GUIDELINES

Consensus Document on the Diagnosis of Severe Uncontrolled Asthma

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Abstract

Background: The concepts of asthma severity, control, and exacerbation are important in the evaluation of patients and their response to treatment. However, terminology is not standardized, and terms are often used interchangeably. Patients with uncontrolled severe asthma pose a major health care problem. Over the last decade, it has become increasingly clear that, in order to facilitate the development of novel targeted therapies, patients must be further characterized and classified.
Objective: To draft a consensus statement on the diagnosis, management, and treatment of severe uncontrolled asthma. The statement is meant to serve as a guideline for health professionals and clinical researchers.
Methods: The consensus was led by the Severe Asthma Working Group of the Spanish Society of Allergology and Clinical Immunology Asthma Committee. A review was conducted of the best available scientific evidence (until December 2011) on severe asthma in adults and children.
Results: Definitions for severe asthma, level of control, and exacerbation are developed. Different phenotypes and endophenotypes of severe uncontrolled asthma and new specific therapeutic interventions are presented.
A systematic algorithm for the evaluation of patients presenting with severe persistent asthma symptoms is proposed.
Conclusions: A consensus statement on the diagnosis, management, and treatment of severe uncontrolled asthma is presented.

Key words: Asthma. Severity. Control. Exacerbations. Algorithm.

Resumen

Introducción: Los conceptos de gravedad del asma, control y las exacerbaciones son importantes para evaluar al paciente asmático y su respuesta al tratamiento. Sin embargo, esta terminología no está aún suficientemente estandarizada y, a menudo, estos conceptos se confunden entre sí. Los pacientes con asma grave no controlada constituyen un importante problema de salud que ha ido en aumento durante la última década junto con el desarrollo de nuevos tratamientos, lo que obliga a una mejor caracterización y clasificación de este grupo de pacientes.
Objetivo: Alcanzar un consenso sobre el diagnóstico, manejo y tratamiento del asma grave no controlada que sirva de guía para los profesionales de la salud y en investigación clínica
Métodos: El consenso fue llevado a cabo por el Grupo de Trabajo sobre Asma Grave perteneciente al Comité de Asma de la Sociedad Española de Alergología e Inmunología Clínica. Se realizó una revisión de la mejor evidencia científica disponible hasta diciembre de 2011 sobre asma grave en niños y en adultos.
Resultados: Se desarrollan definiciones para asma grave y sus diferentes niveles de control, así como para exacerbación. También se describen los diferentes fenotipos y endotipos de asma grave no controlada y las nuevas líneas terapéuticas.
Se propone un algoritmo diagnóstico para evaluar a los pacientes con síntomas de asma persistente grave.
Conclusiones: Se presenta un documento de consenso sobre el diagnóstico, manejo y tratamiento del asma grave no controlada.

Introduction

This document is a consensus statement on the diagnosis, management, and treatment of severe uncontrolled asthma. It was written in light of the best currently available scientific evidence obtained after a thorough review of the literature published until December 2011. The review benefits from the clinical experience of the experts in the field who drafted the manuscript, which is meant to serve as a guideline for health professionals.

The consensus statement addresses (in 2 papers) the epidemiology, diagnosis, and classification of severe asthma, before moving on to examine the phenotypes and endophenotypes of severe persistent uncontrolled asthma and new specific therapeutic interventions.

Asthma is a global health problem that affects approximately 300 million people of all ages, ethnicities, and geographic origins [1]. Every year, approximately 250,000 people die prematurely from asthma [1]. However, geographical diversity means that asthma is a heterogeneous disease in terms of genetic and environmental interactions, pathophysiological mechanisms, environmental exposure, comorbidities, age, severity of underlying disease, access to health care services, care received, psychological factors, treatment response, and characteristics, which include attacks, death, and chronicity [1].

The prevalence of asthma in children from Western European Mediterranean countries is 8%-13.5%, except in Greece, where it is 3.7% [2]. In Spain, the prevalence of asthma among boys and girls aged 6 to 7 years is 10.7% and 8.7%, respectively. Among adolescents aged 13 to 14 years, it is 9.3% and 9.2% for males and females, respectively [3]. It is generally accepted that 5% of the adult Spanish population has asthma [4]. According to the results of the ESCASE study [5], which assessed asthma control in Spain according to the recommendations of the Global Initiative for Asthma [6], more than two-thirds of patients in the study had poorly controlled asthma.

Approximately 5% of asthmatics suffer from severe uncontrolled asthma, a phenotype that accounts for more than 50% of health care resources dedicated to asthma [7]. However, only 55% of patients who are initially suspected of having severe uncontrolled asthma receive a confirmed diagnosis once other problems have been ruled out [8].

According to the Spanish Guideline on the Management of Asthma, GEMA [8], severe asthma should be identified and managed in specialized consultations and by experienced health professionals. Diagnosis and treatment of asthma should be based on a protocol comprising decision algorithms that establish a rational sequence for the administration of procedures and drugs. Recognizing the phenotype of severe asthma may provide therapeutic advantages, and treatment does not necessarily have to pursue complete control of symptoms. It is therefore recommended that practitioners agree with the patient on a tolerable maximum of asthma symptoms and ensure that the patient has a personalized written action plan. The patient should be closely monitored with repeated reviews until optimal outcomes are achieved, at which point the reviews can occur less frequently.

Drug treatment for severe asthma should be intense from the start and include high doses of inhaled corticosteroids (ICS), long-acting $ß_2$-adrenergic agonists, leukotriene receptor antagonists, omalizumab, and even oral corticosteroids (OCS) (eg, 40 mg of prednisolone for 15 days) in order to achieve the best possible control and response. Once an acceptable level of control has been reached, a dose reduction strategy can begin [8].

Severity, Disease Control, and Exacerbations

Severity and Control

The concepts of severity and disease control are important for assessing asthma patients and their response to treatment, as well as for health services, registries, and research studies. However, the terminology applied is often heterogeneous, and the terms are often confused and interchanged. Severe asthma needs to be distinguished from uncontrolled asthma. Severity is an intrinsic characteristic of the underlying disease. In contrast, asthma control is defined as the extent to which the various manifestations of asthma have been reduced or removed by treatment. It is established once treatment is in place and is the main goal of treatment [1,8]. We should attempt to achieve control of both daily symptoms and future risk, especially with respect to exacerbations. In the initial presentation of the disease in patients who are not receiving maintenance treatment, severity should be assessed based on the presence of daytime symptoms, the use of rescue medication, restriction in activities of daily living, lung function, and the number of exacerbations. Based on this assessment, asthma can be classified as intermittent, mild persistent, moderate persistent, or severe persistent, and appropriate drug treatment should be initiated according to the degree of severity [6,8]. Once the patient is being treated, severity is determined by the therapeutic step required to achieve control [8].

Asthma is controlled when daytime and nighttime symptoms disappear or are rare, when lung function remains normal or close to normal, when rescue medication is not necessary, when there are no limitations on daily activity (including exercise), and when the number of exacerbations, emergency room visits, and hospital admissions are minimal or zero [8].

Poor management is associated with a lower quality of life, restrictions on activities of daily living, work/school absenteeism, greater health care costs, and a greater risk of attacks that require assistance from emergency services and admission to hospital. The minimum period for evaluating asthma control is 1 to 4 weeks in adults and at least 4 weeks in children [9].

Asthma control can be assessed with 2 widely used questionnaires: the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT) [6,8]. Both have been validated for use in the Spanish population [10,11]. However, one of the main shortcomings of these questionnaires is that neither properly assesses future risk, specifically exacerbations, which are of considerable importance to the definition of control. In addition, neither the ACQ5 (the shortened version of the ACQ) nor the ACT assesses lung function.

Exacerbations [9]: Commonly referred to as asthma attacks or acute asthma, exacerbations are episodes of progressively increasing dyspnea, coughing, wheezing, and chest tightness, or a combination of these, in which the patient feels the need for a rapid change in medication. They vary in duration of onset (from minutes or hours to up to 2 weeks) and time until resolution. Asthma exacerbations can be considered one of the major components for establishing asthma control (future risk), because they constitute the greatest risk for patients and cause patients and their family anxiety, which in turn leads to greater stress when applying treatment and increases health care costs [12]. Over the past 10 years, exacerbations have been the most widely used endpoint in research on the effectiveness of asthma treatment [13]. Both the underlying disease and the attacks can be controlled by modifying several factors.

Types of Exacerbations [9]

1. *Severe:* Severe exacerbations require urgent treatment to avoid hospitalization and even death. They are often a marker of poor asthma control. Severe exacerbations should include at least 1 of the following criteria:
   - Use of systemic corticosteroids or an increase in the maintenance doses of OCS for at least 3 consecutive days, or
   - Hospitalization or an emergency room visit due to asthma requiring systemic corticosteroids.

Life-threatening, near-fatal, or fatal asthma: Although numerous definitions have been proposed, asthma is considered to be life-threatening when the disease takes the form of very severe attacks and meets the criteria for respiratory arrest or extreme severity, even after it has been evaluated and treated correctly. This type of asthma requires immediate attention in a hospital and even in an intensive care/surveillance unit [14].

Although severe exacerbations are much more frequent in severe asthma and increase its mortality [15], they also appear in mild asthma more often than expected [16,17].

2. *Moderate:* Moderate attacks require temporary changes in treatment to prevent the asthma from becoming more severe. Moderate attacks include 1 or more of the following criteria for 2 or more consecutive days:
   - Symptom deterioration
   - Pulmonary function deterioration
   - Increased use of rescue medication

Emergency room visits that do not require systemic corticosteroids are classified as moderate attacks.

3. *Mild:* These are disregarded.

The main triggers for attacks are viruses (especially rhinoviruses), allergens, some environmental pollutants, various sensitizing substances or irritants in the workplace, and specific medications, such as nonsteroidal anti-inflammatory drugs [18].

To perform a comprehensive assessment of asthma that includes the number of exacerbations, severity, and degree of control, a minimum follow-up period of 6 to 12 months has been proposed [1,9].

Diagnostic Algorithm and Definitions

When faced with suspected severe asthma, it is advisable to follow a diagnostic algorithm and investigate possible associated comorbidities, asthma triggers, and adherence [6,8,19].

This working group proposes the diagnostic algorithm shown in the Figure.

Definitions

To date, there are no clear definitions of severe asthma. This working group proposes the following definitions, based on the main objective of asthma treatment, namely, control of current symptoms and of future risk [6,8,19].

Severe persistent asthma: Asthma that requires high doses of ICS (with or without OCS) to achieve and maintain control over current symptoms, future risk of exacerbation, instability, decrease in pulmonary function, and side effects of the medication. This type of asthma involves treatment with other drugs recommended by the guidelines [6,8], such as long-acting $ß_2$-adrenergic agonists. Table 1 shows the high-dose equivalents for various ICS in adults and children [8].

Undertreated severe persistent asthma: Severe asthma that does not receive an appropriate dose of corticosteroids for control, because of lack of prescription, improper adherence to therapy, or incorrect use of the inhaler.

Difficult-to-control asthma: Asthma in which associated comorbidities and/or triggers are not controlled or other entities that could cause asthma have not been eliminated. These hinder the daily control of asthma and the prevention of exacerbations.

Controlled severe persistent asthma: Asthma controlled with high doses of ICS (in addition to other asthma drugs) that cannot be reduced in order to maintain daily control and prevent the risk of future exacerbations.

Partially controlled severe persistent asthma: Asthma treated with high doses of ICS that is not well controlled on a daily basis or does not completely prevent the risk of future exacerbations. Treatment of this type of asthma involves cycles of OCS or increased doses of ICS.

Uncontrolled severe persistent asthma: Asthma that requires OCS to achieve control and in which the patient experiences side effects of the medication or presents a high risk of experiencing them. Uncontrolled, severe persistent asthma encompasses all patients whose asthma is characterized as particularly aggressive and inadequately or poorly controlled, despite an appropriate therapeutic strategy

Table 1. High-Dose Equivalents for Various Inhaled Corticosteroids for Adults and Children (Adapted From Ref. 8)

	High doses, adults, µg/d	High doses, children, µg/d
Beclomethasone dipropionate	1001-2000	
Budesonide	801-1600	>400
Fluticasone	501-1000	>250
Ciclesonide	321-1280	
Mometasone furoate	801-1200	

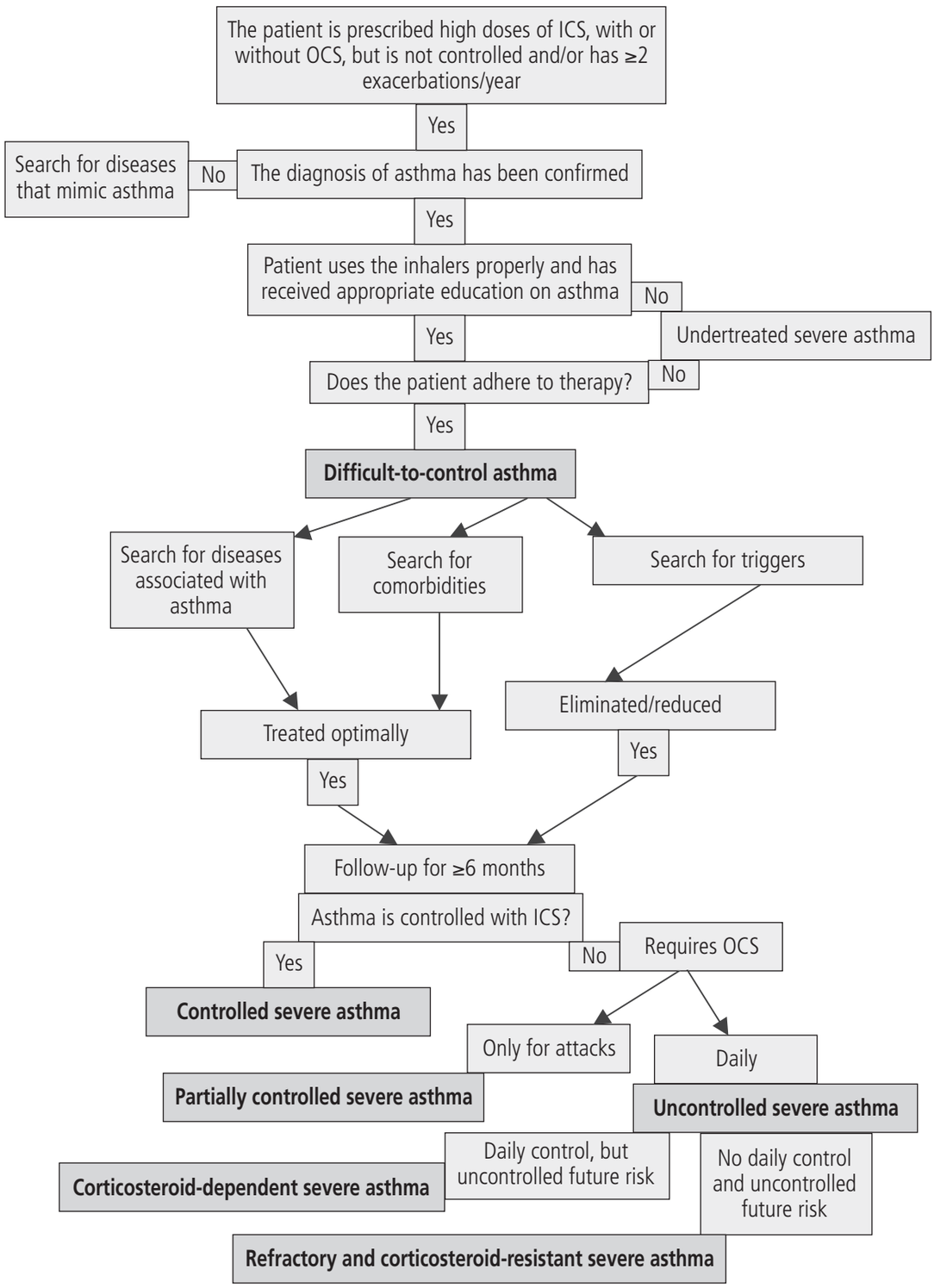

Figure. Diagnostic algorihm of uncontrolled severe persistent asthma. ICS indicates inhaled corticosteroid; OCS, oral corticosteroid.

adjusted to the level of clinical severity [8]. The patient must be followed by a specialist for at least 6 months before this diagnosis can be made [1,9]. Uncontrolled, severe persistent asthma encompasses:

Corticosteroid-dependent severe persistent asthma: Uncontrolled severe asthma that requires daily OCS for daily control of symptoms and prevention of attacks.

Corticosteroid-resistant severe persistent asthma: Uncontrolled severe asthma in which, despite high doses of OCS, daily control is not achieved and the risk of experiencing attacks is not prevented.

Peculiarities of Severe Asthma in Children

No general consensus has been reached on the definition of severe asthma in children, and, with the exception of omalizumab, therapeutic options are based more on expert opinion than on evidence-based guidelines [8].

Moreover, identification of respiratory sounds in preschool children can be complicated, with both parents and practitioners labeling the sounds incorrectly as wheezing [20]. In addition, there is considerable phenotypic heterogeneity among preschool children who present wheezing. The appropriateness of applying the term asthma to very small children with no evidence of inflammation is open to debate. In 2008, a task force of the European Respiratory Society [21] proposed a classification for children <6 years based exclusively on the following symptoms:

– Episodic wheezing (viral): for children with intermittent wheezing who are asymptomatic between episodes.

– Wheezing due to multiple triggers: for children who wheeze during episodes and at other times.

The definitions proposed at the beginning of this article may be valid for children aged ≥6 years. As for future risk in the pediatric population, the reduction in lung growth should be included [22].

Differences With Adults

Skin tests with common aeroallergens are more often positive in children with severe asthma than in adults with severe asthma. No significant differences have been observed in peripheral eosinophil count, fraction of exhaled nitric oxide, and levels of total immunoglobulin (Ig) E between groups with severe and mild-to-moderate asthma. Most children with severe asthma and persistent wheezing will have asthma into adulthood [23].

Male gender is a risk factor for deterioration of pulmonary function among asthmatic children [24]. Comorbidities differ between children and adults, and triggers for severe asthma and attacks are more common in children (ie, brittle asthma). The clinical phenotypes of severe asthma in children change faster.

In preschool children, viral respiratory infections frequently cause morbidity, which can require admission to hospital. Pathophysiology in this age group differs from that of adults, as does the response to drugs and the effect of side effects of corticosteroids on bone growth and maturation, thus highlighting the need for new therapeutic strategies [1].

Most children with persistent asthma have normal symptom-free function between attacks, and abnormalities in pulmonary function occur only during acute attacks. In fact, forced expiratory volume in 1 second (FEV_1) in children does not correlate well with the intensity of asthma symptoms, and values below 80% of the theoretical value have low sensitivity for differentiating the severity of asthma [25].

Young children are especially susceptible to status asthmaticus. Up to one-third of all children who die of asthma had maintained a clinical course that was previously classified as mild [26].

Severe Persistent Asthma: Diagnosis and Adherence to Treatment

When patients have asthma with poor outcomes, the first steps are to check whether the diagnosis of asthma has been confirmed and to review treatment and adherence [6,8].

Confirm the Diagnosis

The diagnosis should be confirmed by the presence of typical symptoms, along with the demonstration of reversible airflow obstruction and/or bronchial hyper-responsiveness (BHR). Bronchial provocation tests are more sensitive and specific than demonstration of reversible obstruction with

Table 2. Differential Diagnosis of Asthma in Adults

– Chronic obstructive pulmonary disease; chronic bronchitis and emphysema
– Eosinophilic bronchitis
– Mechanical obstruction of intraluminal or external airways (larynx, trachea, or main bronchi): vocal cord dysfunction, neoplasms, granulomas
– Acquired tracheobronchomalacia
– Aspiration syndromes: gastroesophageal reflux, foreign body aspiration
– Upper airway syndrome: postnasal drip
– Pulmonary infiltrates with eosinophilia
– Hypersensitivity pneumonitis
– Pulmonary vasculitis
– Chronic cough secondary to drugs: ACEIs, ß-blockers
– Cardiovascular disorders: heart failure, pulmonary thromboembolism
– Lung infections: tuberculosis
– Bronchiectasis
– Hereditary diseases: cystic fibrosis, primary ciliary dyskinesia, α-1 antitrypsin deficiency
– Carcinoid syndrome
– Dyspnea and/or psychogenic hyperventilation
– Allergic bronchopulmonary aspergillosis
– Churg-Strauss syndrome

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor.

Table 3. Differential Diagnosis of Asthma in Children

- Rhinosinusitis: may be a comorbid process or mimic asthma
- Adenotonsillar hypertrophy
- Choanal stenosis
- Postnasal drip
- Congenital malformation or primary ciliary dyskinesia (usually occurs on the first day of life)
- Bronchial/tracheal compression
- Vascular rings
- Elongated cardiac cavities
- Enlarged lymph nodes (tuberculosis, lymphoma)
- Endobronchial disease
- Foreign body (very abrupt onset of symptoms)
- Tumor (eg, carcinoid)
- Viral respiratory infections (may progress with chronic cough but not for longer than 8 weeks)
- Persistent bacterial bronchitis
- Fixed airflow obstruction: bronchiolitis obliterans (usually caused by adenovirus and *Mycoplasma pneumoniae* in previously healthy children)
- Cystic fibrosis (nasal polyps are pathognomonic in children with cystic fibrosis)
- Bronchopulmonary dysplasia
- Congenital or acquired tracheomalacia
- Idiopathic pulmonary hypertension (progresses with syncope, dyspnea from physical exercise, hemoptysis, and hypoxemia)
- Neurological diseases associated with dysphagia
- Gastroesophageal reflux (irritability or wheezing after administration, accompanied by vomiting and worsening in decubitus position; common in very small children)
- Systemic immunodeficiency: agammaglobulinemia, severe combined immunodeficiency (progresses with severe infections that are persistent/recurrent by unusual microorganisms)

Table 4. Complementary Tests

- Computed tomography of sinuses
- High-resolution computed tomography of chest
- Delayed cutaneous response to *Aspergillus* species
- Analytical data: quantification of immunoglobulins and subclasses of antineutrophil cytoplasmic antibodies, total IgE, Aspergillus-specific IgE and IgG, α-1 antitrypsin, thyroid hormones
- Sweat test
- Electrocardiogram
- Pulmonary volumes
- Pulmonary diffusion
- Fiberoptic bronchoscopy
- Otorhinolaryngology assessment (examination of the upper airways if there is suspicion of vocal cord dysfunction syndrome during the episode)
- 24-hour esophageal pH-metry
- Psychological evaluation

Abbreviation: Ig, immunoglobulin.

fast-acting bronchodilators or corticosteroids [27]. However, when the airway obstruction is pronounced, bronchial provocation tests cannot be performed for safety reasons. When the presence of reversible obstruction and BHR has not been demonstrated, other diseases that can mimic asthma should be considered (Tables 2 and 3) [28,29]. Complementary examinations will need to be broadened in order to correctly diagnose these conditions (Table 4) [30,31].

Table 5. Factors Involved in Lack of Adherence

Drug-Related
– Difficulty using the inhaler
– Uncomfortable treatment regimens (eg, 4 times/d, numerous drugs)
– Side effects
– Treatment cost
Not Drug-Related
– Inadequate understanding of the treatment regimen
– Fear of side effects
– Poor relationship with the doctor
– Poor supervision of treatment
– Nonacceptance of disease by the patient
– Underestimation of severity by the patient

Treatment and Adherence

For severe asthmatics, standard treatment should be reviewed and the appropriate measures taken. Adherence should also be reviewed, because lack of adherence can lead to poor outcome. Adherence is often suboptimal [32], and it is estimated that between 30% and 50% of asthmatics do not take their treatment properly [33].

Assessing adherence is difficult, although the number of tablets or inhaler packages can be counted. In terms of daily practice, indirect questions about the use of medication may help (eg, *How many times a day do you use your inhaler?*). Simple questionnaires can be administered to identify inadequate adherence [34]. Table 5 lists the factors involved in lack of adherence [6].

Adherence improves when the doctor-patient relationship is good, the inhalation technique used is the most appropriate for the patient, adherence is monitored periodically, and the necessary information is provided. Regular follow-up is essential, and written recommendations for self-management of asthma should include the steps to follow in case of deterioration [31]. According to a recent study, less than 40% of primary care pediatric consultations involve questions on adherence to inhaler use [35].

Drug treatment for the control of severe asthma should consist of high doses of ICS (1000-2000 μg of beclomethasone dipropionate [BDP] or equivalent for adults and up to 400 μg of BDP for children over 5 years of age) [6,8,9], together with long-acting $ß_2$-adrenergic agonists (LABA), either in a single inhaler (which is more convenient) or with both drugs taken separately. For most ICS, the recommended frequency of inhalation is twice a day, although the administration of budesonide may be more effective when administered 4 times a day [6,8].

Adding leukotrienes may be useful for some patients, especially those with hypersensitivity to aspirin [36], although they are less effective than LABAs [6,8]. Delayed-release theophylline can also be added [6,8,37]. The British Thoracic Society [38] considers it appropriate to include treatment with delayed-release oral $ß_2$-agonists, although with considerable caution, as most patients already take LABAs. Although asthma guidelines do not currently recommend tiotropium bromide [6,38], recent well-controlled trials suggest that the addition of this drug is effective in treating asthma patients [39] and improves pulmonary function in patients with poorly controlled severe asthma [40]. Anticholinergic agents can be used to manage acute episodes (when combined with short-acting $ß_2$-agonists) and as rescue medication in patients with poor tolerance to short-acting $ß_2$-adrenergic agonists, although onset of action is slower than with $ß_2$-agonists [6].

Despite administration of these additional treatments, some patients require OCS to improve control, although the use of OCS is associated with side effects [6,8]. Prednisolone is recommended as an OCS of choice [38], although there is no evidence concerning the most appropriate timing or schedule. The British Thoracic Society [38] recommends raising the doses of ICS in children to more than 800 μg of beclomethasone dipropionate or equivalent prior to starting the OCS.

The systemic side effects of OCS present an additional problem and should be closely monitored in corticosteroid-dependent patients. The most frequent side effects are truncal obesity, ecchymosis, osteoporosis, diabetes, hypertension, gastric ulcer, proximal myopathy, depression, and cataract. It is important to serially measure bone density when starting preventive treatment with bisphosphonates or estrogens in menopausal women with reduced bone density.

Finally, patients with severe persistent allergic asthma can also receive omalizumab [8,41,42], a humanized monoclonal antibody that binds to circulating IgE and considerably reduces levels of free IgE. It is indicated for allergic patients aged >6 years who are symptomatic despite use of the previously mentioned treatments and especially when they have frequent exacerbations.

Omalizumab is administered subcutaneously every 2 or 4 weeks depending on the dose (based on weight and total pretreatment serum IgE levels). The maximum levels of IgE with which this drug can be administered are 1500 IU/mL, without exceeding the maximum dose of 600 mg every 2 weeks.

Clinical trials have shown that a minimum of 12-16 weeks is necessary for treatment with omalizumab to take effect [42-44]. In general, omalizumab is well tolerated, and the most common adverse effects are local reactions. It must be

administered in a hospital setting under the direct supervision of a specialist, given that isolated cases of anaphylaxis associated with the administration of omalizumab have been reported [45].

Difficult-to-Control Asthma

Search for Diseases Associated With Asthma

Allergic bronchopulmonary aspergillosis (ABPA) and Churg-Strauss syndrome deserve special consideration when dealing with patients whose asthma presents specific radiologic and laboratory findings. Both conditions should be ruled out in all patients with severe asthma. The specific diagnostic criteria of ABPA—total IgE, IgE, and IgG specific to *Aspergillus fumigatus*, central bronchiectasis—should be investigated [46]. These patients may benefit from antifungals such as itraconazole [46].

Churg-Strauss eosinophilic granulomatous vasculitis should be suspected in patients with sinusitis and sinus changes visible under radiography, history of multisystem disease, sustained peripheral eosinophilia (greater than 10%), neuropathy, transient pulmonary infiltrates, cardiomegaly, microscopic hematuria, elevated C-reactive protein or erythrocyte sedimentation rate in the absence of infection, and antineutrophil cytoplasmic antibodies [47].

Comorbidities

In cases of suspected uncontrolled severe asthma, knowledge of comorbid conditions before intensifying treatment can help control the disease. Nevertheless, the impact of comorbidities on the development and maintenance of severe asthma is unclear, given that conclusive studies substantiating these data are lacking [48-49].

Rhinitis: The prevalence of rhinitis in asthma patients is much higher than in the general population [8]. A recent study in Spain showed a prevalence of 89.9% [50]. The Allergic Rhinitis and its Impact on Asthma guidelines [51] describe the importance of the upper airways in the onset and maintenance of asthma, as well as in asthma attacks. Moreover, the presence of rhinitis in asthmatics increases the consumption of health care resources [8]. Although both allergic rhinitis and nonallergic rhinitis are associated with poorer control of asthma [52-54], the association between rhinitis and severe asthma is still not clear [51].

Treatment of allergic rhinitis may improve some aspects of asthma [8,51]; however, one systematic review was not able to confirm this hypothesis [55].

Chronic rhinosinusitis: Chronic rhinosinusitis comprises a heterogeneous group of diseases with different etiologies and pathogenic mechanisms and includes conditions such as chronic sinusitis and nasal polyposis [56]. In contrast to rhinitis, chronic rhinosinusitis has been associated with severe asthma, especially if it co-occurs with nasal polyposis and aspirin hypersensitivity [57,58].

Gastroesophageal reflux (GER): Although the Severe Asthma Research Program study found an association between GER and severe asthma [58], this association was complex. GER has been shown to be involved in uncontrolled asthma, but the minimal improvement found with treatment suggests that its contribution to severe asthma is variable [59,60]. Moreover, drugs used in asthma, such as corticosteroids and theophylline, may contribute to the development of GER [61].

Psychosocial factors: Control of asthma may be influenced by several psychosocial factors [61]. Although serious psychological diseases are no more common in patients with severe asthma than in those with moderate or mild asthma [62], the attitude, personality, and social characteristics of the patient and, above all, anxiety and depression, may influence the control of severe asthma and adherence [61,63]. Patients need multidisciplinary care to improve their asthma [64].

Obesity: Obesity seems to be a risk factor for developing asthma [65,66], although several authors found no association between the diagnosis of asthma (based on the presence of symptoms and BHR) and obesity [67-70]. Obesity has been linked to severe asthma, especially in women [57], and weight loss with greater asthma control [71,72], although not with improvement in BHR [73]. Moreover, a greater resistance to corticosteroid treatment has been observed in obese patients [74,75]. These data indicate that obese asthma patients may represent a specific phenotype of the disease [76]. Obese patients should receive support from a nutritionist.

Obstructive sleep apnea syndrome: Obstructive sleep apnea syndrome may be associated with asthma, especially in obese patients, although its influence on severity remains unclear [62,77].

Vocal cord dysfunction: Vocal cord dysfunction is defined as a paradoxical adduction of the vocal cords during inspiration, which produces an obstruction of the airways [8]. It is more frequent in young women. The predominant symptom is stridor with dyspnea, chest tightness, coughing, and, occasionally, wheezing. These clinical conditions are usually self-limiting. The symptoms may be confused with those of asthma, in particular exercise-induced asthma, or may coexist with asthma. As is the case in patients with asthma, inhalation of pulmonary irritants, physical exercise, influenza or viral infection, and GER can trigger the symptoms of vocal cord dysfunction. In contrast to asthma, vocal cord dysfunction often causes more difficulties for inspiration than expiration. Forced spirometry may be normal in the asymptomatic phase, but it has a characteristic morphology during attacks, namely, flattening of the inspiratory flow volume curve, which provides evidence of extrathoracic airflow obstruction with additional restriction of expiratory flow. The definitive diagnosis is performed using laryngoscopy [8].

Menstruation: More than 40% of asthmatic women suffer from premenstrual exacerbation of their symptoms; however, severe premenstrual attacks are rare and do not improve with systemic corticosteroids or $ß_2$-agonists [78].

Smoking: Tobacco smoke is one of the most significant risk factors for poor asthma control. Smoking can contribute to the development and manifestation of severe asthma. Smokers with asthma have more symptoms, more severe exacerbations, more emergency room visits, a lower response to corticosteroids [79-82], and faster deterioration of pulmonary function than nonsmokers, although some authors were not able to demonstrate this last observation [83]. Children whose parents

smoke have more severe symptoms [84]. Asthmatic smokers should be informed about smoking cessation strategies.

Triggers

Exposure to Allergens

Although atopy is more common in mild and moderate asthma, sensitization to aeroallergens has been reported in 60% of patients with severe asthma [57]. A recently published Spanish observational study on uncontrolled, severe persistent asthma analyzed 36 649 patients with asthma, 1423 of whom (3.9%) had uncontrolled, severe persistent asthma, according to clinical criteria. Of these, 55.8% had a positive skin test result to common allergens, and 54.2% had high levels of total serum IgE [85].

In addition to their role as inducers of bronchial asthma, aeroallergens are common triggers of asthma attacks in sensitized individuals. Both the severity of asthma symptoms and functional respiratory disorders have been linked to level of allergen exposure [86]. Sensitized adults and children who have severe asthma caused by allergies are often exposed to higher allergen concentrations, especially at home [87] and at school [88], than patients with mild asthma.

A relationship has also been demonstrated between allergenic burden and the consumption of asthma medication [89], thus highlighting the importance of allergen exposure in the onset and severity of asthma symptoms, more so than other triggers.

Other data indicate a relationship between allergen exposure and asthma-related hospitalization and deaths. An increase in hospitalizations due to asthma attacks during the pollen season has been shown to coincide with a greater presence of allergenic fungi, which can increase the risk of death from asthma by up to 200 times in individuals sensitized to fungi [90].

The relationship between allergic sensitization and asthma attacks seems particularly significant in children. A recent study in a pediatric population with severe asthma showed that 94% were sensitized to indoor allergens [91], suggesting the importance of allergic sensitization as a risk factor for poorly controlled asthma. These data have been confirmed in studies on populations admitted to the emergency room for an asthma attack. The authors showed a predominance of asthmatics sensitized to the allergens that were prevalent in each area, suggesting that the development of hypersensitivity to indoor allergens is the most frequent risk factor for admission to the emergency room with asthma, given that they are involved in up to 90% of hospital admissions [92]. Therefore, sensitization to seasonal allergens has been associated with epidemics of asthma attacks and sudden death due to asthma [93]. Sensitization and exposure to *Alternaria* (with increased risk of respiratory arrest in asthmatic patients) [94] and sensitization to house dust mites, animal dander, and cockroaches have been shown to be risk factors for admission to the emergency room [95].

Moreover, a synergistic interaction has been demonstrated between sensitization, allergen exposure, and viral infection in asthmatic patients during acute attacks, especially in the pediatric population [96].

In any case, a complete assessment of patients diagnosed with severe asthma should undoubtedly include a rigorous workup to detect potential trigger allergens. The study should include allergens that are hidden or otherwise unapparent, given that avoiding these allergens may be highly effective in controlling the disease, as is treatment with omalizumab. One particular type involves severe asthma patients who are sensitized to fungi and have seen their symptoms improve appreciably as a result of antifungal treatment [97].

Exposure to occupational allergens

The risk of suffering from adult-onset asthma increases with exposure to workplace substances that are sensitizers [98]. In a longitudinal study of the European Community Respiratory Health Survey, the population risk for the development of adult-onset asthma attributable to occupational exposure was between 10% and 25%, which is equivalent to an incidence of new-onset asthma of 250-300 cases per million people per year [98]. Occupational exposure contributes to approximately 1 of every 7 severe asthma attacks among exposed workers [99], although there are few data linking exposure to workplace substances with the severity or control of asthma [100]. The French Epidemiological Study on the Genetics and Environment of Asthma [100] evaluated the relationship between exposure to substances causing occupational asthma and disease severity. The methodology involved an asthma severity score based on clinical indicators (frequency of exacerbations, persistence of symptoms between exacerbations, and hospitalizations for asthma in the last 12 months), and an asthma-specific job exposure matrix was applied to assess the type of occupational exposure. The protocol combined a case-control study with a family study of relatives of patients with asthma; 148 adult patients (mean age 43 years) were recruited in chest clinics, and 228 control individuals without asthma were recruited from the general population. Workplace exposure involved either substances known to cause the disease (high- or low-molecular-weight agents and environments with mixed exposure) or irritants that do not cause asthma. The study observed that the patients with severe asthma had occupational exposure to asthma-inducing substances more often than patients with mild asthma or the control individuals. At the same time, the study revealed a reverse pattern for exposure to irritants (greater frequency of exposure in control subjects). When specific agents that cause occupational asthma were considered, the study revealed a significant association between asthma severity and exposure to highly reactive chemicals (OR, 4.8; 95%CI, 1.7-13.2), industrial cleaning products (OR, 7.2; 95%CI, 1.3-39.9), sensitizing metals (OR, 6.6; 95%CI, 1.5-29.5), and latex (OR, 3.3; 95%CI, 0.8-14.1). The study also revealed an association between severity and working in mixed environments such as textile production (OR, 24.8; 95%CI, 2.6-240.4).

In the published cases of fatal occupational asthma, the causal agents identified included cereal flour (baker), isocyanates [101,102], green coffee powder, gum arabic spray (graphic arts), bicycloheptane bromide, papain, and shark cartilage powder [101]. In most cases of fatal occupational asthma, no specific IgE determinations or provocations with suspected agents were performed.

Evidence-based guidelines on the diagnosis, prevention, and management of occupational asthma have recently been published [103]. General standards of treatment for asthmatics should be applied, and if the asthma worsens markedly at work, the patient should be removed from the area or job that caused the worsening and, when exposure to the causative agent ceases, the patient's asthma should be reassessed to evaluate possible improvement. Primary and secondary prevention strategies should be directed towards controlling occupational exposure and include intensive educational programs and improved management of asthma.

Respiratory infections

Viral—and in some cases bacterial—respiratory infections contribute to severe asthma exacerbations and can persist in the airways for long periods of time after the attack. However, the role of infections in the development of persistent severe asthma remains unknown [61]. Prospective cohort studies have suggested that rhinovirus infections are a risk factor for developing asthma, although it is unclear how they affect severity [104]. Rhinovirus infections are the most common cause of asthma exacerbations [105] and one of the major reasons for hospitalization [106]. These attacks are more severe and prolonged and are associated with neutrophilic inflammation. They are also more refractory to treatment with corticosteroids than other types of attacks [107]. The results of one in vitro study showed that the bronchial epithelium cannot spontaneously generate interferon in response to rhinovirus infection [108]. These findings may explain why the virus continues to replicate and cause cytotoxic damage and why viral infections respond poorly to treatment with corticosteroids. Intracellular bacterial infections, such as those caused by *Chlamydia*, have also been associated with chronic severe asthma [109]. Their diagnosis requires a combination of regular serology testing based on polymerase chain reaction in lung samples. The use of antibiotics in these patients would improve their asthma [110].

Pollutants and toxins

Asthmatics are more vulnerable to pollutants, which can worsen their condition, even at concentrations below those recommended by the US Environmental Protection Agency [111]. Several studies have shown an association between hospitalization for asthma and concentrations of SO_2, NO_2, ozone, and particles [112-114]. During the pollen season, high levels of pollutants can lead to increased frequency of symptoms and use of bronchodilator rescue medication among pollen-allergic patients [115,116].

Pollutants interact with pollen on 3 levels: *(1)* they increase the allergenic potency of the pollen, making them more reactive, and act as adjuvants in the immune response; *(2)* they can transport the allergenic particles of the pollen grains or other parts of the plant, thus facilitating access to the airways [118]; and *(3)* they can induce oxidative stress in the respiratory epithelium [119], thus provoking an inflammatory response that facilitates penetration by allergens, which in turn initiates the onset of symptoms in allergic individuals.

Drugs

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs): The prevalence of hypersensitivity to NSAIDs varies between 0.6% and 2.5% in the general population and between 3% and 11% in adult asthma patients [120]. A patient's history of aspirin-induced asthma begins during the fourth decade of life, with persistent rhinitis. Onset of asthma, aspirin intolerance, and nasal polyposis have an average latency period of 5 years [121]. Aspirin-induced asthma is more common in women, and approximately one-third of affected patients are atopic [122]. Ingestion of aspirin and other NSAIDs precipitates acute attacks of severe asthma in the first 3 hours after exposure to the drug, which can be associated with profuse rhinorrhea, conjunctival injection, and occasional involvement of other organs [123].

The only definitive method for confirming the diagnosis is the controlled provocation test with increasing doses of aspirin [123], which can be performed orally (the most frequent method), bronchially, and nasally. Lysine acetylsalicylate in aerosol form is used for the inhalation test, and a positive result is characterized by mild bronchospasm that is easily reversed with $ß_2$-adrenergic agonists [124].

Aspirin-induced asthma is the result of the inhibition of the cyclooxygenase (COX) enzyme in the airways of sensitive patients [125]. At least 2 isoenzymes (COX-1 [constitutive] and COX-2 [inducible]) have been reported, and their production is determined by 2 different genes. The inhibition of COX-1 precipitates asthma attacks in sensitive individuals, but the inhibition of COX-2 does not.

Doctor and patient education is very important for avoiding administration of aspirin and other COX-1–inhibiting NSAIDs, which can cause severe and potentially fatal asthma reactions. Patients can receive alternative drugs, such as sodium salicylate and salicylamide, although these are not as potent as analgesics or anti-inflammatory agents. Nabumetone and meloxicam, which inhibit COX-2 more selectively than COX-1, may induce bronchospasm when administered in high doses. The most specific inhibitors of COX-2, celecoxib and etoricoxib, are well tolerated by patients with aspirin-induced asthma [126,127].

Treatment of aspirin-induced asthma does not differ from that of persistent asthma. Most patients present moderate-to-severe persistent asthma, and approximately half require ongoing treatment with OCS to control the disease [121]. In addition, many cases require rhinosinusitis surgery, and desensitization is indicated in some patients. A number of guidelines recommend training these patients in the self-administration of adrenaline [8].

Angiotensin-converting enzyme inhibitors (ACEIs): Depending on the series, coughing associated with the use of ACEIs occurs in 3% to 20% of treated patients. Coughing is more common in women, regardless of the drug dose and drug treatment time, and can appear a week after starting treatment; however, onset can be delayed by up to 6 months [128,129].

Coughing is persistent, nonproductive, and accompanied by irritation and pharyngeal itching. It does not occur more frequently in asthmatics and does not tend to obstruct the airflow, but often worsens when the patient is lying down. In general, coughing requires treatment to be withdrawn

and resolves 1-4 weeks after discontinuing treatment with ACEIs. If the treatment is reintroduced, coughing reappears after approximately 3 weeks. Similarly, asthma attacks and respiratory failure may appear, although they are also usually sporadic (0.01%-0.1%) [129,130].

It is believed that the coughing is caused by bradykinin and prostaglandins, since NSAIDs and sulindac suppress the coughing caused by ACEIs. Treatment consists of discontinuing the ACEI, although some authors show improvement with the use of theophylline, sodium cromolyn, and picotamide, a thromboxane inhibitor [129].

ß-Blockers: ß-Blockers can cause episodes of bronchospasm in both asthmatic patients and healthy individuals, regardless of the route used (oral, intravenous, and even conjunctival) [130,131].

Blocking of ß-adrenergic receptors in the bronchi and bronchioles can cause increased air resistance, and the increase in parasympathetic activity can trigger coughing and even bronchospasm, which is sometimes very severe and even fatal. Therefore, we should be very careful when prescribing this group of drugs to patients with asthma or chronic obstructive pulmonary disease, even when the prescribed agent is a cardioselective or partial agonist. This is because the selectivity of these agents is not absolute: cardioselectivity is usually dose-dependent, and with sufficient doses, these agents block all receptors [132]. The respiratory side effects usually disappear a month after discontinuing treatment with ß-blockers [133].

Uncontrolled Persistent Severe Asthma

We can distinguish between 2 types of patients with uncontrolled persistent severe asthma [1]:

- Those who require multiple high-dose treatments (including OCS) for control (corticosteroid-dependent asthma) and present relative insensitivity to therapy.
- Those who do not achieve adequate control of the disease, despite following high-intensity treatment, and who show resistance to OCS (refractory or corticosteroid-resistant severe asthma).

Performing a differential cell count in induced sputum can help determine the phenotype of these patients [8]. The presence of eosinophilic inflammation indicates a potentially good response to corticosteroids.

The term treatment-resistant asthma refers to asthma that does not respond to corticosteroids, which, given their anti-inflammatory effect, constitute the cornerstone of treatment strategies for this disease. Woolcock [134] defined treatment-resistant asthma as a limited improvement (increase in FEV_1 <15%) after a cycle of 2 weeks of 40 mg/d of prednisolone in patients with significant bronchial obstruction (FEV_1, <70%) and a positive bronchodilatory response (improvement in FEV_1, >15%) to inhaled salbutamol. Absolute resistance to corticosteroids is very rare, even in very severe asthma, with a prevalence of less than 1 per 1000 asthmatics [135]. A rightward shift in the dose-response curve can be observed in many patients with severe asthma, who require higher doses of corticosteroids to manage and control their asthma, ie, doses that are higher than normal or expected for their severity level. Corticosteroid-resistant asthma is at the lower end of the response scale of the dose-response curve [136,137].

Various epidemiological studies have attempted to profile this type of asthmatic, including the multicenter study by The European Network For Understanding Mechanisms Of Severe Asthma [57], which found a series of factors associated with uncontrolled severe asthma, including absence of an allergic component, aspirin intolerance, neutrophilic inflammation, fixed airway obstruction, and a predominance of female gender. Despite treatment with high doses of OCS, these patients presented high levels of eosinophils and neutrophils in sputum as a marker of resistance to treatment.

Conflicts of Interest

P Barranco has received speaker's honoraria from MSD, Novartis, and Chiesi.

C Pérez-Francés has received speaker's honoraria from Almirall and GSK.

S Quirce has been on advisory boards and has received speaker's honoraria from AstraZeneca, GlaxoSmithKline, MSD, Novartis, Almirall, Altana, Chiesi, and Pfizer.

E. Gómez-Torrijos has received speaker's honoraria from MSD, GSK, and Alk-Abelló.

R Cárdenas, S Sánchez-García, F Rodríguez-Rodríguez, and P Campo declare that they have no conflicts of interest.

JM Olaguibel has received speaker's honoraria from Astra-Zeneca, Chiesi, GlaxoSmithKline, and MSD and has participated in research supported by MSD.

J Delgado has received speaker's honoraria from GlaxoSmithKline, MSD, Novartis, and Chiesi and has coordinated studies promoted by Esteve and Pfizer.

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