RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Guidelines for the Diagnosis and Management of Difficult-to-Control Asthma

Assembly on Asthma of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)*

Definition and Types

Current clinical practice guidelines (Global Initiative for Asthma [GINA][1] and Spanish Guidelines for Asthma Management [GEMA][2]) establish that asthma is well controlled when there are no symptoms, exacerbations, requirement for rescue medication, restrictions on normal physical activity, or adverse effects of treatment, and when lung function is normal. In contrast, one or more of these criteria is not met in poorly controlled asthma. Thus, difficult-to-control asthma can be defined as that which is inadequately or poorly controlled despite an appropriate therapeutic strategy that is adjusted to clinical severity. The English-language literature tends to contain a variety of terms—including refractory asthma,[3] difficult-to-control asthma,[4] and difficult/therapy-resistant asthma[5]—to define this most severe type. In these guidelines, we will use the term difficult-to-control asthma to reflect the term considered appropriate in Spanish. This term encompasses variants or phenotypes of the disease such as very severe, life-threatening, unstable, corticosteroid-dependent, and corticosteroid-resistant asthma.

The GEMA guidelines distinguish 2 subgroups of difficult-to-control asthma, true and false (level D evidence).[2] The false type groups together asthma affected by factors commonly unrelated to the disease itself (see following section) that lead to limited treatment response and, therefore, a form of disease that is only apparently difficult to control. The sections Epidemiology and Risk Factors, Lung Function, Pathology, and Poor or Altered Response to Medication contained within these guidelines are presented from a perspective in which only asthma that is itself genuinely difficult to control is considered true difficult-to-control asthma. The Diagnostic Approach and Treatment sections consider both types of difficult-to-control asthma, since in order to reach a definitive diagnosis of true difficult-to-control asthma it is necessary to rule out or adequately treat all factors that influence the management of the disease. The Diagnostic Approach section specifies the tests and therapeutic regimens that should be used to arrive at a diagnosis of true difficult-to-control asthma, through a process in which all causes of false difficult-to-control asthma are ruled out. Finally, the Treatment section describes the recommendations that should be followed for patients in whom the disease is not well controlled despite treatment with the highest level regimen (severe asthma),[2] as well as possible

TABLE 1
Diagnostic Criteria for Difficult-to-Control Asthma*

A diagnosis of difficult-to-control asthma is established when, once false difficult-to-control asthma has been ruled out, 2 major criteria or 1 major and 2 minor criteria are met. Criteria are modified in part from the proposal of the American Thoracic Society Workshop on Refractory Asthma[3]

Major criteria
- Use of oral corticosteroids continuously or for more than 6 months in the last year
- Continuous use of inhaled corticosteroids at high doses (budesonide or equivalent >1200 µg/day or fluticasone >880 µg/day) alongside another antiasthmatic drug, usually a long-acting β_2-adrenergic

Minor criteria
- Daily requirement for short-acting β_2-adrenergic rescue medication
- FEV_1 less than 80% of theoretical value or greater than 20% variability of PEF
- One or more visits to the emergency department in the last year
- Three or more courses of oral corticosteroids in the last year
- Prior episode of life-threatening asthma
- Rapid deterioration of lung function

*FEV_1 indicates forced expiratory volume in the first second; PEF, peak expiratory flow.

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Manuscript received April 14, 2005. Accepted for publication April 26, 2005.

alternatives for patients who are refractory to treatment (ie, those with true difficult-to-control asthma).

Based on the criteria shown in Table 1, a diagnosis of difficult-to-control asthma is established when 2 major criteria, or 1 major criterion and 2 minor criteria coexist (level D evidence).[5] The criteria shown are those normally used to establish the degree of control of asthma.

Difficult-to-Control Asthma Attributable to Factors Other Than the Disease Itself

In the majority of patients referred to specialist clinics as a result of poorly controlled asthma, the situation has been brought about by factors unrelated to the disease itself. These include incorrect diagnosis of the asthma, the fact that the patient suffers from other diseases with similar symptoms that lead to confusion, the presence of uncontrolled aggravating symptoms, or inadequate treatment adherence. Thus, the first step is to rule out these types of problem, embraced by the definition of false difficult-to-control asthma (Table 2).

1. The diagnosis of asthma is incorrect. Other respiratory diseases (extrinsic allergic alveolitis, chronic eosinophilic pneumonia, bronchiectasis, or pulmonary embolism), and even nonrespiratory diseases (left heart failure), can create confusion that leads to errors in diagnosis and treatment. This category would also include the so-called pseudoasthmas, which are obstructive diseases of the upper airway, such as vocal cord dysfunction, laryngotracheal tumors, inhalation of foreign bodies, tracheomalacia, and tracheobronchial malformations. These conditions can manifest clinically as asthma and their diagnosis is particularly difficult. Consequently, the criteria on which a diagnosis of asthma is based should be carefully analyzed and differential diagnosis to rule out these types of clinical condition should be undertaken in each case (Table 3).

2. The patient has asthma but may also have other diseases that share symptoms with asthma and, therefore, have not been considered or strategies have not been implemented for their diagnosis and subsequent treatment. Thus, it should be considered whether a patient with asthma may also have obstruction of the upper airway, bronchiectasis, anxiety and hyperventilation, hyperthyroidism, or more frequently, rhinosinusitis and/or gastroesophageal reflux. Between 75% and 80% of patients with asthma present seasonal or perennial rhinitis and 7% to 15% have nasal polyposis. Appropriate treatment of these conditions improves the symptoms of asthma (level B evidence).[6] The reported prevalence of gastroesophageal reflux disease in asthmatic patients is variable, ranging from 15% to 72% according to the diagnostic procedure used (clinical symptoms, pH measurement, esophageal manometry).[7] Although patients with asthma and gastroesophageal reflux exhibit poorer control of their asthma (level C evidence), it is not clear whether treatment of reflux improves asthma.

TABLE 2
Situations Leading to False Difficult-to-Control Asthma

Incorrect diagnosis of asthma
Comorbid conditions with similar symptoms
– Obstruction of the upper airway (vocal cord dysfunction, tracheal stenosis, etc)
– Hyperventilation syndrome
– Hyperthyroidism
– Rhinosinusitis
– Gastroesophageal reflux
– Bronchiectasis
Uncontrolled aggravating factors
– Exposure to allergens (pets)
– Occupational asthma
– Drugs (β-blockers, nonsteroidal antiinflammatory drugs, etc)
Treatment nonadherence

TABLE 3
Diagnoses That Can Be Confused With Difficult-to-Control Asthma in Adults

Cystic fibrosis
Bronchiectasis
Inhalation of a foreign body
Tracheobronchomalacia
Recurrent aspiration
Chronic obstructive pulmonary disesase
Congestive heart failure
Tumors affecting the central airways
Obstructive bronchiolitis
Vocal cord dysfunction
Bronchial amyloidosis
As part of a predisposition to asthma: allergic bronchopulmonary aspergillosis and pulmonary eosinophilic syndromes

3. Intercurrent factors can aggravate asthma and make it more difficult to control. The patient may be habitually exposed to an allergen to which they are sensitive (pets or occupational allergens) or regularly take medications that trigger asthma. Patients should be questioned about any medications they are taking, with particular emphasis on the following: *a)* β-blockers, both oral and topical (conjunctival), and *b)* acetylsalicylic acid and other nonsteroidal antiinflammatory drugs (NSAIDs). In the latter case, it should be remembered that NSAIDs are contraindicated in patients who present prior episodes of intolerance and it is recommended that they not be used in asthmatic adults (level D evidence), since between 4% and 28% are susceptible to exacerbations related to treatment with these drugs, particularly in patients with nasal polyposis.

4. Treatment adherence is poor or nil. All chronic diseases that require prolonged treatment are associated with an appreciable number of patients who stop taking their medication. This lack of treatment adherence can be partial or total and voluntary or involuntary. Treatment adherence in asthma is thought to be in the region of 30% to 50%.[8] Consequently, when the therapeutic response differs from expectations, doctors should first confirm whether the patient is adhering to the prescribed treatment.

It is very difficult to use direct methods (analytic measurements of drug levels in biological samples) to evaluate adherence in asthma patients; consequently, indirect methods are required. Although certain parameters, such as plasma cortisol and exhaled nitric oxide (NO), can be measured, their usefulness has yet to be established. While it is also possible to quantify leftover medication or use electronic register devices in inhalers, these procedures are complex and not entirely accurate. Consequently, treatment adherence in asthmatic patients is usually assessed through open and indirect questions[9] or through simple questionnaires such as that described by Chambers et al,[10] which addresses the frequency of use of inhaled corticosteroids. The high rate of nonadherence depends on a number of factors. Some of these factors are related to the characteristics of the drugs used, such as type of device, route of administration, complexity of the therapeutic regimen leading to the patient not understanding the instructions given, fear of side effects, or high cost, while others are related to patient characteristics, such as emotional difficulties (especially depression) or social problems (including alcohol abuse, social isolation, and lack of familial support). The patient's personality, attitude towards the illness, and perception of its severity are particularly relevant to adherence (level B evidence). It is also possible for a patient to take the medication but to use an incorrect inhalation technique. Inhalation, which is commonly used to deliver treatment in asthma, requires some degree of training and specific preparation to support correct performance. Health workers should explain the characteristics of the chosen inhaler to the patient, show them how it is used, and ask them to perform the maneuver with a placebo in order to correct possible errors (level B evidence). In addition, it is advisable to confirm the patient's technical skill during subsequent appointments.

Epidemiology and Risk Factors

The prevalence of difficult-to-control asthma is not known with any degree of accuracy. In the literature, it is usually suggested to be around 5% of all patients with asthma,[3,11] a figure that has been extrapolated from studies performed using various methods in patients with severe asthma. What is clear is that patients with difficult-to-control asthma have a disproportionate impact on health resources and the cost, both direct and indirect, of asthma.[12,13]

Factors that contribute to asthma being refractory to treatment have yet to be clearly identified. Some studies have established weak associations with certain genetic alterations and various environmental factors. However, due to the weakness of the evidence, they cannot be considered clearly demonstrated risk factors.

Genetic Factors

Various mutations have been linked to difficult-to-control asthma. Mutations in the genes that encode interleukin 4 (IL-4) and its receptor appear to be associated with reduced lung function and episodes of life-threatening asthma.[14] Factors implicated in airway remodeling, such as transforming growth factor β1 (TGF-β1) and monocyte chemoattractant protein (MCP-1)— both possible promotors of fibrotic reactions—have been linked to asthma severity.[15,16] Another important factor is the possibility of mutations in the receptors for the main drugs used in the treatment of bronchial asthma, β_2-adrenergics[17] and corticosteroids,[18,19] leading to a poor treatment response to these drugs. Links with genetic factors have been considered in various types of asthma that frequently behave like difficult-to-control asthma, including corticosteroid-resistant asthma, corticosteroid-dependent asthma, and aspirin-induced asthma (a syndrome characterized by severe asthma, nasal and sinus polyposis, and NSAID intolerance).[20]

External and/or Environmental Factors

The following have been linked to some aspect of asthma severity: continuous exposure to allergens (mainly from dust mites,[21] alternaria,[22] and cockroaches[23]), smoking,[24] intolerance to NSAIDs,[25] and infection with respiratory syncytial virus,[26] chlamydia,[27] and mycoplasma.[28]

Lung Function

The functional alterations that are traditionally considered to define difficult-to-control asthma can be grouped into 3 categories:

1. Obstructive airflow limitation that is not modified by corticosteroid treatment of at least 15 days.

2. Intense bronchial hyperreactivity triggered by stimuli that do not usually produce bronchospasm.

3. Excessive variability in airway patency.

In addition to these anomalies, which represent an extreme of what are considered functional characteristics of asthma, there are also differences in the mechanical behavior of the lung that alter the relationship between respiratory pressure and flow and lead to changes in lung volume. The causes of these anomalies are not well understood and are assumed to be due to changes at the interface of the airways with the lung parenchyma.

Bronchial obstruction and reduced lung elastic recoil lead to hyperinflation phenomena, premature airway closure, and limited expiratory flow. Diffusing capacity remains unaltered.

Measurement of lung volume in these patients reveals a pattern of air trapping with increases in residual volume, functional residual capacity, and total lung capacity; in contrast, vital capacity and all of its subdivisions are reduced. Closing volume tends towards being equal to or greater than residual volume.[29]

Trapping and obstruction of airflow deteriorate further during effort, leading to the appearance of

dynamic hyperinflation. This phenomenon, manifested by progressive reduction of inspiratory capacity and limited expiratory flow, is the main cause of the dyspnea and limited exercise capacity presented by these patients (level B evidence).

Changes in lung volume affect inspiratory muscle activity by causing muscle shortening. This load is opposed by an increase in tonic inspiratory activity, both of the diaphragm and the intercostal muscles, that persists at the onset of expiration. Consequently, the end-expiratory lung volume never reaches the volume at muscle relaxation, thus further increasing air trapping.[30]

Airway resistance increases to up to 3 times its normal value in patients with chronic persistent asthma. This increased airway resistance is mainly dependent upon inflammatory alteration of the bronchial mucosa and the extent of smooth muscle contraction. The relationship between volume and peak expiratory flow (PEF) reveals a reduction of flow at all levels, especially the flow obtained at lower volume forced expiratory flow, midexpiratory phase. It is precisely this resistance to improvement of flow, expressed at isovolume, that characterizes the difficulty of controlling asthma in these patients.

The main alterations in gas exchange occur only during asthma attacks and consist of a shunt effect due to the presence of mucus plugs and peripheral atelectasis.

In patients with severe asthma, especially those presenting altered emotional state or a history of life-threatening asthma, a reduction in the voluntary ventilatory stimulus has been described that reduces muscle recruitment and, therefore, the risk of muscle fatigue, but implies an increase in alveolar hypoventilation. The causes mainly originate in the central nervous system and coincide with a reduction in the perception of dyspnea,[31] sensitivity to hypoxic ventilatory stimulus, and inspiratory resistive load (level B evidence).

Pathology

The pathologic processes that underlie difficult-to-control asthma are still to be clearly elucidated. Most studies have identified airway remodeling with thickening of the basement membrane, hypertrophy of the smooth muscle, and glandular hyperplasia. These changes have even been seen in children with severe asthma.[32] Distal airway involvement with inflammation of the terminal bronchioles has also been described.

Based on bronchial biopsy and bronchoalveolar lavage in patients with severe asthma despite treatment with high doses of corticosteroids, 2 pathologic patterns have been proposed according to the presence or absence of eosinophils.[33] Patients with increased numbers of eosinophils in the lungs display greater thickening of the basement membrane and increases in the number of CD3, CD4, and CD8 lymphocytes, macrophages, mastocytes, and levels of TGF-β. From a clinical perspective, patients with this pattern present more episodes of respiratory failure that require intubation. However, a recent randomized, controlled, double-blind trial questioned whether the eosinophilic phenotype is a refractory phenomenon, since the number of eosinophils in sputum was found to return to normal following treatment with high doses of parenteral corticosteroids (triamcinolone).[34]

Although increased numbers of neutrophils have been identified in all cases of severe asthma, the pathologic significance of this finding is not clear. It may reflect the action of corticosteroid treatment in preventing apoptosis of these cells and it is not clear whether neutrophil number plays a direct role in the pathophysiology of the disease.

Poor or Abnormal Response to Medication

Resistance to corticosteroid treatment is rare and only affects 1 in every 1000 to 10 000 asthmatic patients. Resistance to corticosteroids is defined by a poor response of forced expiratory volume in the first second (FEV_1)—less than 15% and 200 mL—following treatment with prednisone or prednisolone at 40 mg/day (20 mg taken twice daily) for 2 weeks.[3] If the patient does not respond, the dose should be doubled and the response monitored over the course of 2 more weeks. Some patients with severe asthma do not meet the criteria for corticosteroid resistance but, nevertheless, respond to higher doses than expected, indicating an altered, but not absent, response to corticosteroids.

A number of mechanisms could explain the resistance to corticosteroids observed in asthmatic patients. Monocytes and T lymphocytes isolated from these patients have a reduced response to corticosteroids in vitro. In some of those patients, the affinity of the glucocorticoid receptor for the corticosteroid ligand is reduced, an effect that can be reproduced by incubating T cells with IL-2 and IL-4.[35] This reduced affinity of the receptor for its ligand leads to a functional inhibition of the effects of corticosteroids. In these same patients, there is a reduction in the inhibitory effects of corticosteroids on activating protein-1 (AP-1) activation and cytokine expression; these effects are probably secondary to an increased activation of the AP-1 and jun kinase pathways.[36] The increased activation of AP-1 may be due to sequestration of the glucocorticoid receptor, preventing its interaction with other proteins and, therefore, generating resistance to corticosteroids. Corticosteroid resistance would occur at sites of inflammation but not in other areas, an observation that would explain why these patients are resistant to the antiinflammatory effects but not the secondary effects of corticosteroids.[37]

In most asthmatic patients, a direct correlation exists between the ability of the glucocorticoid receptor to be translocated to the nucleus of mononuclear cells and the extent of histone acetylation, which translates into increased transcriptional activity. However, in a small percentage of these patients nuclear translocation of the glucocorticoid receptor occurs without leading to histone acetylation.[38] Through the use of specific antihistone antibodies, this defect has been localized to

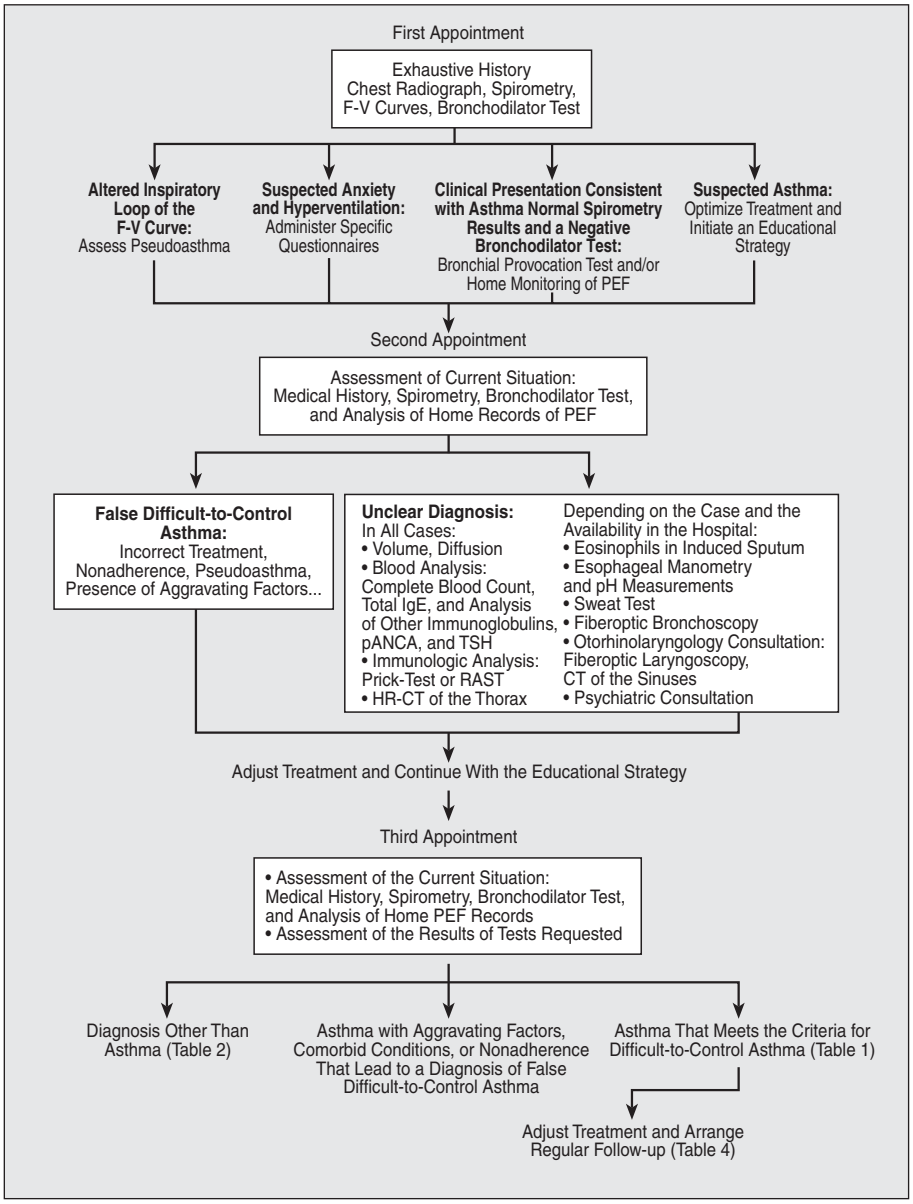

Figure 1. Action plan for medical appointments. F-V indicates flow/volume; PEF, peak expiratory flow; IgE, immunoglobulin E; pANCA, perinuclear antineutrophil cytoplasmic antibodies; RAST, radioallergosorbent test; CT, computed tomography; HR-CT, high-resolution CT; TSH, thyroid stimulating hormone.

lysine 5 of histone H4.[39] This residue is critically important for the action of corticosteroids, since it regulates apoptosis of T cells and the secretion of secretory leukocyte protease inhibitor. Taken together, these observations suggest that defects exist in the nuclear translocation of the glucocorticoid receptor and/or its interaction with the transcriptional machinery of the cell, factors which explain the poor or null response to corticosteroid treatment.

Diagnostic Approach to Suspected Difficult-to-Control Asthma in Specialized Clinics

When difficult-to-control asthma is suspected, a diagnostic procedure must be followed that rules out false disease. This first requires unequivocal diagnosis of asthma and ruling out of overlapping conditions that display similar symptoms to asthma and that could account for apparent difficult-to-control asthma. In addition, it is important to assess aggravating factors and treatment adherence. Secondly, attempts must be made to control the disease with a specific therapeutic strategy and, finally, establish a diagnosis of difficult-to-control asthma according to the criteria shown in Table 1.

Although the use of diagnostic protocols can be helpful,[4,40-42] there is currently no single, internationally accepted protocol. The GEMA guidelines recommend a diagnostic approach with multiple levels of test complexity.[2]

The guidelines provided here propose a protocol based on consensus recommendations,[2,3,5] expert reviews,[4,42,43] and the experience of the authors

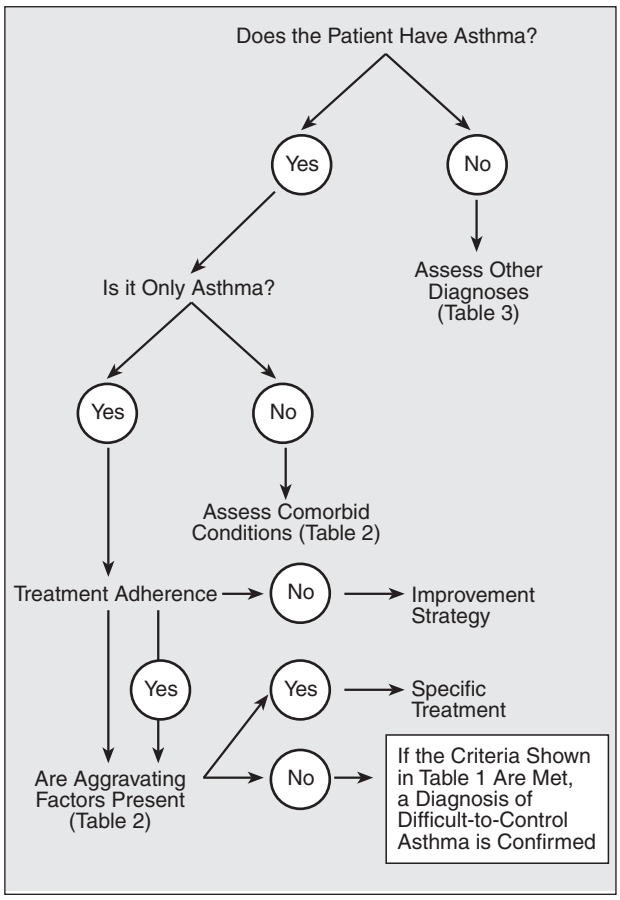

Figure 2. Diagnostic algorithm for difficult-to-control asthma.

themselves. It is structured by medical appointments—a minimum of 3 appointments, but in some cases more appointments will be necessary over the course of 6 to 12 months—until a diagnosis is confirmed (Figure 1), and it is complemented by an action plan that leads to diagnosis of difficult-to-control asthma (Figure 2).

First Appointment

1. Exhaustive history (taking a new medical history even if the patient is known) of the main symptoms, type of asthma attack, previous hospitalization, existence of triggers (occupational, domestic allergens, drugs, etc), potential comorbidity (gastroesophageal reflux, vocal cord dysfunction, rhinosinusitis, etc), and previous treatments.

2. Chest radiograph if one is not already available.

3. Spirometry, flow-volume curve, and bronchodilator test.

4. If the inspiratory loop of the flow-volume curve (with FEV_1 values close to normal) is abnormal, the presence of pseudoasthma should be evaluated.

5. When anxiety disorder with hyperventilation syndrome is suspected, specific questionnaires on hyperventilation[44] and anxiety[45] are useful.

6. When spirometry results are normal and the bronchodilator test negative, a bronchial provocation test and home monitoring of PEF can also be informative.

7. Once a diagnosis of suspected asthma is established, treatment should be optimized and an educational strategy initiated that will include the following:

– Explain to the patient the presumptive diagnosis, the tests that are going to be performed, and the treatment strategy to be followed.
– Establish a relationship of trust with the patient and discuss the concerns and beliefs that the patient has about the disease and the outcomes they are hoping for.
– Demonstrate correct use of inhalers.
– Demonstrate home monitoring of PEF.
– Discuss treatment adherence and suggest methods to avoid forgetting to take medication.

8. Arrange a second appointment to take place within a short period of time (between 7 and 30 days, depending on the individual case).

Second Appointment

1. Assessment of current condition and response to treatment, inquiring about symptoms, use of short-acting β_2-adrenergic drugs, and treatment adherence, performing spirometry and a bronchodilator test, and analyzing home PEF records.

2. Putting together all of the information obtained from point 1, a diagnosis of false difficult-to-control asthma will be reached in many cases (as a result of incorrect treatment, lack of treatment adherence, the presence of aggravating factors, or pseudoasthma) and action should be taken accordingly. In other cases, the diagnosis will still be unclear and it will be necessary to perform more tests to reach a clear diagnosis of difficult-to-control asthma, ruling out other similar diseases (Table 3):

– Lung function tests: flow-volume curves, static volumes, and diffusion.
– Blood analysis: complete blood count total immunoglobulin E (IgE), and analysis of other immunoglobulins, perinuclear antineutrophil cytoplasmic antibodies, and thyroid stimulating hormone.
– Immunologic analysis (prick test or radioallergosorbent test).
– High-resolution computed tomograph (CT) of the thorax.
– Analysis of eosinophils in induced sputum.
– Esophageal manometry and pH measurements.
– Sweat test.
– Fiberoptic bronchoscopy.
– Otorhinolaryngology consultation (fiberoptic laryngoscopy, CT of the sinuses).
– Psychiatric consultation.

Tests in the first 4 categories are always necessary, while the rest, particularly the most invasive, will depend on suspected diagnoses.

TABLE 4
Treatment Plan

1. Address the factors that could influence the lack of control of the disease (treat comorbid conditions, remove triggers, improve adherence, etc)
2. Initial intensive treatment until the best possible response is achieved. This should begin with the regimen recommended for severe asthma[2] and a short course of oral corticosteroids. The decision of whether or not to add other drugs will depend upon patient response
3. Investigate the possible causes when a deficient response to oral corticosteroids is observed: incomplete absorption, failure of conversion to the active form, rapid elimination, or resistance
4. Do not use "alternative" treatments (gold salts, cyclosporin, methotrexate, and others) except in exceptional cases
5. Organize regular follow-up appointments as appropriate for the individual patient, along with written action plans

3. The educational strategy initiated in the first appointment should be continued.

4. Treatment should be maintained or adjusted according to the current condition of the patient and an appointment arranged for between 1 and 3 months.

Third Appointment

1. Assessment of current condition and response to treatment, inquiring about symptoms, use of short-acting β_2-adrenergic drugs, and treatment adherence, performing spirometry and a bronchodilator test, and analyzing home testing records for PEF.

2. Assessment of the results of the tests requested at the previous appointment.

3. Based on the data obtained, the diagnostic algorithm shown in Figure 2 should be followed to reach or rule out a definitive diagnosis of difficult-to-control asthma, also confirming that the criteria shown in Table 1 are met.

4. Periodic follow-up should be planned over time scales appropriate to the degree to which the disease is controlled.

Treatment

Guidelines for asthma management recommend a treatment scale according to disease severity, aimed at controlling the disease at all times.[1,2] These recommendations are universally accepted because they are based on strong scientific evidence. However, there are no clear, internationally accepted regimens for those patients whose asthma remains uncontrolled despite treatment at the highest point on the scale (severe asthma). This is due to a relative absence of studies and the fact that those studies that are currently available have used various different definitions of difficult-to-control asthma.[46-49] Consequently, the scientific evidence is insufficient.

When optimal control cannot be achieved, the aim of treatment should be to obtain the best possible results with the fewest undesirable effects (level D evidence).[50] This is the philosophy behind the treatment plan recommended in these guidelines (Table 4).

Remove All Factors That Can Interfere With the Control of the Disease

– Treat comorbid conditions, mainly rhinosinusitis and gastroesophageal reflux.

– Implement strict environmental controls.

– Assess and improve treatment adherence through specific strategies.

Intensive Initial Treatment Until the Best Possible Results Are Achieved

In an effort to achieve control of the disease or the best possible response, the initial treatment regimen should be that recommended for severe asthma: high-dose inhaled corticosteroids (budesonide at 1600 µg/day or fluticasone at 1000 µg/day), long-acting β_2-adrenergics twice daily, and a short course of oral corticosteroids (40 mg/day prednisolone for 15 days). Subsequently, a strategy to reduce the dosage of the drugs should be introduced.

If clinical or functional deterioration is observed upon withdrawal of oral corticosteroids, other drugs should be added to the regimen (theophyllines, antileukotrienes, anticholinergics, and continued oral corticosteroids). No studies are available to help define the most effective combinations. The best strategy is likely to be to try drugs, monitor clinical and functional parameters along with inflammation, and then withdraw drugs that do not achieve a response prior to trying the next.

Measures to prevent osteoporosis should be recommended to patients who require continuous oral corticosteroids.

When a Deficient Response to Oral Corticosteroids Is Observed the Possible Causes Must Be Investigated

– Anomalies in the pharmacokinetics of corticosteroids: incomplete absorption of corticosteroids due to gastrointestinal disorders, failure to convert the inactive form (prednisone) to the active form (prednisolone) due to enzymatic alterations, and rapid elimination through increased metabolism due to interaction with other drugs that induce cytochrome P450, such as rifampicin, phenytoin, carbamazepine, and phenobarbital.[37]

– Corticosteroid resistance. Resistance to corticosteroids is confirmed in patients whose FEV_1 is less than 70% of predicted and who present a positive bronchodilator response by treatment with a 2-week course of oral corticosteroids (40 mg/day prednisone or prednisolone taken as 20 mg twice daily); if there is no response, the dose should be doubled for another 2 weeks. Those patients who respond to higher doses have an altered, but not absent, response to corticosteroids. Some patients with apparent corticosteroid resistance show clinical and functional improvement in response to intramuscular

corticosteroids such as triamcinolone (40 mg every 10 days; level C evidence).[37,52,53] The use of intramuscular corticosteroids is limited in practice by adverse effects; consequently, they should be tested on an individual basis and their efficacy confirmed with serial spirometry. They would only be used as an alternative to very high doses of oral corticosteroids.

When the patient responds to any regimen, the dose should be progressively decreased to maintain it at the minimum level (in a single morning dose) required to maintain the best possible control. It is always recommendable to use prednisolone (the active form) in case of conversion failure.

Alternative Treatments to Reduce the Dose of Oral Corticosteroids

Some patients require high doses of oral corticosteroids for maintenance, and this carries with it undesirable effects. The use of other drugs for which a useful antiinflammatory effect has been demonstrated in other chronic inflammatory processes (mainly systemic collagenosis and vasculitis) is being tested in these patients. The following have been most widely used in efforts to reduce the consumption of oral corticosteroids: colchicine, chloroquine, dapsone, troleandomycin, immunoglobulins, azathioprine, gold salts, cyclosporin, and methotrexate. All of these drugs have modulatory effects on inflammation, along with side effects that must be closely monitored.

The scientific evidence available to date supports the following assertions:

– There is currently insufficient data to justify the use of the following drugs as corticosteroid sparing agents in asthmatic patients: colchicine,[54] chloroquine,[55] dapsone[56] (level C evidence in all 3 cases), troleandomycin (level B evidence),[57] intravenous immunoglobulins (essentially IgG subclasses obtained from healthy individuals),[58,59] and azathioprine (level B evidence).[60]

– Oral or parenteral gold salts[61] and cyclosporin[62] allow a small reduction in the consumption of oral corticosteroids that is only likely to have limited clinical significance. Consequently, taking into account their potential side effects, they cannot be recommended at this stage for routine use in the reduction of oral corticosteroid treatment (level B evidence).

– Most well-designed clinical studies have been performed with methotrexate (evidence level B).[63-65] However, only modest conclusions can be drawn: a reduction in the daily consumption of oral corticosteroids can be achieved but it may be insufficient to significantly reduce the side effects of chronic treatment with oral corticosteroids and, in turn, justify the appreciable risk of hepatotoxicity associated with methotrexate. When used, the drug is administered in a weekly oral dose, with frequent analyses, simultaneous administration of folinic acid, and with safe contraceptive treatment when used in women of a fertile age.

Another drug that should be considered in omalizumab, a monoclonal antibody against IgE that has been extensively evaluated in allergic diseases. In atopic asthma with high levels of IgE, it has been observed to achieve a reduction in the dose of corticosteroids required in 50% of patients (level B evidence).[66] Although omalizumab is well tolerated, its safety profile requires long-term evaluations. It is administered subcutaneously and the dose (150-375 mg every 2 or 4 weeks) depends on the baseline level of IgE and the weight of the patient. A table has been developed to simplify determination of individual dosage.[67] A clinical trial has recently been published that demonstrates the efficacy of omalizumab in patients with difficult-to-control asthma and shows a reduction in the number and severity of asthma attacks, as well as a lower number of visits to the emergency department (level A evidence).[68] As yet, this drug is not commercially available in Spain.

Regular Follow-up and Written Action Plans

Close monitoring is essential in patients with difficult-to-control asthma and regular follow-up appointments (2 or 3 in the first 2 months) should be programmed until the best results are achieved. These appointments should then continue on a less frequent basis (every 3 months) alongside a flexible system for communication between patient and doctor at other times (telephone, telematic system, etc).

All patients with difficult-to-control asthma must have an individual written action plan based on symptoms and PEF values. In order to put it into action, adequate training must be provided. Availability of a self-treatment plan helps to avoid life-threatening asthma attacks[69] and deaths caused by asthma[70] (level C evidence).

Issues Specific to Children

Fortunately, difficult-to-control asthma is very rare in children. Asthma is well controlled by current treatments in most children, and when this is not the case, incorrect diagnosis, incorrect treatment, or a lack of implementation of environmental controls should be suspected. Diagnosis and management of difficult-to-control asthma in older children is very similar to that of adults, while in small children the difference is greater.

Problems Associated With Defining Difficult-to-Control Asthma in Small Children

Firstly, there are a large number of diseases in the first few years of life that are manifested with wheezing and have a clinical presentation that varies little from one to another, presenting a significant challenge in distinguishing between them (Table 5). The younger the child with respiratory problems, the greater the probability of other diseases that mimic asthma being

TABLE 5
Diseases That Can Cause Wheezing in Infants

Upper airways
– Congenital anomalies of the laryngeal area: laryngomalacia, vocal cord paralysis, laryngeal angiomatosis
Obstruction of the large airways
– Congenital anomalies of the trachea and main bronchi: tracheomalacia, bronchomalacia, tracheal or bronchial stenosis
– Vascular rings or laryngeal membranes
– Foreign body in the trachea or bronchi
– Tumors or diseased lymph nodes
Obstruction of the small airways
– Viral bronchiolitis or bronchiolitis obliterans
– Cystic fibrosis
– Bronchopulmonary dysplasia
– Primary ciliary dyskinesia
– Heart disease
Others
– Gastroesophageal reflux and aspiration syndromes

present.[71] Secondly, the definition of difficult-to-control asthma includes a lack of response to appropriate treatment. It is not uncommon to find children with even severe episodes of bronchospasm only during respiratory infections, and who show a poor response to appropriate antiasthmatic treatment; no improvement is seen in many of these patients despite increasing the treatment, although fortunately time normally brings improvement.[72,73] Thirdly, it is not easy to assess lack of control of the disease at these ages, since persistent symptoms (cough, wheezing, etc) are often not specific to asthma and it is difficult to assess bronchial obstruction with lung function tests in smaller children.[74,75]

Pathology

Studies using bronchoalveolar lavage have demonstrated that small children with frequent episodes of wheezing have more pronounced increases in the numbers of lymphocytes and neutrophils than of eosinophils.[76] In older children, although a significant component of the inflammation is also mediated by lymphocytes or neutrophils, it is more common to come across eosinophilic inflammation.[77] There are likely to be different subgroups of patients with difficult-to-control asthma. Some have increased levels of NO that are reduced by treatment with prednisolone, while in others NO remains elevated despite treatment.[78]

Management of Difficult-to-Control Asthma in Small Children

In a child who presents a clinical picture suggestive of asthma that does not respond adequately to treatment, the first response should be to undertake an exhaustive differential diagnosis that allows all of the pathologies indicated in Table 5 to be ruled out. The studies necessary will be indicated according to the clinical presentation of the patient. At least cystic fibrosis, gastroesophageal reflux, immunodeficiency, and bronchopulmonary or vascular malformations should be ruled out.

Once a diagnosis of asthma is confirmed by exclusion of other diseases, it will be necessary to confirm that treatment and environmental control measures are being correctly followed.

Various authors recommend that bronchoscopy is performed with bronchoalveolar lavage and bronchial biopsy in children with difficult-to-control asthma,[79] and suggest that the result of the biopsy, along with the response to a course of systemic corticosteroid treatment and the results of lung function tests, could help to better define the type of asthma presented by the child and in that way to individualize treatment.[80]

The pharmacological management of difficult-to-control asthma in children is similar to that of adults. Firstly, conventional treatment with inhaled corticosteroids at high doses in combination with long-acting bronchodilators should be optimized. Leukotriene antagonists have an additive effect with inhaled corticosteroids in childhood asthma,[81] but no information is available on their effects in severe asthma. Children whose asthma is not sufficiently controlled with this treatment should be treated with oral corticosteroids at an initial dose of 2 mg/kg/day for the shortest period possible. Although it is preferable to use short treatment cycles of no more than 7 days, when these need to be prolonged their use should be restricted to the lowest dose possible in a single morning dose. There is evidence that children whose asthma is not well controlled with oral corticosteroids improve in response to treatment with intramuscular triamcinolone.[82] It is not clear whether this improvement is due to improved treatment compliance or because triamcinolone has a better antiinflammatory profile than oral corticosteroids. Although there are no controlled clinical trials that support the use of immunosuppressant drugs such as methotrexate or cyclosporine in children with severe asthma, some studies have suggested a possible effect.[83,84] Consequently, given the very real possibility of significant side effects, they should only be used with extreme caution.

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