylsalicylic acid - Systemic and topical non-selective ß-blockers - NSAIDs	
	Food	- Cow milk - Egg - Dried fruit - Cereals - Fish - Seafood	
		- Sulfite-containing food Dried fruit; wine; lemon, lime and grape juice; desiccated potatoes; vinegar; seafood; beer; etc.	
		- Plant panallergens such as prophyllines or lipid transfer protein (LTP)	

1.4 Pathogenesis

Despite the highly variable clinical spectrum of asthma, airway **inflammation** is a common pathological feature affecting the whole airway (including the nasal mucosa) that is present even when symptoms are episodic. However, the relationship between the severity of asthma and the degree of inflammation has not been consistently established[41]. In most asthma patients, the typical inflammatory pattern includes an increase in the number of mastocytes, activated eosinophils, natural killer cells and type-2 T-helper lymphocytes, all of which release mediators that cause disease symptoms (table 1.4)[42]. Structural cells throughout the airways also produce inflammatory mediators that facilitate persistent inflammation

Table 1.4. Inflammatory cells involved in asthma

T lymphocytes (TL): are increased in number in the airways, with an imbalance in the Th1/Th2 ratio and predominance of Th2 that release specific cytokines, including IL 4, 5, 9 and 13. The cytokines orchestrate the eosinophilic inflammation and IgE-production by B lymphocytes. Levels of LT regulators are decreased, while those of LT NK are increased.[48]
Mastocytes: are increased in the bronchial epithelium and infiltrate the bronchial wall smooth muscle. Their activation releases mediators with bronchoconstrictor and proinflammatory activity, such as histamine, leukotrienes and prostaglandin D2.[49] They are activated by allergens, osmotic stimuli (such as those causing exercise-induced bronchoconstriction) and neuronal connections.
Eosinophils: their number is increased in the airways and correlates with disease severity. They are activated and their apoptosis is inhibited. They release inflammatory enzymes that harm epithelial cells and generate mediators that amplify the inflammatory response.[50]
Neutrophils: are increased in the airways of some patients with severe asthma, during exacerbations and in smokers with asthma. Their pathophysiological role is not well defined and their increase may be due to treatment with glucocorticoids.[51]
Dendritic cells: act as antigen-presenting cells that interact with lymph node regulating cells and stimulate the production of Th2 lymphocytes.[52]
Macrophages: These cells may be activated by allergens through the low affinity IgE receptors and release mediators that boost the inflammatory response, particularly in severe asthma.[53]

Table 1.5. Cells and structural elements of the airways involved in asthma

Bronchial epithelium: It is damaged, with a loss of both ciliated and secretory cells. Epithelial cells are sensitive to changes in their microenvironment, express multiple inflammatory proteins and release cytokines, chemokines and lipid mediators in response to physical changes. Their production can also be stimulated by pollutants and viral infections. The repairing process following epithelial damage may be abnormal, which enhances the bronchial obstruction associated with asthma.[54]
Bronchial smooth muscle: Its cells show an increased proliferation (hyperplasia) and growth (hypertrophy) with the expression of proinflammatory mediators similar to those found in epithelial cells.[55]
Endothelial cells: They participate in the recruitment of inflammatory cells from the blood vessels to the airways through the expression of adhesion molecules.
Fibroblasts and myofibroblasts: After being stimulated by inflammatory mediators and growth factors, these cells produce some components of the connective tissue, such as collagen and proteoglycans that are involved in airways remodeling.
Airway cholinergic nerves: These can be activated by neural reflexes and cause bronchoconstriction and mucus secretion. Sensorial nerves may provoke symptoms like cough and chest tightness, and may release inflammatory neuropeptides.

Table 1.6. Relevant molecules involved in the asthma inflammatory process

Chemokines: These are mainly expressed by epithelial cells and are important in the recruitment of inflammatory cells in the airways.
Cysteine-leukotrienes. Potent bronchoconstrictors released by mastocytes and eosinophils.
Cytokines. They drive and modify the inflammatory response in asthma, and determine its severity.42 The most relevant are: • IL-1β and TNFα: amplify the inflammatory response. • GM-GSF: prolongs eosinophil survival in the airways. • Cytokines derived from Th2 lymphocytes, including: - IL-4: Important to the differentiation of Th2 lymphocytes and IgE synthesis. - IL-5: Necessary for the differentiation and survival of eosinophils. - IL-13: Important to the synthesis of IgE.
Histamine. Released by mastocytes, it contributes to bronchoconstriction and the inflammatory response.
Nitric oxide: A potent vasodilator predominantly produced in epithelial cells by the inducible nitric oxide synthase enzyme.
Prostaglandin D2: A bronchoconstrictor mostly derived from mastocytes; it is involved in the recruitment of Th2 lymphocytes to the airways.

GM-GSF: Granulocyte-macrophage colony-stimulating factor; TNF: Tumor necrosis factor

Table 1.7. Mechanisms of airway obstruction in asthma

Contraction of bronchial smooth muscle: It occurs in response to multiple mediators and neurotransmitters with bronchoconstrictor effects and is the most prominent mechanism of airway narrowing. It is largely reversible with bronchodilators.
Edema of the airways: It is caused by the microvascular exudation in response to inflammatory mediators. It is particularly important during acute exacerbations.
Mucus hypersecretion: It is due to an increased number of epithelial goblet cells and an increased size of submucosal glands. It can occlude the airway lumen.
Structural changes in the airways: subepithelial fibrosis due to deposition of collagen fibers and proteoglycans under the basal membrane; smooth muscle hypertrophy and hyperplasia and increased circulation within the blood vessels of the bronchial wall, with enhanced permeability.

Table 1.8. Mechanisms of bronchial hyperresponsiveness

Excessive contraction of airway smooth muscle: It may result from increased volume and/or contractility of bronchial smooth muscle cells.
Uncoupling of airway contraction as a result of inflammatory changes in the airway wall that may lead to its narrowing and to loss of the maximum level of contraction, which can be found in healthy airways when a bronchoconstrictor substance is inhaled.
Thickening of the airway wall. Edema and structural changes amplify the bronchial wall narrowing due to the airway muscle contraction.[43]
Sensitized sensory nerves. Their sensitivity may be enhanced by inflammation, which results in excessive bronchoconstriction in response to sensorial stimuli.[181]

through a number of different mechanisms (table 1.5). Cell interactions enabling this inflammatory process depend on cell mediators and molecules with very different roles (table 1.6).

In addition to the inflammatory response, patients with asthma often exhibit characteristic structural changes, known as airway ***remodeling***, which include thickening of the reticular layer of the basal membrane, subepithelial fibrosis, hypertrophy and hyperplasia of the bronchial smooth muscle, vascular proliferation and dilatation, mucosal gland hyperplasia and mucus hypersecretion, all of which are associated with a progressive deterioration of pulmonary function[43]. Some of these phenomena are related to the severity of asthma and may lead to a bronchial obstruction, which is occasionally irreversible[43]. These changes may result from a repairing response to chronic inflammation or may occur independently of the inflammatory process[44].

Bronchial obstruction is the common end-result of all the pathophysiological changes occurring in asthma and the cause of most asthma symptoms. However, the airflow limitation and the symptoms it triggers may resolve either spontaneously or in response to medication, or even remain absent during some time in a given patient. A number of factors have been reported as contributing to bronchial obstruction (table 1.7).

Various triggering agents may cause, through different mechanisms, a significant airway narrowing, thus leading to the typical symptoms of asthma exacerbation. The most severe episodes usually occur in association with viral infections of the upper respiratory tract (mainly rhinovirus and respiratory syncytial virus) or exposure to allergens[45]. Non-steroidal anti-inflammatory drugs (NSAIDs), exercise, cold air and certain non-specific irritants may induce asthma exacerbations. The intensity of the response to these stimuli is related to the underlying inflammation.

Bronchial hyperresponsiveness (BHR) or hyperreactivity is an additional pathophysiological characteristic of asthma, which leads to airway narrowing in response to stimuli that are harmless to people without asthma. BHR results in a variable airflow limitation and the onset of intermittent symptoms. BHR is linked to airway inflammation and repair, and is partially reversible with therapy. Mechanisms involved in BHR are shown in table 1.8. The degree of BHR is partially correlated with the clinical severity of asthma and the inflammation markers[46]. Anti-inflammatory therapy improves asthma control and attenuates BHR, but does not completely suppress it[47].

Variability is another feature of asthma. It is defined as the variation or fluctuation of both symptoms and pulmonary function over time, even during the same day, beyond physiological circadian changes. It can be assessed by daily measurement of peak expiratory flow.