

Referral criteria for asthma: Consensus document

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Abstract

Asthma is one of the most prevalent chronic diseases in Spain. Current treatments ensure that the disease is controlled in most cases. However, disease is often uncontrolled in daily clinical practice, mainly owing to underdiagnosis, loss to follow-up, and poor adherence to therapy. In order to improve this situation, we must coordinate all those health professionals who intervene in patient care. Therefore, the Spanish Society of Allergology and Clinical Immunology (SEAIC), the Spanish Society of Primary Care Physicians (SEMERGEN), the Spanish Society of Family and Community Medicine (semFYC), the Spanish Society of General and Family Physicians (SEMG), and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) have drawn up a consensus document in which they establish criteria for referral and guidelines for the diagnosis, control, and follow-up of patients with asthma. The document aims to facilitate continuing and improved care in this area.

Key words: Asthma. Referral. Specialized care. Primary care. Follow-up. Continuing care.

Resumen

El asma es una de las enfermedades crónicas más prevalentes en España. Los tratamientos disponibles permitirían tener controlados a la mayoría de los pacientes; aunque, en la práctica diaria, no se alcanza en muchos casos debido, fundamentalmente, al infradiagnóstico, pérdida de seguimiento y escasa adhesión terapéutica. Para mejorar esta situación es fundamental la coordinación de todos los profesionales que intervienen en la atención del paciente asmático. La Sociedad Española de Alergología e Inmunología Clínica (SEAIC), la Sociedad Española de Médicos de Atención Primaria (SEMERGEN), la Sociedad Española de Medicina Familiar y Comunitaria (semFYC), la Sociedad Española de Médicos Generales y de Familia (SEMG) y la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) han consensuado un documento donde se establecen criterios de derivación y pautas de actuación en el diagnóstico, control y seguimiento del paciente asmático que faciliten la continuidad asistencial y una mejor atención en cada ámbito

Palabras clave: Asma. Derivación. Atención especializada. Atención primaria. Seguimiento. Continuidad asistencial.

Introduction

Asthma is one of the most prevalent chronic diseases in Spain, affecting more than 10% of children and more than 5% of adults. Current treatments make it possible to control the disease in most patients, with no significant alterations in daily activity. However, control is not usually achieved, owing to factors such as lack of diagnosis and follow-up and/or lack of adherence.

Asthma patients are seen in primary care and in specialized care, depending on the severity of the disease, the patient's individual circumstances, and the characteristics of the disease itself. In order to improve this situation, it is necessary to coordinate the health professionals involved in the follow-up of asthma patients and to accurately clarify the criteria for referral so that we can provide genuinely continuous and improved care in all areas in order to ensure optimal disease control. With this objective in mind, we have prepared this consensus document, which sets out the criteria for referral among the various professionals involved in the care of patients with asthma.

1. Initial primary care diagnostic work-up when asthma is suspected

When faced with a patient who attends the primary care clinic with symptoms compatible with asthma (cough, dyspnea, wheezing, and chest tightness) and no previous diagnosis, we recommend performing a systematic work-up. After taking a detailed clinical history, every attempt should be made to identify the characteristics that define the disease (bronchial obstruction, reversibility, bronchial hyperresponsiveness, variability) using the means available at the health center, namely, spirometry with bronchodilation or determination of variability in peak expiratory flow (PEF). If the tests necessary to make a definitive diagnosis are not available at the health center or if the health professional does not have the appropriate training to make a diagnosis, then the patient must be referred to specialized care in order to confirm the diagnosis.

We must also take into consideration the patient's symptoms during the visit and follow the steps set out in Figure 1.

The definitive diagnosis cannot be made until an effective response to treatment is observed (usually inhaled corticosteroids with[out] long-acting β_2 -agonists [LABA]).

Additional tests

The additional tests applied include determination of lung function and measurement of the degree of inflammation and atopy.

Lung function tests

All patients with a clinical suspicion of asthma should undergo spirometry and bronchodilator testing, although a normal result in spirometry does not rule out the diagnosis. In primary care, spirometry confirms obstruction in only 16%-39% of patients with intermittent symptoms [1-4].

In adults, a positive response in spirometry with bronchodilation testing is defined as an increase in forced expiratory volume in the first second (FEV_1) $\geq 12\%$ and ≥ 200 mL, with respect to baseline.

If spirometry is not conclusive, daily variability in PEF can be evaluated by taking measurements in the morning and in the afternoon for 2 weeks. If the daily variability is $>20\%$ on ≥ 3 days of a single week, then the diagnosis of asthma is highly likely, although a negative result does not rule it out.

If the results of the tests are negative, then we can measure bronchial hyperresponsiveness to bronchoconstrictors such as methacholine. Alternatively, we can measure the response to osmotic stimuli such as inhalation of mannitol or hypertonic saline, or to bronchial provocation tests with allergens or occupational agents.

Measurement of inflammation and atopy

The fraction of exhaled nitric oxide (FeNO) is a noninvasive manner of evaluating eosinophilic inflammation of the airways. A value of ≥ 40 -50 ppb may be useful for confirming a diagnosis of asthma. However, a normal value does not rule out the diagnosis, especially in nonatopic persons.

An increased blood eosinophil count has very little predictive value, and a consensus has been reached on a threshold value of $300/\mu\text{L}$. However, the eosinophil count is recommended for the diagnosis of patients with asthma and is useful in phenotyping, especially in patients with severe disease.

2. Treatment of asthma

The objective of treatment is to achieve early disease control, in addition to preventing exacerbations and reducing mortality. Treatment should be intensified or reduced depending on the patient's clinical situation. Therapy should be planned after taking into account not

only pharmacological treatment, but also other measures such as education, control of the environment, the possibility of allergen-specific immunotherapy, and control of comorbid conditions and risk factors. Adherence and inhalation technique should also be evaluated [1,5,6]

The basic pillars underlying decisions on maintenance treatment and dose adjustment are severity and degree of control, according to the recommendations of the Spanish Guidelines on Asthma Management (Guía Española para el Manejo del Asma [GEMA]) [7]

Inhaled corticosteroids alone or in combination with LABAs are the most effective maintenance treatment for persistent asthma, since they control symptoms and reduce the risk of exacerbations [8]

Cases of severe uncontrolled asthma can be addressed using other approaches, which should be evaluated in specialized care. These include the following:

- *Biological treatments* with anti-IgE monoclonal antibodies (omalizumab), anti-IL-5 monoclonal antibodies (mepolizumab, reslizumab), or anti-IL-5 receptor antibodies (benralizumab).
- *Macrolides*. Exacerbations improve after long-term azithromycin.[9,10] Macrolides should be restricted and tailored owing to their potential adverse effects.
- *Bronchial thermoplasty*. This bronchoscopic procedure should be carried out in experienced centers. Bronchial thermoplasty is currently indicated in very specific and limited cases of severe uncontrolled asthma with chronic airflow limitation (FEV₁ 50-80%) and no bronchial hypersecretion.

3. Evaluation of asthma control

Control of asthma should be evaluated both in primary care and in specialized care.

Control is a situation in which the manifestations of asthma are absent or reduced as much as possible by therapy, thus indicating—to a large extent—that therapy is appropriate [7,11]

Control of asthma is evaluated in 2 domains: current control and future risk.

Current control is defined by the following:

- The ability to prevent daytime and nighttime symptoms.
- Infrequent use of rescue medication.
- Maintenance of normal lung function.
- Absence of limitations in activities of daily living (occupational, physical, and social).

Control of future risk includes prevention of the following:

- Exacerbations.
- Diminished baseline lung function or considerably marked decline therein.
- Adverse effects of treatment.

Evaluation of control should include clinical control (presence of symptoms, presence of exacerbations, effect of the disease on daily life, need for rescue medication, degree of adherence to treatment, comorbidities, and adverse effects) and lung function (Table 1).

Methods used to evaluate asthma control

- Questionnaires to objectively evaluate the degree of disease control include the *Global Initiative for Asthma* (GINA),[5] the Asthma Control Test (ACT) [12,13], and the Asthma Control Questionnaire (ACQ) [14,15]. The evidence suggests that the use of validated questionnaires, particularly the ACT, to control the symptoms of asthma could prove beneficial in the long term [16]. We recommend the use of these questionnaires to reduce clinical variability in the interpretation of symptoms and to facilitate referral of patients with uncontrolled asthma to specialist care.
- Measurement of FEV₁ makes it possible to evaluate the risk of exacerbations [17].

Patients with poorly controlled disease

In the case of a patient with poor control of symptoms and/or exacerbations despite treatment, we recommend the following:

- Evaluation of the degree of adherence and verification of the inhalation technique using validated questionnaires such as the Test of Adherence to Inhalers [18]. Poor inhaler technique [19] and poor adherence [20] are the most common causes of failure to achieve good control of asthma.
- Confirmation of the diagnosis of asthma: identification of the variability in airflow and consideration of other diseases such as upper airway dysfunction, asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS), and bronchiectasis [21].
- Identification of triggers such as continuous environmental exposure to toxins, smoking, electronic cigarettes, heat not burn cigarettes (IQOS), marijuana, cocaine, exposure to allergens, exposure to occupational allergens, and exposure to infectious pathogens. The patient should be asked about ingestion of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) during the hours immediately preceding the attack.
- Identification and treatment of comorbid conditions (rhinosinusitis, nasal polyposis,

gastroesophageal reflux disease, sleep apnea-hypopnea syndrome, obesity), which are often associated with poor control of asthma [22,23].

- Possibility of stepping up treatment or evaluating alternative treatments.
- Referral of the patient to specialized care if asthma remains uncontrolled or in cases of severe asthma.

4. Follow-up

Table 2 shows the steps recommended for follow-up of the patient with asthma. Patients should be evaluated both in primary care and in specialized care (depending on the availability of additional tests).

The risk factors for exacerbation are as follows:

- Poor current control
- Overuse of reliever medication
- Psychological or socioeconomic problems
- Allergens, including food allergens
- High FeNO
- Previous intubation or admission to the intensive care unit
- ≥ 1 severe exacerbation in the previous year

Low FEV₁ *The risk factors for limitation to airflow are as follows:*

- Undertreatment with inhaled corticosteroids
- Exposure to tobacco smoke, and chemical irritants, occupational exposure
- Peripheral blood eosinophilia
- Low FEV₁ Our recommendation is that once asthma has been diagnosed, follow-up should involve symptom control (targeted questions and/or ACT) and measurement of lung function (spirometry and/or PEF) every 3 months until control is achieved. After 3 months with controlled disease, the patient should be re-evaluated in order to decide whether it is appropriate to go down 1 therapy step. Once the minimum dose able to control the disease is set, the patient should undergo check-ups every 6-12 months (Figure 2).

Severe asthma should be managed in specialized care, although this does not prevent the patient from attending check-ups in primary care in order to reinforce adherence and review the inhalation technique.

5. Criteria for referral from primary care to specialized care

Confirmation of the diagnosis of asthma

Referral to specialized care is recommended in the following cases:

- a) When spirometry with bronchodilation testing cannot be performed in primary care with the necessary standards of quality.
- b) When a diagnosis of asthma cannot be confirmed based on spirometry or variability in PEF.
- c) In order to confirm the presence of bronchial hyperresponsiveness using bronchoconstriction tests or bronchial inflammation tests (measured as FeNO), if it has not been possible to make a diagnosis with the previous tests.

Study of comorbidities when this is not possible in primary care

Table 3 shows the main comorbid conditions that require study, the necessary diagnostic tests, and how these are managed.

Severe asthma and uncontrolled asthma

Severe asthma is that which requires multiple drugs at high doses to maintain control (steps 5-6 of GEMA[7] and 5 of GINA[5]), whereas *severe uncontrolled asthma* is that which remains uncontrolled despite fulfillment of the treatment steps [24].

Patients should be referred to specialized care with uncontrolled asthma in the following situations:

- When, in the absence of exacerbations, symptoms are poorly controlled (ACT <20 or ACQ >1.5 points) at 2 successive visits after ensuring that controller treatment is appropriate and verifying that adherence is good.
- When the patient has had ≥ 2 severe exacerbations during the previous year, that is, exacerbations requiring courses of systemic corticosteroids lasting more than 3 days each.
- When the patient has had a very severe exacerbation during the previous year, that is, an exacerbation requiring hospital stay, admission to the intensive care unit, or mechanical ventilation.
- In the case of limited airflow not previously confirmed or limited airflow that has worsened, that is, $FEV_1/FVC < 0.7$ or postbronchodilation $FEV_1 < 80\%$ predicted.
- When the patient's condition worsens on reducing high doses of inhaled corticosteroids or systemic corticosteroids.
- Suspicion of severe asthma requiring special treatment such as thermoplasty or

biologics.

Special situations

Patients will be referred to specialized care in the following cases: need for an allergology work-up, suspicion of occupational asthma, respiratory disease induced by acetylsalicylic acid or other NSAIDs (aspirin-exacerbated respiratory disease [AERD]) and (in some cases) exercise-induced asthma and asthma during pregnancy.

a) Allergology work-up

An allergology work-up should be performed in all patients whose asthma is thought to be allergic in origin, if immunotherapy is considered, when the patient does not respond to pharmacological treatment, and in cases where the stimulus persists and the patient cannot avoid it.

b) Suspicion of AERD

AERD is a phenotype that is usually associated with more severe asthma and/or chronic rhinosinusitis/nasal polyposis. It comprises acute reactions of both the upper and the lower airways after administration of acetylsalicylic acid or other COX-1-inhibiting NSAIDs. AERD affects 7% of asthmatics and 20% of patients with severe asthma[25]. It is important to identify patients with AERD, since ingestion or even topical administration of NSAIDs can cause very severe attacks and even fatal bronchospasm.

c) Asthma and pregnancy

The advantages of treating asthma during pregnancy outweigh the potential drawbacks of medication [26]. Experts [7] advise using the habitual medication, with the dose adjusted to the necessary minimum. A clear association has been described between asthma exacerbations during pregnancy and long-term complications associated with pregnancy, labor, and the neonate [27]; therefore, prevention of exacerbations is a key objective.

d) Asthma and exercise

Exercise-induced asthma involves transient obstruction of the lower airways after vigorous exercise. Since diagnosis can prove difficult, the patient must be referred so that diagnosis can be confirmed.

Table 4 shows the proposed model for the report used, with emphasis on the minimum data needed to refer a patient from primary to specialized care. Similarly, Appendixes 1 and 2 show a model report from specialized to primary care after referral and a proposal for a follow-up report that should be available to both primary and specialized care professionals in cases of a notable change in any of the care levels.

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Conflicts of Interest

During the last 3 years, Marina Blanco Aparicio has received fees for lectures, courses, participation in special articles and guidelines and for providing scientific consultancy from AstraZeneca, Esteve, GSK, Menarini, Novartis, and TEVA.

During the last 3 years, Julio Delgado has received fees for lectures and scientific consultancy from GSK, ALK-Abello, Astra/Zeneca, Chiesi, Mundipharma, Sanofi, and TEVA.

During the last 3 years, Jesús Molina has received fees for lectures sponsored by AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Menarini, and Roche. He has received funding for research projects from various governmental agencies, scientific societies, and Boehringer-Ingelheim.

During the last 3 years, José Tomás Gómez Sáenz has received fees for writing papers or giving courses sponsored by scientific societies, GlaxoSmithKline, Menarini, BIAL, Boehringer-Ingelheim, and Rovi.

During the last 3 years, Sara Núñez has received fees for writing special articles or giving courses and lectures sponsored by scientific societies, GlaxoSmithKline, Pfizer, and Rovi. Dr. Núñez has also received funding for research projects from various governmental agencies and scientific societies.

During the last 3 years, Francisco Javier Alvarez has received fees for giving lectures and courses, writing special articles, and providing scientific consultancy services from ALK-Abello, AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Esteve, GSK, Menarini, Mundipharma, Novartis, and TEVA.

During the last 3 years, Javier Domínguez Ortega has received fees for scientific consultancy services and giving lectures and talks from ALK-Abello, AstraZeneca, Chiesi, GSK, Mundipharma, Novartis, Sanofi, and TEVA.

During the last 3 years, José Ángel Carretero Gracia has received fees for providing and receiving continuous training and for scientific and research projects from Boehringer Ingelheim, GlaxoSmithKline, Menarini, Novartis, TEVA, and Fundación Pneumaragon de la Sociedad Aragonesa de Aparato Respiratorio.

During the last 3 years, Fernando Gómez Ruiz has received fees for giving lectures and courses and providing scientific consultancy services from Pfizer SL, Mundipharma, GSK, and Lilly.

During the last 3 years, Antonio Hidalgo Requena has received fees for giving lectures and courses, investigation, help assistance to scientific meetings, and providing scientific consultancy services from Esteve, Astra Zéneca, GSK, Bohëringuer Inguelheim, Menarini, Novartis, Pfizer, Mundifarma, Teva, Rovi and Faes farma.

During the last 3 years, Diego Vargas Ortega has been received speaker's honoraria from AstraZéneca, Boehringer-Ingelheim, GlaxoSmithKline, Menarini, Mundipharma and Pfizer.

During the last 3 years, María J. Alvarez Puebla has been received honoraria for participating in consensus and courses from GlaxoSmithKline and Stallergenes.

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Figure 1 Management of patient with suspicion of asthma in Primary Care

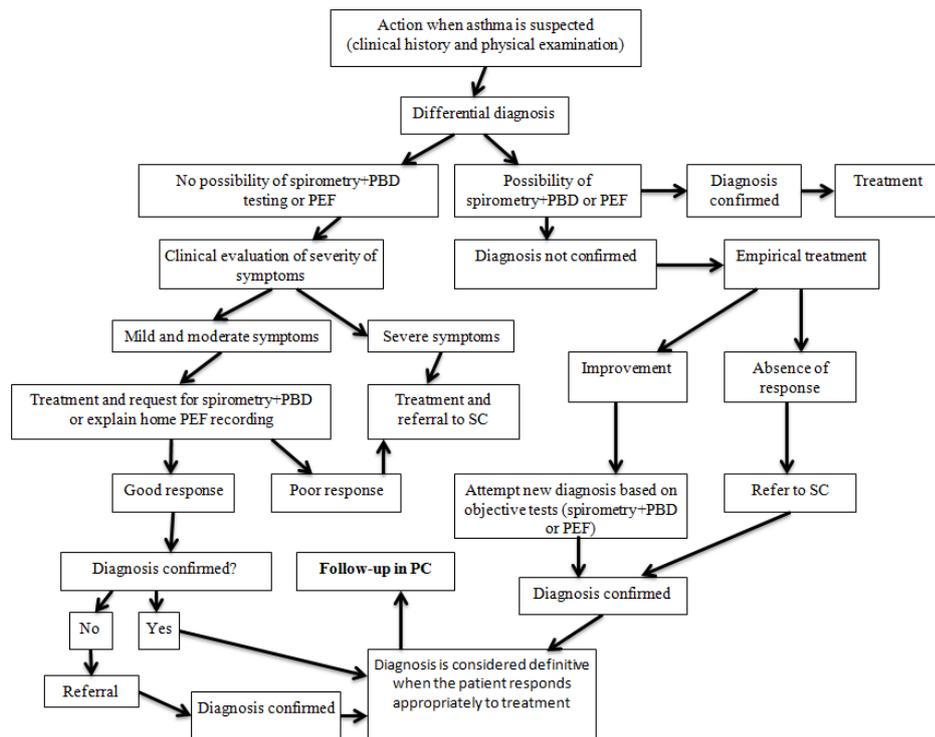


Figure 2 Asthma follow-up algorithm

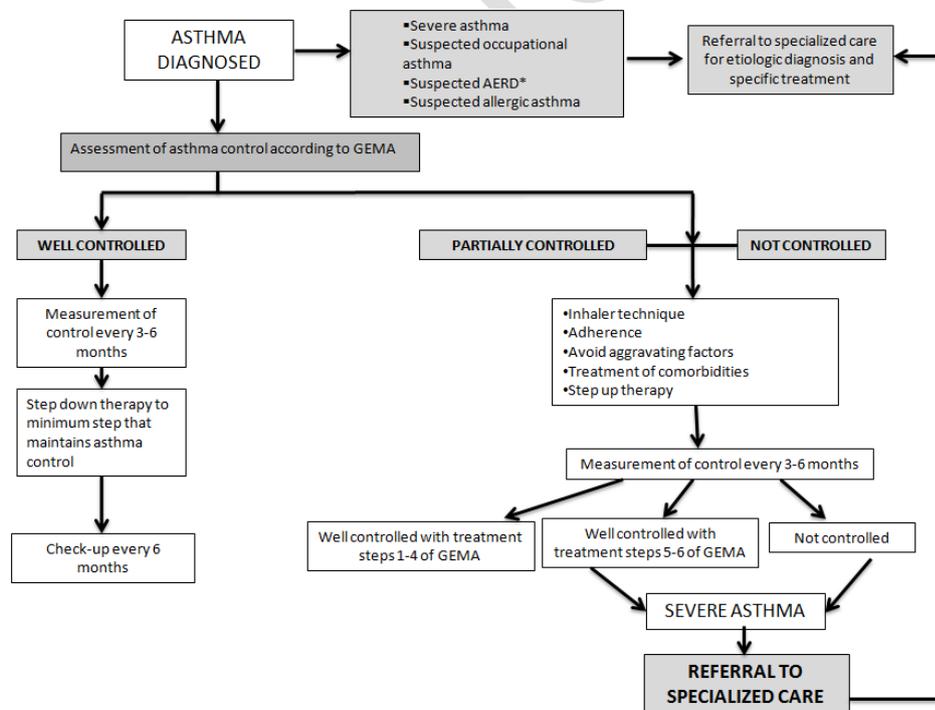


Table 1. Evaluation of asthma control

	During the last month, has the patient experienced any of the following?	Yes	No	CONTROL
Clinical Control	Daily asthma symptoms > 2 times/wk			All NO: well controlled
	Nighttime awakening or symptoms because of asthma			
	Need for rescue medication (SABA) > 2 times/wk?			
	Limitation in activity because of asthma			
	Severe asthma exacerbation during the last year			
	FEV ₁ and/or PEF < 80% predicted/personal best			
Causes of Poor control	Associated with asthma treatment	Adherence and inhalation technique Adverse effects		
	Comorbidities	Rhinosinusitis, nasal polyposis, gastroesophageal reflux, obesity, psychological disorders, etc.		
	Aggravating factors and continuous exposure to allergens (in allergic individuals) or irritants	Tobacco smoke and other inhaled toxins (marijuana, cocaine) Occupational factors, allergens, etc.		
	Other diseases that share a differential diagnosis with asthma	ACOS, upper and lower airway disorders, functional dyspnea, etc.		
	Incorrect diagnosis of asthma	Vocal cord dysfunction, heart failure, etc.		

Abbreviations: SABA, short-acting β_2 -agonist; FEV₁, forced expiratory volume in the first second; PEF, peak expiratory flow; ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome.

Adapted from GINA 2017 (www.ginasthma.org) and GEMA (www.gemasama.com)

Table 2. Steps recommended for the follow-up of patients with asthma.

<p>1. Control of symptoms and of lung function</p> <ul style="list-style-type: none"> • Control of symptoms¹: <ul style="list-style-type: none"> - Has the patient had daytime symptoms of asthma (number of times per week)? - Has the patient had nighttime symptoms of asthma (number of nights per month)? - Has asthma prevented the patient from performing daily activities (yes/no)? - Has the patient needed rescue medication (times per week)? - Has the patient had an asthma attack requiring courses of oral corticosteroids, visits to the emergency department, or admission to hospital? - ACT questionnaire (optional in primary care) • Lung function² (according to availability in primary care)
<p>2. Evaluate treatment</p> <ul style="list-style-type: none"> • Verify that the treatment step is appropriate to the severity of the disease • Verify the inhalation technique, adherence, and adverse effects • Verify that the patient is familiar with the written action plan (in uncontrolled or severe asthma) • Verify the patient's approach to asthma and preferences • Messages: <ul style="list-style-type: none"> ○ Chronic inflammatory disease that needs maintenance treatment ○ Know that the disease involves reliever medication (recognize initial symptoms of deterioration) ○ Avoid smoking and responsible allergens ○ Adherence (correct technique and dose)
<p>3. Avoid comorbid conditions and aggravating factors³</p> <ul style="list-style-type: none"> • Rhinitis/rhinosinusitis/nasal polyposis, GERD, SAHS • Obesity, anxiety-depression, hyperthyroidism • Drugs: NSAIDs, nonselective β-blockers, ACEIs • Smoking and other inhaled toxins
<p>4. Identify risk factors for exacerbations</p> <ul style="list-style-type: none"> • Poor current control • Overuse of reliever medication • Psychological or socioeconomic problems • Allergens, including food allergens • High FeNO⁴ • Previous intubation or admission to the ICU • ≥ 1 severe exacerbation in the previous year
<p>5. Identify risk factors for limitation of airflow</p> <ul style="list-style-type: none"> • Undertreatment with inhaled corticosteroids • Exposure to tobacco smoke, chemical irritants, occupational exposure • Peripheral blood eosinophilia • Low FEV₁, especially if $<60\%$ (if this information is available)
<p>6. Risk of adverse effects of medication</p> <ul style="list-style-type: none"> • Systemic: frequent oral corticosteroids in the long term or at high doses and/or potent inhaled corticosteroids • Local: high doses of ICSs or high-potency ICSs, poor inhalation technique

¹ Follow-up of the patient with symptoms must be based on these being asthma symptoms and not symptoms of another condition.

² The ideal test for measuring lung function is spirometry with a bronchodilator test. However, in those cases where tests are not available, it is recommended to at least measure peak expiratory flow. This is recommended at the beginning of treatment, at 3-6 months, and at least once per year thereafter.

³ In the case of uncontrolled asthma, verify all aggravating factors and comorbid conditions described in the corresponding chapter.

⁴ Data available for many patients who are being followed up in specialized care.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACT, Asthma Control Test; GERD, gastrointestinal reflux disease; ICS, inhaled corticosteroid; SAHS, sleep apnea-hypopnea syndrome; NSAID, nonsteroidal anti-inflammatory drug; FeNO, fractional exhaled nitric oxide; ICU, intensive care unit; FEV₁, forced expiratory volume in the first second.

Table 3. Comorbid conditions and aggravating factors associated with poor control of asthma.

Comorbid condition	Diagnostic tests	Treatment
Rhinosinusitis	<ul style="list-style-type: none"> Nasal endoscopy Sinus CT 	<ul style="list-style-type: none"> Antileukotrienes Nasal corticosteroids Nasal irrigation (saline) Antihistamines Nasal surgery
Gastroesophageal reflux	<ul style="list-style-type: none"> Esophageal manometry/pH Therapy with PPIs 	<ul style="list-style-type: none"> Dietary-hygiene measures PPIs, prokinetic drugs Surgery
Obesity	BMI	<ul style="list-style-type: none"> Weight loss Bariatric surgery
SAHS	Polysomnography	<ul style="list-style-type: none"> CPAP Weight loss
Psychopathology (anxiety, depression)	Psychological/psychiatric evaluation	<ul style="list-style-type: none"> Psychotherapy Specific treatment
Functional dyspnea	Nijmegen questionnaire	<ul style="list-style-type: none"> Psychotherapy Breathing re-education
Vocal cord dysfunction	Laryngoscopy during the attack or challenge with methacholine/exercise	Speech therapy
Drugs: NSAIDs, ACEIs, nonselective β -blockers	Clinical history Bronchial, nasal, oral provocation tests	Withdrawal
Smoking	<ul style="list-style-type: none"> History CO-oximetry 	Cessation
Food allergy and anaphylaxis	Allergy tests (prick-test, IgE, challenge tests)	<ul style="list-style-type: none"> Specific allergen avoidance measures Specific immunotherapy Biologics

ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; CPAP, continued positive airway pressure, CT, computed tomography; Ig, immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SAHS, sleep apnea-hypopnea syndrome.

Taken from the SEPAR guidelines on severe uncontrolled asthma²³

Appendix 1. Report from specialized care to primary care after the first referral

Results of tests confirming asthma	
Classification of severity and control	
Phenotype	
Confirmed, excluded, or suspected comorbid conditions	
Recommended treatment	

Appendix 2. Patient follow-up report

Degree of clinical control	
Exacerbations	
Adherence (interview, TAI) and inhaler technique	
Results of lung function tests (depending on availability in primary care)	
New comorbid conditions	
Changes in phenotype	
Changes in treatment	

TAI, Test of Adherence to Inhalers