# 2. Diagnosis

## 2.1 Clinical features

C A diagnosis of asthma should be considered in the presence of a high level of clinical suspicion based on signs and symptoms, such as wheezing (the most typical symptom)[56], dyspnea (or breathing difficulty), cough and chest tightness (key symptoms). These clinical manifestations are usually variable, occur mainly at night or in the early morning and are caused by different triggers (viral infections, allergens, tobacco smoke, exercise, emotions, etc.). Seasonal variations, along with a family and personal history of atopy are important aspects to be considered[57,58]. None of these symptoms and signs are specific to asthma[59], hence the need to include an objective test for the diagnosis, usually respiratory function tests.

C The patient's clinical history should also include other aspects such as the onset of symptoms, the presence of allergic rhinitis or eczema, and a family history of asthma or atopy[58], all of which increases the probability to establish a diagnosis of asthma. Table 2.1 shows the key questions for the identification of patients with suspected asthma[60,61].

C On physical examination, wheezing on auscultation of the chest is most characteristic finding, and sometimes nasal obstruction on anterior rhinoscopy, as well as dermatitis or eczema. However, a normal physical examination does not exclude a diagnosis of asthma.

C If asthma is suspected, a differential diagnosis with other diseases, particularly chronic obstructive pulmonary disease (COPD) should be made, as shown in table 2.2.

## 2.2 Asthma phenotypes

### *2.2.1 Adults*

D Asthma is a heterogeneous syndrome resulting from complex interactions between environmental and genetic factors. Numerous studies have characterized a number of disease phenotypes in certain groups of patients with recognizable demographic, clinical and pathophysiological features[59,62-64]. However, although this classification may help to guide the use of specific therapies in patients with severe uncontrolled asthma (see chapter 8), no robust evidence is yet available to recommend a disease classification based on asthma phenotypes in general, and particularly on the phenotype that is controlled with the standard treatment.

Asthma phenotypes may be divided into three main groups (not mutually excluding): clinical or physiological, trigger-related and inflammatory (table 2.3).

### *2.2.2 Children*

D In early childhood (first years of life), the diagnosis of asthma may be difficult to establish. Therefore, during that period, evaluations and guidelines rely on the presence of wheezing, a term that can be used as a surrogate for difficult-to-diagnose asthma, mainly because of difficulty in performing pulmonary function tests[65].

C The first description of asthma phenotypes in childhood was reported in the study of Tuc-son (table 2.4)[66]. Since then, a number of prospective clinical studies (cohorts of children

Table 2.1. Key questions for the diagnostic suspicion of asthma[60,61]

| |
|---|
| Have you ever had "whistling" in the chest? |
| Have you had cough especially at night? |
| Have you had cough, wheezing, breathing difficulty in certain periods of the year or when in contact with animals, plants, tobacco or at the workplace? |
| Have you had cough, "whistling", breathing difficulty after a moderate or intense physical exercise? |
| Have you had colds lasting more than 10 days or "going down into the chest"? |
| Have you used inhaled medications that relieve your symptoms? |
| Do you have any kind of allergy? Do you have any relatives with asthma or allergy? |

Table 2.2. Differential diagnosis of asthma[2,6]

| | ASTHMA | COPD |
|---|---|---|
| Age at onset | Any age | After 40 years of age |
| Smoking | Irrelevant | Always present |
| Atopy | Common | Uncommon |
| Family history | Common | Not assessable |
| Symptom variability | Yes | No |
| Reversibility of obstruction | Significant | Usually less significant |
| Response to glucocorticoids | Very good, almost always | Indeterminate or variable |
| | Other conditions | Typical symptoms |
| Age between 15 and 40 years | • Vocal cord dysfunction<br>• Hyperventilation<br>• Inhaled foreign body<br>• Cystic fibrosis<br>• Bronchiectasis<br>• Congenital heart disease<br>• Pulmonary thromboembolism | • Dyspnea, inspiratory stridor<br>• Fainting, paresthesia<br>• Sudden onset of symptoms<br>• Excessive cough and mucus<br>• Recurrent infections<br>• Heart murmurs<br>• Sudden onset of dyspnea, chest pain |
| Age older than 40 years of age | • Vocal cord dysfunction<br>• Hyperventilation<br>• Bronchiectasis<br>• Parenchymal lung disease<br>• Heart failure<br>• Pulmonary thromboembolism | • Dyspnea, inspiratory stridor<br>• Fainting, paresthesia<br>• Recurrent infections<br>• Exertional dyspnea, non-productive cough<br>• Exertional dyspnea, nighttime symptoms<br>• Sudden onset of dyspnea, chest pain |

Table 2.3. Asthma phenoytpes[62]

| | |
|---|---|
| Clinical or physiological | • Severe asthma.<br>• Asthma with severe exacerbations.<br>• Treatment-refractory asthma, particularly in patient without allergy and corticosteroid-dependent asthma.<br>• Early-onset asthma, in children younger than 12 years old, which is usually allergic.<br>• Late-onset asthma, mostly in women, starts in adulthood and is usually unrelated to allergy.<br>• Asthma with airflow limitation, due to bronchial wall; asthma-COPD overlap syndrome.<br>• Asthma and obesity, with more severe symptoms |
| Trigger-related | • Allergic asthma, due to environmental and occupational allergens.<br>• Asthma induced by non-steroidal anti-inflammatory drugs (NSAIDs).<br>• Asthma induced by menstruation.<br>• Exercise-induced asthma. |
| Inflammatory | • Eosinophilic asthma, is usually allergic, in general with good response to inhaled glucocorticoids.<br>• Neutrophilic asthma, usually occurring in patients with severe disease and severe exacerbations, with poorer response to inhaled glucocorticoids.<br>• Paucigranulocytic asthma. |

D

followed since birth)[67,68] or complex biostatistical studies (cluster of populations with no previous hypothesis)[69] have identified different phenotypes of childhood asthma. However, further studies are needed to establish their clinical value[67,70].

C

Based on the findings from these studies, some tools have been developed to predict the future risk in children with asthma but a few of these instruments have been validated. The best known instrument is the Asthma Predictive Index (table 2.5), which was developed from children included in the Tucson cohort[71]. However, these systems, based on scores obtained from the evaluation of certain factors, have been shown to have modest predictive values and are not sufficiently precise to enable a reliable prognostic assessment[72].

C

## 2.3 Pulmonary function

D

The diagnosis of asthma is established when in a patients with suspected symptoms of disease, a pulmonary function test (preferably spirometry) objectively demonstrates an alteration compatible with asthma (usually a variable obstruction of expiratory flows).

Table 2.4. Traditional phenotypes in wheezing children from the Tucson study based on their long-term time-course[66]

| |
|---|
| 1. Early-onset transient wheezing |
| • Onset within the first year of life with resolution by 3 years of age.<br>• Negative IgE and/or skin tests, with no traits or history of atopy.<br>• Decreased pulmonary function at birth with low values at 16 years of age.<br>• Negative findings in bronchial hyperresponsiveness and variability of peak expiratory flow (PEF) studies at 11 years of age.<br>• Risk factors: maternal smoking during pregnancy, male sex, prematurity, cohabitation with older brothers and/or daycare attendance. |
| 2. Persistent (non-atopic) wheezing |
| • It usually starts before the first year and persists at 6 years of age.<br>• Both sexes affected equally.<br>• Negative IgE and/or skin tests, with no traits or history of atopy.<br>• Normal pulmonary function at birth, although decreased at 6 and 11 years of age.<br>• Bronchial hyperresponsiveness that decreases with age.<br>• Remission normally occurs in adolescence. |
| 3. Late-onset (atopic) wheezing |
| • The first episode occurs after the first year of age; more common in boys.<br>• Increased IgE and/or positive skin tests, atopic traits and family history of atopy.<br>• Normal pulmonary function at birth followed by a decline until 6 years of age; thereafter, pulmonary function stabilizes at below levels of normal.<br>• Bronchial hyperresponsiveness.<br>• Persistence in adolescence. |

Table 2.5. Asthma Predictive Index[71]

| |
|---|
| Previous condition |
| • Infants with 3 or more wheezing episodes per year during the first 3 years of life who meet one major criterion and 2 minor criteria. |
| Major criteria |
| • Medical diagnosis of asthma in one of the parents.<br>• Medical diagnosis of atopic eczema (at 2-3 years of age). |
| Minor criteria |
| • Presence of allergic rhinitis diagnosed by a physician (at 2-3 years of age)<br>• Wheezing not associated with colds<br>• Peripheral blood eosinophilia equal or higher than 4 % |
| Predictive values for asthma diagnosis at any time between 6 and 13 years of age |
| • Positive predictive value 77 %<br>• Negative predictive value 68 % |

### 2.3.1 Adults

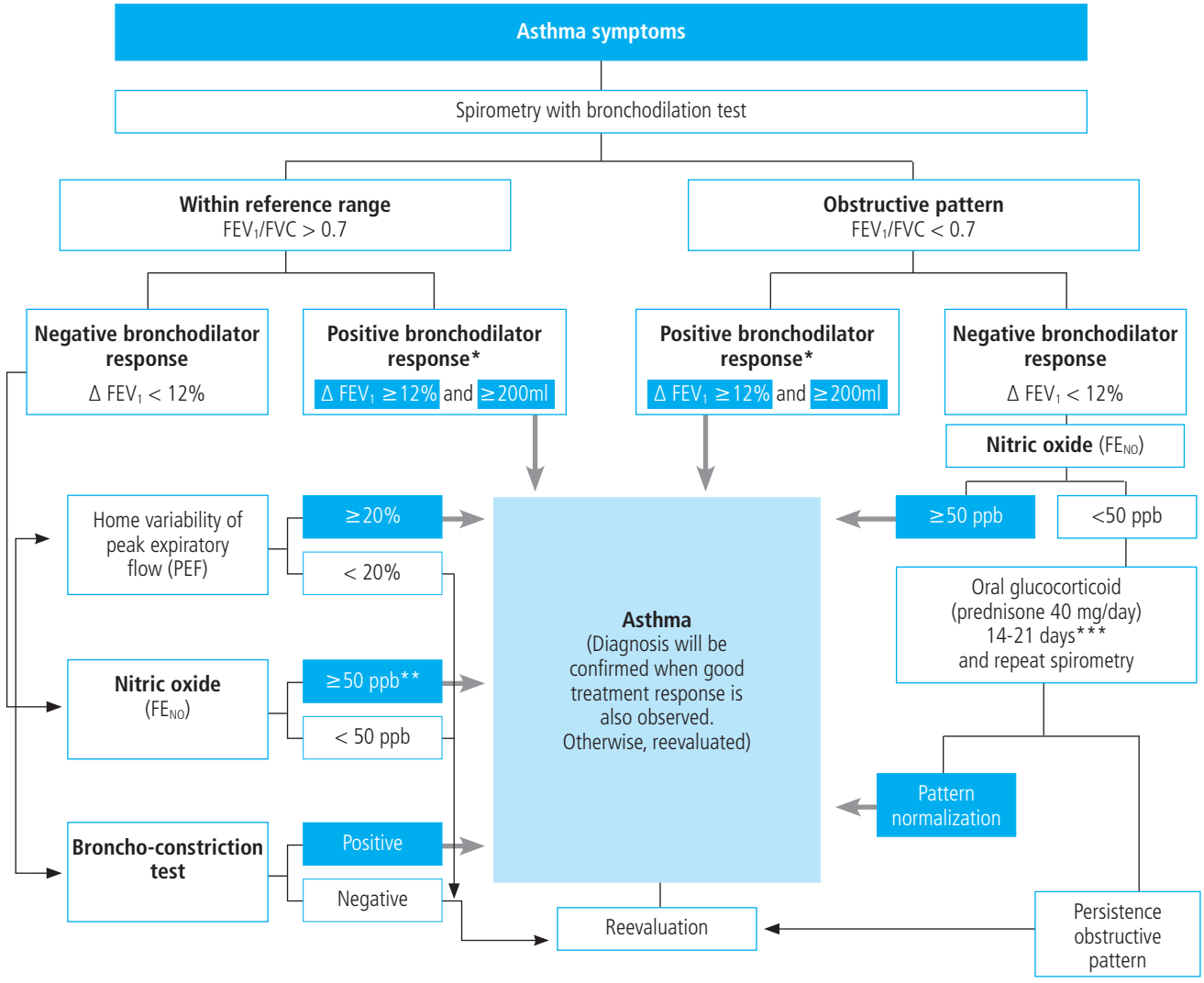
C

The main functional changes occurring in asthma are reversible and variable airflow obstruction, and bronchial hyperresponsiveness.

**Spirometry** is the first-choice diagnostic test, as shown in the algorithm of the diagnostic process (figure 2.1). The main parameters to be determined are forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$). Reference values must be adjusted to the patient's age and ethnic group/race. Airway obstruction is defined as a $FEV_1$/FVC ratio below the lower limit of reference values, which has been arbitrarily set at 0.7[73]. This criterion, however, may lead to an overestimation of airway obstruction in patients of advanced age[73]. A reduced $FEV_1$ value confirms the obstruction, helps to establish its severity and indicates a greater risk of exacerbations[74]. On the other hand, many patients with asthma may show spirometric values close to the reference range or even a non-obstructive (restrictive) pattern due to air trapping.

C

For the **bronchodilation test**, the administration of 4 successive/puffs of 100 µg salbutamol, or its equivalent of terbutaline, using a pressurized inhaler with spacer and repeating spirometry after 15 minutes is recommended. A response is considered to be positive (or significant bronchodilatation) when there is a ≥ 12% and a ≥ 200 ml increase in $FEV_1$ from baseline (table 2.6)[73]. An alternative




*In children, a 12 % increase is sufficient to consider this test as positive, even if < 200 ml. **In case of a negative broncoconstriction test, a diagnosis of eosinophilic bronchitis should be considered. ***Alternatively, inhaled glucocorticoids at very high doses, 1500 – 2000 µg of fluticasone, 3 or 4 times a day for 2-8 weeks may be used.

**Figure 2.1.** Algorithm for asthma diagnosis

C criterion for bronchodilatation is a > 60 l/min or > 20% rise in the peak expiratory flow (PEF)[75]. Reversibility can also be identified as an improvement in $FEV_1$ or PEF after 2 weeks of treatment with systemic glucocorticoids (prednisone 40 mg/day or equivalent) or 2-8 weeks of inhaled glucocorticoids (1500-2000 mg/day of fluticasone or equivalent)[76]. Although reversibility of bronchial obstruction is a typical characteristic of asthma, it is not present in all patients.

C **Variability, or excessive fluctuation of pulmonary function** over time, is essential for the diagnosis and control of asthma. The most widely recommended daily variability index is the PEF amplitude in relation to the averaged mean over at least 1-2 weeks and recorded before medication is given (table 2.6)[77]. A PEF variability greater than 20 % is diagnostic of asthma[78].

C The identification of an excessive bronchodilator response (**bronchial hyperresponsiveness**) may be useful in patients with clinically suspected asthma and normal pulmonary function. Either direct agents, such as methacholine or histamine, or indirect agents, such as monophosphate adenosine, mannitol or hypertonic saline can be used[79]. These latter agents show a better relationship with inflammation and a higher sensitivity to the effect of glucorticoids[80]. Furthermore, mannitol offers the advantage of being administered via a dry powder inhaler[81].

C The analysis of bronchial hyperresponsiveness is carried out in terms of sensitivity or threshold, by determining the dose or concentration leading to a 20% decrease in $FEV_1$ as compared to the post-diluent value[82,83]. Bronchial challenge test has a high sensitivity but a limited specificity[84], thereby being

Table 2.6. Reversibility and daily variability criteria recommended for the diagnosis of asthma

| | |
|---|---|
| Reversibility | Post-Bd $FEV_1$ – pre-Bd $FEV_1 \geq 200$ ml<br>and<br>$\frac{\text{Post-Bd } FEV_1 - \text{pre-Bd } FEV_1}{\text{pre-Bd } FEV_1} \times 100 \geq 12\ \%$ |
| Daily variability | $\frac{\text{Maximum PEF} - \text{minimum PEF}}{\text{Maximum PEF}} \times 100$<br>Variability ≥ 20 % during ≥ 3 days per week, in a 2-week recording |

$FEV_1$: forced expiratory volume in one second; PEF: peak expiratory flow; Bd: broncodilatation.

C more useful for excluding than for confirming the diagnosis of asthma. Bronchial hyperresponsiveness is also present in other diseases, such as allergic rhinitis, COPD, bronchiectasis, cystic fibrosis or heart failure.

C The mannitol test is considered to be positive when a 15% fall in $FEV_1$ from baseline (PD15) occurs or when there is an incremental decrease of $FEV_1$ of ≥ 10% between two consecutive doses[83]. This test is more useful to confirm the diagnosis of asthma (particularly exercise-induced asthma) because its specificity is higher than 9 %, although its sensitivity is 60%.

B The **fractional exhaled nitric oxide ($FE_{NO}$)** is a non-invasive method that measures eosinophilic inflammation in the airways. The measurement procedure has been standardized[85] and the cut-off point has been established at 50 ppb in adults[86]. $FE_{NO}$ has a highly sensitivity and specificity for the diagnosis of asthma in non-smokers not receiving inhaled glucorticoids[87], particularly if associated with a reduced $FEV_1$[88]. However, a normal $FE_{NO}$ value does not exclude the diagnosis of asthma especially in non-atopic subjects[89].

### 2.3.2 Children

C The usefulness of respiratory function tests for the diagnosis of asthma diagnosis in children is lower than in adults, since most children, even those with moderate or severe forms of the disease, have $FEV_1$ values within the reference values[90,91]. These tests may aid in diagnosis which, nevertheless, cannot be excluded if normal results are found. Respiratory function tests do not sufficiently discriminate the severity level[92].

C *Assessment of respiratory function in children capable of performing an effort-dependent maneuver*: from 5-6 years of age onwards, functional diagnosis of asthma in children is similar to that in adults. In the child, the $FEV_1$/FVC ratio is better correlated with the severity of asthma than $FEV_1$[80,93]. Airway obstruction in children is defined as a $FEV_1$/FVC ratio < 80-85%.

C A bronchodilator test is considered positive when the increase of $FEV_1$ from baseline is equal or higher than 12%, although it is possible that an 8% increase from baseline or a 9% increase in relation to the predicted value may define better the bronchodilator response in children[94,95].

C As children can exhale all the air in 2-3 seconds, an expiration lasting this amount of time may be considered valid provided its validity can be confirmed by an expert's visual inspection of the correctness of the maneuver[96]. Less strict reproducibility criteria are also acceptable: 100 ml or 10% of $FEV_1$[97].

C $FEF_{25-75\ \%}$ values do not provide any relevant information and therefore do no contribute to clinical decision-making[98].

International reference values, "All ages equations", which are suitable for all ages, have recently been published.

If diagnosis is uncertain, methacholine and exercise challenge tests may be of special interest in children, since exercise challenge test is relatively easy to perform, reproducible and has a high specificity for diagnosing asthma, although its sensitivity is low[99].

D *Respiratory function in early childhood (preschool children):* reliable forced spirometric tests can be performed in 3-year-old children or older, provided an appropriate methodology is used. Using the right methodology and appropriate reference values (without extrapolating the values from older children) is essential[100,101]. Since these children may occasionally have expiration times lower than 1 second, the most useful value would be $FEV_{0.5}$ rather than $FEV_1$[102]. As for the use of the bronchodilator test at this age, the cut-off point for both $FEV_1$ and $FEV_{0.5}$ or $FEV_{0.75}$ remains to be determined[103].

Other tests that may be useful in the management of preschool children with asthma include forced impulse oscillometry (IOS), the measurement of airway resistance using the interrupter technique (Rint), the tidal flow-volume curve or measurement of airway resistance by plethysmography. Any of these techniques must be adapted to ATS/ERS guidelines on pulmonary function in preschool children[102]. For children under 2 years of age, the rapid thoracoabdominal compression is the most widely used technique.

D To perform reliable pulmonary function tests in children, particularly in those younger than 5-6 years of age, it is essential to have nursing staff specifically trained in these techniques as well as laboratories adapted for children.

D $FE_{NO}$ values also correlate with the degree of bronchial eosinophilic inflammation in children[104]. The assessment of $FE_{NO}$ in young children is not relevant for predicting a diagnosis of asthma at school age[105]. The diagnostic reliability of $FE_{NO}$ in asthma is compromised by the wide confidence intervals of this measurement. Population-based studies[106] have established cut-off values quite similar to those proposed by the ATS[107]: high > 35 ppb in children younger than 12 years (> 50 ppb in older children); low < 20 ppb in children younger than 12 years (25 ppb in older children); intermediate ranges 25-35 in those younger than 12 years (25-50 ppb in older children). The data should be assessed according the objective, that is, whether the purpose is to exclude or to confirm the diagnosis of asthma (table 2.7). At follow-up, it is important to know the best value of the patient since therapeutic decisions should be based on variations regarding this optimum value[108]. Treatment with inhaled glucocorticoids reduces $FE_{NO}$ concentration, so that measurement of $FE_{NO}$ may be a predictor of response[109] and a useful tool to estimate both response and the risk of relapse[110].

C

Table 2.7. General profile for interpreting $FE_{NO}$ according to the presence or absence of symptoms and the purpose of diagnosis or follow-up in children[86]

| | $FE_{NO}$ < 20 ppb | $FE_{NO}$ 20-35 ppb | $FE_{NO}$ > 35 ppb | PURPOSE |
|---|---|---|---|---|
| Symptoms present at ≥ 6 weeks | Eosinophilic inflammation unlikely; consider other diagnosis; unlikely benefit from IGC. | Evaluate clinical context. Monitor $FE_{NO}$ over time | Eosinophilic inflammation present; likely benefit from IGC | DIAGNOSIS |
| In the presence of symptoms# | Possible alternative diagnoses. Unlikely benefit from IGC. | Allergen exposure; inadequate IGC dose; poor adherence; corticosteroid resistance | Allergen exposure; poor technique or adherence; inadequate IGC dose; risk of exacerbation; corticosteroid resistance | MONITORING |
| In the absence of symptoms | Adequate IGC dose; good adherence; tapering of IGC dose | Adequate IGC dose; good adherence; monitor $FE_{NO}$ | Withdrawal or tapering of IGC dose might trigger a relapse; poor adherence and technique | |

$FE_{NO}$: fractional exhaled nitric oxide. IGC: inhaled glucocorticoids
#Cough and/or wheezing and/or dyspnea

C Although potentially useful as guidance, the available evidence does not confirm its reliability to evaluate adherence to IGC treatment.

No benefits of $FE_{NO}$ on follow-up and treatment adjustment have been demonstrated, albeit studies evaluating these aspects have several limitations.

C $FE_{NO}$ can be determined in young children using by the multiple breath-exhalation technique, with reference values having being established for the age between 1 and 5 years[111].

## 2.4 Allergy evaluation

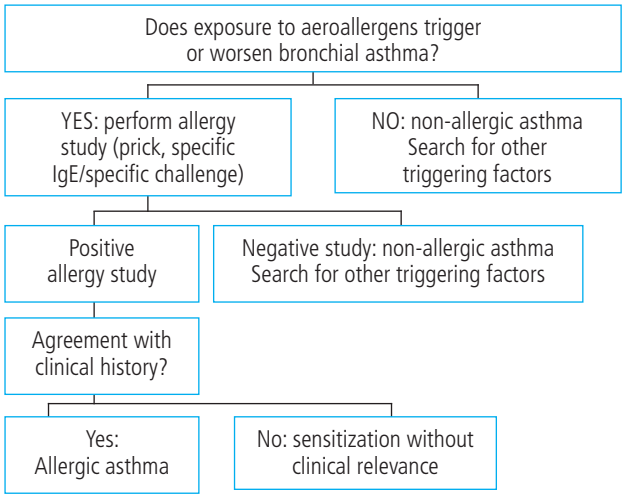
C The aim of allergy testing is to determine the presence of a potential sensitization to aeroallergens that may influence the development of the allergic asthma phenotype or to trigger exacerbations. These tests can be performed in all patients with asthma regardless of their age. History-taking helps to evaluate personal and family history of atopy (rhinoconjunctivitis, eczema, food allergy) and the relationship between symptoms and allergen exposure (indoor, outdoor and occupational allergens). To make a diagnosis of allergic asthma, in addition to sensitization to inhaled allergens, it is important to assess the clinical relevance of the results obtained[112] (figure 2.2).

C The **prick test** is the first-choice method because of its high sensitivity, low cost and immediately available results. Best results are obtained when standardized extracts are used (table 2.8), the variables affecting the results (such as drugs or dermographism) are known and the test can be interpreted by skilled personnel (cross-reactivity, panallergens)[113]. Measurement of **specific serum IgE** to complete allergens, although having the same significance as the *prick test*, is less sensitive and more expensive[114]. In most patients, the use of the *prick test* may be sufficient for diagnosis, although in younger children a greater diagnostic accuracy is obtained when combining both techniques[115].

B

C The specific IgE against allergenic components (either purified or recombinant) can be determined by **molecular diagnosis**. This is a second-level procedure that enables to evaluate a true primary sensitization (with a selective reactivity against species-specific allergen components) in polysensitized patients. It can also determine whether a positive prick test result is due to the recognition of cross-reactivity markers[116]. Also, it may be a supporting tool for improving the indication and selection of allergens for specific immunotherapy[117].

C The **specific bronchial challenge testing** with the suspected aeroallergen may be useful when a discrepancy exists between the clinical history and the results of sensitization, as well as in occupational asthma[118]. The procedure is not routinely recommended and considerable experience is required for performing bronchial provocation test.




To establish a diagnosis of allergic asthma an agreement between clinical history and results of diagnostic tests is required

Figure 2.2. Allergy studies

Table 2.8. Standard battery* of aeroallergens used in intraepidermal skin tests or prick test[113]

| | |
|---|---|
| Mites | *Dermatophagoides pteronyssinus*<br>*Dermatophagoides farinae*<br>*Lepidoglyphus destructor* |
| Dander | Cat, dog |
| Cockroaches | *Blatella orientalis*<br>*Blatella germanica* |
| Pollens | Cypress, plane tree, olive, grass mixture, *Artemisia, Parietaria, Salsola* |
| Molds | *Alternaria, Cladosporium, Aspergillus, Penicillium* |

*Other allergens suspected from the clinical history or geographic prevalence can be added.

## 2.5 Classification of asthma in adults

### 2.5.1 Severity

Asthma has usually been classified according to its severity, although both the definition and assessment of severity has changed with time[2,6,119]. Severity is an intrinsic property of asthma that reflects the intensity of its pathophysiological abnormalities[120]. It should be kept in mind that asthma severity involves both the intensity of the process and its response to treatment[121]. Severity is usually evaluated while the patient is being treated and it is classified according to the need for maintenance therapy to achieve control of symptoms and exacerbations[122]. It is traditionally divided into four categories: intermittent, mild persistent, moderate persistent and severe persistent[2].

Severity is not a constant characteristic of asthma and needs to be periodically reassessed since may vary with time (months or years). In patients with controlled asthma, severity is evaluated retrospectively according to the therapeutic step they have been assigned to, and hence to the amount of medication needed for disease control[122,123]; treatment may be stepped down if required to define the minimum amounts of medication[6]. Severity may be established in a patient not receiving maintenance therapy but this circumstance is infrequent. Table 2.9 shows the various levels for adult asthma when no maintenance treatment is being given. The severity of asthma is determined according to the most affected parameter.

### 2.5.2 Control

Asthma control is the extent to which disease manifestations can be either absent or maximally reduced by therapeutic interventions, and treatment goals are met[122,123]. Control largely reflects the adequacy of asthma management[124] (figure 2.3). However, another factor that should considered is treatment response (a feature that differs from patient to patient), along with the ease and speed in achieving disease control[121]. While control is a broad-meaning term and can encompass all the clinical and pathophysiological aspects of asthma, from a practical viewpoint, it includes the clinical features of the disease (symptoms and exacerbations) and pulmonary function tests.

Asthma has been arbitrarily classified according to the degree of disease control in: *well-controlled asthma, partially controlled asthma* and *poorly controlled asthma*, based on the criteria shown in table 2.10[2,125]. Some asthma patients may show a good control of both symptoms and pulmonary function, while simultaneously experiencing exacerbations, whereas some other patients have daily symptoms and very few exacerbations. These factors should be taken into account when evaluating asthma control and it is important to explicitly report which is the current status of asthma control and the risk for exacerbations (table 2.11).

Thus, when trying to minimize the clinical expression of asthma two major aspects should be borne in mind[2,119]: on the one hand, the day-to-day disease manifestations (*current control*) and, on the other side, its future consequences (*future risk*), as shown in figure 2.4.

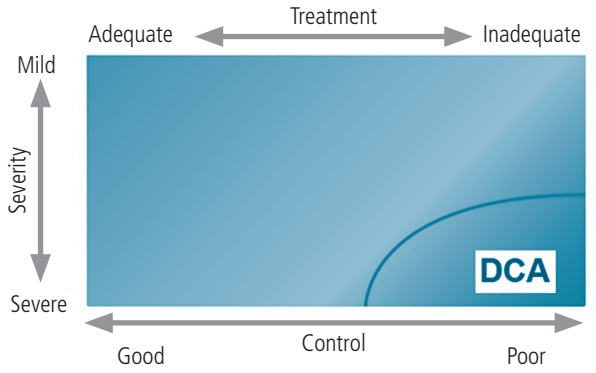
Within the *current control* domain, control would be defined by the ability to prevent the presence of daytime and nighttime symptoms and the frequent use of rescue medication for symptomatic relieve; maintenance of pulmonary function within or close to normal limits; the absence of limitations of

Table 2.9. Classification of asthma severity in adults (before treatment)

| | Intermittent | Mild persistent | Moderate persistent | Severe persistent |
|---|---|---|---|---|
| Daytime symptoms | No (twice a week or less) | More than twice a week | Daily symptoms | Continuous symptoms (several times a day) |
| Reliever medication (short-acting β2-agonist) | No (twice a week or less) | More than twice a week but not daily | Everyday | Several times a day |
| Nighttime symptoms | No more than twice a month | More than twice a month | More than once a week | Frequent |
| Affect on limitation of activities | No affect | Minor affect | Moderate affect | Major affect |
| Lung function ($FEV_1$ o PEF) % predicted | > 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 one second; PEF: peak expiratory flow.

D daily living activities, including family, social, work or school activities, and physical exercise; and finally, the fulfillment of expectations of both patients and their families regarding the quality of care received.




The level of control largely reflects the appropriateness of treatment. Some patients suffer from difficult-to-control asthma (DCA).

**Figure 2.3.** Relationship between severity and control of asthma[124].

As for the *future risk* domain, control includes the absence of exacerbations especially the avoidance of visits to emergency departments and hospitalizations; the prevention of an excessive loss of pulmonary function and the development of a fixed airway obstruction or, in the case of children, an anomalous lung development; and finally, the prescription of an optimal treatment with minimum or no adverse effects. D

In the treatment of asthma, the concepts of severity and control are used as follows:

- ***Evaluation of severity before starting treatment***. At disease onset, if the patient is not on maintenance therapy, asthma severity should be evaluated (see above for classification) and used as a guide to selecting drug therapy and therapeutic decision-making. Once a patient is being treated, severity should be assessed on the basis of the least amount of medication required to maintain control[2,6,122]. Consequently, patients whose asthma is well-controlled with step 1 treatment would have intermittent asthma; with step 2 treatment, mild persistent asthma; with steps 3 and 4 treatments, persistent moderate asthma; and with steps 5 and 6 treatments, persistent severe asthma (table 2.12). D

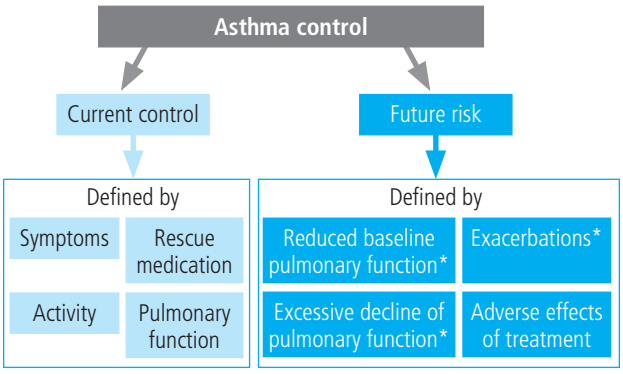
**Table 2.10.** Classification of asthma control in adults

| | WELL controlled (all of the following) | PARTIALLY controlled (any measure in any week) | POORLY controlled |
|---|---|---|---|
| Daytime symptoms | None or ≤ twice weekly | > twice weekly | If ≥ 3 characteristics of partially controlled asthma |
| Limitation of activities | None | Any | |
| Nighttime symptoms/awakenings | None | Any | |
| Need for reliever (rescue) medication (SABA) | None or ≤ twice weekly | > twice weekly | |
| Lung function<br>- $FEV_1$<br>- PEF | > 80 % predicted<br>> 80 % personal best value | < 80 % predicted<br>< 80 % personal best value | |
| Exacerbations | None | ≥ 1/year | ≥ 1 in any week |

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; $FEV_1$: forced expiratory volume in one second; PEF: peak expiratory flow; SABA: short-acting $\beta_2$-agonist.

**Table 2.11.** Major risk factors for exacerbations[6]

| |
|---|
| Poor current control. |
| At least one exacerbation in the previous year. |
| Prior admission to the ICU or intubation due to asthma management. |
| Peripheral blood eosinophilia. |
| Excessive use of SABA (more than 200 doses in a month). |
| Undertreatment with IGC (not prescribed, poor adherence, poor inhalation technique). |
| Low baseline $FEV_1$. |
| Psychosocial problems. |
| Exposure to tobacco smoke or work-related substances. |
| Comorbidities: obesity, sleep apnea-hypopnea syndrome, rhinosinusitis, food allergy. |
| Pregnancy. |




*Evaluate risk factors.

**Figure 2.4.** Domains that make up and determine the degree of control.

**Table 2.12.** Classification of asthma severity when it is well-controlled with treatment (stratified by steps)

| Severity | Intermittent | Persistent | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| Minimal treatment requirements to maintain control | Step 1 | Step 2 | Step 3 or Step 4 | Step 5 or Step 6 |

D

- ***Evaluation of control for treatment adjustment.*** Once asthma treatment is initiated, the clinical and therapeutic management should be aimed at achieving and maintaining disease control (including symptoms, exacerbations and pulmonary function). Therefore, the degree of control will guide the decisions on maintenance therapy and dose adjustment, according to the therapeutic steps described in the corresponding section.

## 2.6 Methods for measuring asthma control

D

According to the definition of 'control' a number of procedures should be used for its evaluation[126]. The essential tool for assessing asthma control is the regular follow-up medical visit. At each visit, symptoms will be recorded together with signs of disease activity, baseline pulmonary function and any excessive functional decline (quantified by $FEV_1$), presence of exacerbations and visits to the emergency department. Other aspects that should be assessed are the impact of the disease on the patient's daily life and activities, the presence of possible adverse events and, finally and most importantly, the adherence to treatment, including a reminder of the self-management plan and actions to be taken in case of disease decompensation, and trying to reinforce the patient-healthcare professional relationship at each visit.

C

With a view to facilitating and standardizing the evaluation of the control of asthma, different simple and easy to be completed by the patient have been developed. The Asthma Control Test (ACT)[127,128] and the Asthma Control Questionnaire (ACQ)[129] have been validated and culturally adapted for use in Spain. Validation of the ACT questionnaire is more detailed for its use in clinical practice with well-defined cut-off points, so that a score equal to or greater than 20 is highly consistent with well-controlled asthma, between 19 and 16 with partially controlled/not well-controlled asthma, and equal to or lower than 15 with poorly controlled asthma[106,107]. The minimum clinically relevant difference is 3 points[130]. The initially established cut-off points for the ACQ are $\leq 0.75$ for well-controlled asthma and $\geq 1.5$ for not well-controlled asthma[131]. However, the Spanish version of the ACQ questionnaire has been recently validated with new cut-off values[132]: well-controlled asthma $< 0.5$, partially controlled asthma between 0.5 and 0.99, and uncontrolled asthma $\geq 1$. Nevertheless, the reliability of both questionnaires to detect poorly controlled asthma is low[133], and for this reason should not be used as the only tools to evaluate asthma control.

C

There are specific tools validated and adapted to the Spanish language to assess the quality of life in both adults[134] and children with asthma[135]. At present, however, their use is considered more appropriate for research then in routine clinical practice. Furthermore, their completion is usually time-consuming, although short versions are available[136]. For both reasons, their use in daily practice is not recommended[119].

D

Forced spirometry is the second instrument used to evaluate control of the disease. Measurement of $FEV_1$ allows for a more precise adjustment of the 'current control' domain[127,128], and also provides data to assess the risk of exacerbations[137]. Therefore, baseline $FEV_1$ should be considered for evaluating both 'current control of asthma' and future risk of exacerbations, particularly when $FEV_1$ is $< 60\%$[138]. It is a good measure to quantify the non-reversible progressive loss of pulmonary function, bearing in mind that the mean decrease in $FEV_1$ for non-smoking, healthy adults is 15-20 ml/year[139].

Other risks factors for an excessive decline of $FEV_1$ are as follows: lack of treatment with inhaled glucocorticoids[140], exposure to tobacco smoke[141] or occupational substances[142], chronic mucus hypersecretion[141] and sputum or peripheral blood eosinophilia[143].

The usefulness of the so-called non-invasive markers of inflammatory activity for measuring asthma control is still controversial and continues to be the subject of intense research especially the measurement of $FE_{NO}$. Some studies, including a meta-analysis, have reported that measurement of $FE_{NO}$ does not add any benefits to the traditional follow-up defined in the guidelines[144,145]. However, the use of these markers may be of value in some groups of patients[86]. Sputum cytology may play a role in assessing control in adult patients with severe asthma and multiple exacerbations, but data of a meta-analysis concludes that there is insufficient evidence to advocate the routine use of sputum analysis in everyday clinical practice[144]. Blood[146] or sputum eosinophilia[147] is a risk factor for exacerbations.

## 2.7 Classification of asthma in children

### 2.7.1 Severity

D Traditional classifications based on adult asthma are difficult to apply to children, particularly to the younger ones. Childhood asthma is characteristically episodic (with occasional occurrence of serious attacks), although with few symptoms between exacerbations. The level of severity depends on the symptoms (number of attacks and between-attack status: mainly exercise tolerance and nighttime symptoms), the need for a rescue bronchodilator and the values of respiratory function tests. In small children in whom lung function testing is not feasible, severity is only classified according to symptomatology.

D Two major patterns have been defined in children: episodic asthma and persistent asthma. Episodic asthma may be either occasional or frequent, depending on the number of exacerbations. Persistent asthma in childhood cannot be regarded as mild, but rather as moderate or severe (table 2.13)[148].

D Childhood asthma varies substantially with time, even over a single year, which makes its classification difficult. Most young children experience asthma symptoms only during viral infections; they may experience, therefore, moderate or severe asthma in the winter and remain asymptomatic in spring and summer seasons. In other children, such as those allergic to pollens, asthma may occur only in spring (more often in continental climate regions). In order to typify correctly a case of asthma in children, it is necessary to specify, in addition to severity, the triggering factors in the individual patient and de degree of control of asthma.

D Classification should be established when the patient is untreated. Once asthma control is achieved, the medication needed for the child to remain asymptomatic is a better indicator of the severity level than asthma symptoms.

### 2.7.2 Control

C As in adults, asthma control is defined by the extent to which clinical manifestations have declined or disappeared, with or without treatment[149]. It also includes the two components: current symptom control and future risk[6,119].

C The assessment of *current symptom control* in children may be difficult, particularly in the younger ones, since information is obtained from their parents and/or carers. An evaluation should be made of the frequency of both diurnal and nocturnal symptoms, the need for rescue medication and any limitations to physical activities.

C *Future risk* assesses the presence of risk factors for exacerbations (table 2.11), for developing a fixed airflow limitation (undertreatment with IGC, environmental exposure to tobacco smoke, contaminants, allergens, etc., low initial $FEV_1$, severe asthma and having required several hospitalizations), and for suffering medication-related side effects (frequent cycles of oral GC, high doses of IGC)[6].

C To facilitate symptom evaluation, a few specific questionnaires have been designed, some of which have been validated in Spanish. One of these questionnaires is the CAN questionnaire (*Control de Asma en Niños*, Asthma Control Questionnaire in Children) with a version for 9-14 year-old children and another version for parents (2-8 year-old children). This instrument evaluates nine questions about clinical manifestations within the last 4 weeks and is scored between 0 (good control) and 36 (poor control). A patient is considered to be poorly controlled when scores are equal to or higher than 8[150] (table 2.14). Also available is the Childhood Asthma Control Test (C-ACT) whose original version[151] has been recently validated in Spanish[152,153].

C In addition to the control of clinical symptoms and pulmonary function, measurement of $FE_{NO}$ has been advocated as an approach to assess the control of inflammation. Although potentially useful in some patients, this procedure does not seem to add any relevant benefits to the aforementioned follow-up and treatment strategies.

Table 2.13. Classification of asthma severity in children

| | Occasional episodic | Frequent episodic | Moderate persistent | Severe persistent |
|---|---|---|---|---|
| Episodes | - Lasting a few hours or days < one every 10-12/weeks<br>- Maximum 4-5 attacks/year | - < one every 5-6 weeks<br>- Maximum 6-8 attacks/year | > one every 4-5 weeks | Frequent |
| Symptoms between attacks | Asymptomatic, with good tolerance to exercise | Asymptomatic | Mild | Frequent |
| Wheezing | – | On intense exercise | On moderate exercise | On minimum exercise |
| Nighttime symptoms | – | – | ≤ 2 nights a week | > 2 to nights a week |
| Reliever medication (SABA) | – | – | ≤ 3 days a week | 3 days a week |
| Lung function<br>- $FEV_1$<br>- PEF variability | <br>> 80 %<br>< 20 % | <br>> 80 %<br>< 20 % | <br>> 70 % - < 80 %<br>> 20 % - < 30 % | <br>< 70 %<br>> 30 % |

$FEV_1$: forced expiratory volume in one second; PEF: peak expiratory flow. SABA: short-acting β2-agonist.

On the basis of current control and future risk, asthma may be classified as well-controlled, partially controlled or uncontrolled. Criteria established to define control vary between guidelines; those proposed by pediatric international consensus are shown in table 2.15[154].

Table 2.14. Asthma Control Questionnaire in Children[100]

| **1. In the last 4 weeks, how often have you coughed during the day without having a cold?** | **4. In the last 4 weeks, how often have you had wheezing at night?** | **7. When the child exercises (plays, runs, etc.) or bursts out laughing, does he/she coughs or wheezes?** |
|---|---|---|
| 4. More than once a day | 4. More than once a night | 4. Always |
| 3. Once a day | 3. Once a night | 3. Almost always |
| 2. 3 to 6 times a week | 2. 3 to 6 times a week | 2. Sometimes |
| 1. Once or twice a week | 1. Once or twice a week | 1. Almost never |
| 0. Never | 0. Never | 0. Never |
| **2. In the last 4 weeks, how often have you coughed at night without having a cold?** | **5. In the last 4 weeks, how often have you had breathing difficulty during the day?** | **8. In the last 4 weeks, how many times has he/she had to visit the emergency department because of his/her asthma?** |
| 4. More than once a night | 4. More than once a day | 4. More than 3 times |
| 3. Once a night | 3. Once a day | 3. 3 times |
| 2. 3 to 6 times a week | 2. 3 to 6 times a week | 2. Twice |
| 1. Once or twice a week | 1. Once or twice a week | 1. Once |
| 0. Never | 0. Never | 0. Never |
| **3. In the last 4 weeks, how often have had wheezing/whistling sounds in your chest during the day?** | **6. In the last 4 weeks, how often have you had breathing difficulty during the night?** | **9. In the last 4 weeks, how many times has the child been admitted to hospital because of her/his asthma?** |
| 4. More than once a day | 4. More than once a night | 4. More than 3 times |
| 3. Once a day | 3. Once a night | 3. 3 times |
| 2. 3 to 6 times a week | 2. 3 to 6 times a week | 2. Twice |
| 1. Once or twice a week | 1. Once or twice a week | 1. Once |
| 0. Never | 0. Never | 0. Never |

Table 2.15. Classification of asthma control in children

| | | Level of control | | | |
|---|---|---|---|---|---|
| | Component | Complete | Good | Partial | Poor |
| Disability | Daytime symptoms | None | ≤ 2/week | > 2/week | Continuous |
| | Nighttime symptoms | None | ≤ 1/week | > 1/week | Weekly |
| | Need for relieving medication | None | ≤ 2/week | > 2/week | Daily use |
| | Limitation of activities | None | None | Some | Important |
| | Pulmonary function: $FEV_1$, PEF (predicted or personal best value) | > 80 % | ≥ 80 % | 60-80 % | < 60 % |
| Risk | Exacerbations (per year) | 0 | 1 | 2 | > 2 |
| | Side effects of medication | None | Variable | Variable | Variable |

$FEV_1$: forced expiratory volume one second; PEF: peak expiratory flow.

## RECOMMENDATIONS

| | | |
|---|---|---|
| 2.1. | Key symptoms for the suspicion of asthma are wheezing, dyspnea (or breathing difficulty), cough and chest tightness of varying severity and frequency of presentation. | R2 |
| 2.2. | Spirometry is recommended as an objective measurement of functional impairment to establish the diagnosis of asthma in adults and (cooperative) children. | R2 |
| 2.3. | Forced spirometric values within the reference range and negative results of a bronchodilator test do not exclude the diagnosis of asthma. | R2 |
| 2.4. | Periodic spirometry tests (at least once a year) are recommended for children with asthma requiring continuous treatment. | R2 |
| 2.5. | Asthma diagnosis should be considered in case of a daily PEF **variability** exceeding 20% or an increased in $\mathbf{FE_{NO}}$ in glucocorticoid naïve patients, particularly if associated with a reduced $FEV_1$. | R2 |
| 2.6. | When spirometric results are inconclusive regarding asthma diagnosis, a non-specific bronchial challenge test is recommended. | R2 |
| 2.7. | Assessment of the allergic component is particularly indicated when aeroallergens are suspected to be involved in the development of asthma or asthma exacerbations, or when other associated atopic diseases are present. | R2 |
| 2.8. | The diagnosis of allergic asthma will be based on the agreement between the patient's clinical history and the results of diagnostic studies. | R2 |
| 2.9. | The severity of asthma will be established according to the minimum maintenance therapy needed to achieve control. In untreated patients, the severity of asthma should be established at the beginning, with further re-evaluations once control is attained. | R2 |
| 2.10. | Asthma control should be periodically evaluated, and treatment should be adjusted in order to achieve and maintain control. The risk of exacerbation should be specifically assessed. | R2 |
| 2.11. | Asthma control includes two major components that must be addressed: current control and future risk. | R2 |
| 2.12. | It is convenient to determine the degree of asthma control by regular follow-up visits in which at least the following information should be obtained: detailed and specific anamnesis, complete physical examination and forced spirometry. | R2 |
| 2.13. | When assessing the degree of asthma control, the use of validated asthma symptoms questionnaires (preferable ACT) as a complement to anamnesis should be recommended. | R2 |