

3. Maintenance Treatment

3.1 Targets

The main aim of asthma treatment is to achieve and maintain control of the disease as soon as possible, as well as to prevent exacerbations and chronic airflow obstruction, and to reduce mortality. Treatment targets (Table 3.1), both in terms of controlling daily symptoms (current control) and preventing exacerbations and the progressive loss of pulmonary function (future risk), can be achieved in the vast majority of patients if they receive suitable treatment.

To achieve these objectives a comprehensive strategy, which is individualized in the long term and based on optimal adjusted pharmacological treatment and supervision measures, environmental control and asthma education, must be followed [90]. Pharmacological treatment must be adjusted in accordance with the level of patient control, without forgetting the most effective therapeutic options, safety and the cost of the various alternatives, taking into account the patient's satisfaction with the level of control achieved. Regular patient assessment is required to determine whether targets are being met. There are validated questionnaires that estimate objectively the level of control of the disease.

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3.2 Prevention of Exacerbations and Control of Asthma

Asthma treatment must follow a comprehensive plan, agreed upon by the doctor and the patient (and eventually his/her family), in which the targets, the means to achieve them and the procedures for their modification or adaptation to the changing circumstances of the disease must be clearly defined. The distinction between the terms current control and future risk as different aspects of control is important, because it has been reported that they may respond differently to treatment [91]. For example, some patients may achieve good daily control of asthma and yet they suffer exacerbations.

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Treatment must be continually adjusted so that the patient is always controlled. This cyclical way of adjusting treatment implies that asthma control must be assessed objectively (Table 3.2), and that the patient must be treated to achieve control and have regular check-ups to maintain control. In other words, if asthma is not well controlled, the

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Table 3.1. Asthma treatment targets

Current Control

- Prevention of symptoms in the daytime, at night and during physical exercise.
- Use of a short-acting β_2 agonist no more than two days a week.
- Maintenance of normal or virtually normal lung function.
- No restrictions on daily life and physical exercise.
- Fulfilment of the expectations of patients and their families.

Future Risk

- Prevention of exacerbations and mortality.
- Minimization of the progressive loss of lung function.
- Avoidance of the adverse effects of treatment.

treatment must progress through as many therapeutic stages as necessary in order to ensure control is achieved.

If asthma has been controlled for at least three months, maintenance treatment can gradually be reduced to determine the minimal therapeutic needs required to maintain control [92].

Drugs for treating asthma are classified as control or maintenance and relief medications, the latter also being called "rescue" drugs. Control or maintenance medications, which must be administered every day for prolonged periods, include inhaled or systemic glucocorticoids, leukotriene antagonists, prolonged-action β_2 adrenergic agonists, slow-release theophylline and monoclonal anti-IgE antibodies (omalizumab). Chromones have fallen into disuse, due to their lower efficacy.

Relief medications are used as needed to rapidly treat or prevent bronchoconstriction and they include (selected) inhaled short-acting β_2 adrenergic agonists (Table 3.2) and inhaled anticholinergics (ipratropium bromide).

The six therapeutic stages (Fig. 3.1) for achieving asthma control are:

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3.2.1 Stages

Stage 1

The first step consists of using inhaled short-acting β_2 adrenergic agonists (salbutamol or terbutaline) exclusively as needed. Stage 1 is only for patients with occasional and mild

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Table 3.2. Characteristics of inhaled β_2 adrenergic agonists

Drug	Quantity inhaled (μg)		Time required to take effect (minutes)		
	Pressurized Inhaler	Dry Powder	Onset	Maximum	Duration
Short-acting drugs					
Salbutamol	100	100	3-5	60-90	180-360
Terbutaline	–	500	3-5	60-90	180-360
Long-acting drugs					
Formoterol	12	4.5-9-12	3-5	60-90	660-720
Salmeterol	25	50	20-45	1210-240	660-720

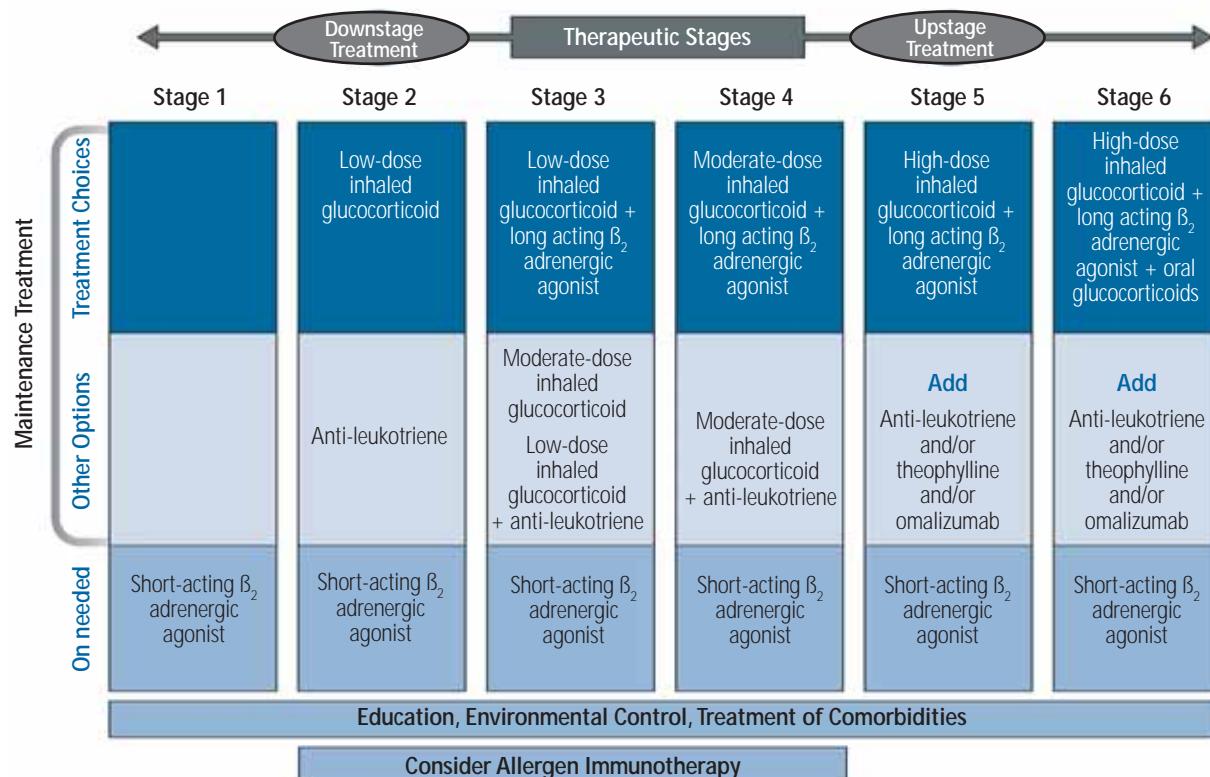


Figure 3.1. Therapeutic stages of adult asthma maintenance treatment.

A daytime symptoms (a maximum of two days a week and short-lived episodes), no nocturnal symptoms and asthma well controlled. The patient should be asymptomatic between episodes and maintain normal pulmonary function, although he is not exempt from the risk of suffering exacerbations. For the vast majority of patients the treatment indicated for fast symptomatic relief is an inhaled shortacting β_2 adrenergic agonist [93].

The use of an inhaled short-acting β_2 adrenergic agonist as required more than two days a week to treat symptoms

(except when it is used preventively before exercise) indicates inadequate control of asthma and requires maintenance therapy to be initiated or increased [93]. Inhaled short-acting β_2 adrenergic agonists administered 10-15 minutes in advance are the drugs of choice for preventing bronchoconstriction induced by exercise [94].

An inhaled anticholinergic is only recommended as relief medication in rare cases of intolerance to inhaled short-acting β_2 adrenergic agonist [2].

Stage 2

A The treatment of choice at this level is an inhaled glucocorticoid (beclomethasone, budesonide, fluticasone or mometasone) taken regularly at low doses [95-98]. This is usually the first stage for the majority of patients with persistent asthma who have not received previous treatment.

A The usual dose ranges from 200 to 400 mg/day of budesonide or its equivalent. The equipotent dose for the most widely used glucocorticoids is shown in Table 3.3.

Table 3.3. Equipotent doses of inhaled glucocorticoids

Drug	Low Dose ($\mu\text{g}/\text{day}$)	Average Dose ($\mu\text{g}/\text{day}$)	High Dose ($\mu\text{g}/\text{day}$)
Beclomethasone dipropionate	200-500	501-1000	1001-2000
Budesonide	200-400	401-800	801-1600
Fluticasone	100-250	251-500	501-1000
Ciclesonide	80-160	161-320	321-1280
Mometasone furoate	200-400	401-800	801-1200

A Inhaled glucocorticoids constitute the most effective maintenance treatment for persistent asthma, both for controlling daily symptoms and for reducing the risk of exacerbations [98]. The possibility of using glucocorticoids intermittently is controversial and the same level of control of daily symptoms as with regular treatment is not achieved [99].

A At this level leukotriene receptor antagonists or antileukotrienes (montelukast and zafirlukast) can also be used as an alternative form of treatment [100,101], although for long-term treatment inhaled glucocorticoids are more effective [100]. Patients who are well controlled on a low dose of inhaled glucocorticoids fail to maintain the same level of control with montelukast [102].

B Antileukotrienes are specially indicated as an alternative in patients who cannot or do not wish to receive inhaled glucocorticoids, experience side effects from them, have difficulties with the inhalation technique or have concomitant allergic rhinitis [103,104].

B There is no evidence that the addition of a long-acting B_2 adrenergic agonist affords any significant benefit at this level [105]. There are other options, but they are not recommended as the first line of treatment. Slow-release theophyllines show a certain efficacy as bronchodilator and anti-inflammatory agents [106,107] but they can cause side effects that may be mild or even serious. Chromones (disodium cromoglycate and nedocromil sodium) demonstrate a comparatively lower efficacy, although they are well tolerated [108].

Stage 3

A The treatment of choice at this level is a combination of a low-dose glucocorticoid with a long-acting B_2 adrenergic agonist (salmeterol or formoterol), both of which are inhaled [77,109-113] and can be administered preferably using the same device or separately. With this combination the symptoms subside, pulmonary function improves and exacerbations and the use of relief medication are reduced more noticeably than when the dose of glucocorticoids is increased. However, it is necessary to conduct a proper individualized risk/benefit assessment with both strategies. The combinations marketed in Spain are: fluticasone with salmeterol, budesonide with formoterol and beclomethasone with formoterol. Long-acting B_2 adrenergic agonists must never be used as monotherapy.

A Formoterol is a long-acting B_2 adrenergic agonist, but the onset of its action is rapid. This is why, if the budesonide/formoterol combination is chosen, it can be used both as a maintenance and relief treatment (SMART). This strategy ensures a reduction in exacerbations and better asthma control, despite requiring a smaller amount of glucocorticoids [114-120].

A Another option at this level would be to increase the dose of glucocorticoids to moderate doses [110,121,122]. Alternatively, low doses of an inhaled glucocorticoid combined with an antileukotriene, which has shown itself to be better than glucocorticoid monotherapy, can be used. Although it is not as effective as the glucocorticoid-long-acting B_2 adrenergic agonist combination, it offers excellent safety [123-125].

Stage 4

B At this level the treatment of choice is the combination of moderate doses of an inhaled glucocorticoid and a long-acting B_2 adrenergic agonist [77,110,126].

B As an alternative, the combination of moderate doses of an inhaled glucocorticoid and an antileukotriene can be used, although the addition of a long-acting B_2 adrenergic agonist to a glucocorticoid is more effective in preventing exacerbations, controlling daily symptoms and improving pulmonary function [124].

Stage 5

C This step consists of increasing the amount of inhaled glucocorticoids to a high dose and combining it with a long-acting B_2 adrenergic agonist [77,110,126]. At moderate and high doses inhaled glucocorticoids are usually administered twice a day, but with budesonide, therapeutic efficacy can be improved by increasing the frequency of administration to up to four times a day [127].

C Other maintenance drugs can be added; a subgroup of patients may respond to the addition of antileukotrienes [128] and delayed release theophyllines [129].

A In cases of allergic asthma that is poorly controlled with high doses of glucocorticoids and a long-acting B_2 adrenergic agonist, the monoclonal anti-IgE antibody (omalizumab), which improves daily symptoms [130] and exacerbations

A [131-133], can be added subcutaneously, increasing overall control of the disease.

Stage 6

D In patients whose asthma continues to be poorly controlled, despite the use of high doses of inhaled glucocorticoids combined with a long-acting β_2 adrenergic agonist, with or without other maintenance drugs (antileukotrienes, theophylline, omalizumab), and who are limited in their daily activities and have frequent exacerbations, the addition of oral glucocorticoids should be considered (always at the lowest effective dose and for as short a time as possible) [134,135], although this treatment is associated with side effects, that are sometimes serious.

3.2.2 Inhalers and Nebulisers

C Asthma drugs can be administered in different ways (oral, inhaled and intravenous delivery), but the advantages of inhalation make it the route of choice [136,137]. The most common inhalation devices are the pressurized inhaler, which can be used with or without a spacing chamber (Volumatic®, Aerochamber®, Aeroscopic®, Babyhaler®, Nebuchamber®, Inhalventus®, Prochamber®, Optichamber® and Ildor®), the pressurized inhaler with a solution of extrafine particles (Modulite®), powder inhalers (Turbuhaler®, Accuhaler®, Aerolizer®, Novolizer®, Handihaler®, Easyhaler® and Twisthaler®) and (jet or ultrasonic) nebulizers, each with different characteristics that need to be considered when they are prescribed [138,139]. The age and ability to use

RECOMMENDATIONS

- In patients with asthma symptoms at any therapeutic stage, the use of a short-acting β_2 adrenergic agonist as needed is recommended for **rapid relief**. **R1**
- Short-acting β_2 adrenergic agonists, administered 10-15 minutes in advance, are the medication of choice for preventing bronchoconstriction induced by physical exercise. **R1**
- The administration of an inhaled short-acting β_2 adrenergic agonist as needed is recommended for the treatment of intermittent asthma (**stage 1**). **R1**
- The treatment of choice in mild persistent asthma (**stage 2**) is an inhaled glucocorticoid taken regularly at low doses. Leukotriene receptor antagonists can be considered as an alternative treatment. **R1**
- In moderate persistent asthma, the combination of an inhaled glucocorticoid at low (**stage 3**) or moderate doses (**stage 4**) with an inhaled long-acting β_2 adrenergic agonist is recommended as the treatment of choice. **R1**
- In moderate persistent asthma an inhaled glucocorticoid at low (**stage 3**) or moderate doses (**stage 4**) in conjunction with a leukotriene receptor antagonist might be considered as an alternative. **R1**
- The budesonide/formoterol combination can be employed as maintenance and as needed treatment. With this form of treatment a reduction of exacerbations and an improvement in daily symptoms are achieved, even when the dose of glucocorticoids is reduced. **R1**
- In severe persistent asthma (**stage 5**) an inhaled glucocorticoid at high doses and combined with a long-acting β_2 adrenergic agonist is recommended. **R1**
- In patients with **poorly controlled severe allergic asthma** the use of omalizumab should be considered. **R1**
- In severe asthma that is poorly controlled, despite using high doses of inhaled glucocorticoids and a long-acting β_2 adrenergic agonist (**stage 6**), with or without other maintenance drugs, the addition of oral glucocorticoids will need to be considered. **R2**
- **Inhalation is the route** of choice for the treatment of asthma. The use of **spacers** avoids the problem of coordinating actuation and inspiration, and improves the distribution and the amount of drug reaching the bronchial tree. **R2**

a particular inhaler are the most important factors when choosing the most suitable inhaler in each case. The use of hydrofluoroalkanes (HFA) as a propellant in pressurized inhalers increases pulmonary deposits [140], so their use can affect the dose, which should be adjusted in accordance with the indications of the manufacturer.

The main disadvantage of this route is the difficulty of the inhalation technique for different inhalation devices, especially pressurized inhalers, because of the need to coordinate actuation and inhalation. The use of spacers avoids this problem, improves the distribution and the amount of drug which reaches the bronchial tree, reduces the deposition of particles in the oropharynx, decreases coughing and the possibility of oral candidiasis (which may be associated with the use of inhaled glucocorticoids), and reduces systemic bioavailability and, consequently, the risk of deleterious systemic effects [141-143]. In the case of powder inhalers the inhalation technique is easier, although pulmonary deposition depends on the inspiratory flow, which needs to be relatively high (> 60 l/minute) [139]. A fundamental aspect of the use of inhalation devices is that the patient must be trained to use them [138,144,145]. Therefore, once the device has been chosen, its characteristics and the appropriate inhalation technique must be explained to the patient and he must be shown how to use it. He would be asked to demonstrate how the device is used (with a placebo inhaler) and errors must be corrected. The inhalation technique must be checked at all successive visits.

Nebulizers are not the devices of choice for routine maintenance treatment and should only be used in special situations [139].

3.3 Other Treatments

3.3.1 Environmental Control

Asthma patients who smoke have more severe symptoms, a poorer response to glucocorticoid treatment and an accelerated loss of pulmonary function [146,147]. The proportion of asthma patients who smoke is high and similar to that of the general population, which is why the first aim of environmental control is to get the patient to stop smoking. In order to accomplish this the patient must be informed about suitable methods to help him deal with his addiction [148]. Exposure to environmental pollutants and passive smoking have a negative effect on the course of the disease and, in addition, they are a risk factor for developing asthma in childhood [30].

In allergic asthma, specific recommendations must be taken into consideration, once the sensitivity of each patient to different allergens has been confirmed. The most effective measures, such as those which can be applied in many cases of occupational asthma (change of job) or asthma caused by exposure to epithelia (removal of animals from the home) [149-152], are those which enable exposure levels to be drastically reduced and that ensure the introduction of such interventions at an early stage in the development of the disease (see occupational asthma).

Isolated individual measures, such as the use of mattress covers or acaricides, are not effective, not even in reducing levels of exposure [153-155]. However, with the application of specific combined interventions a significant reduction in the level of allergenic exposure and, consequently, clinical efficacy is achieved [149,156,157].

A randomized trial, involving 937 patients with uncontrolled moderate-severe asthma and sensitized to at least one domestic allergen, in which a series of measures were applied (impermeable mattress covers, vacuum cleaners and air purifiers in bedrooms [both devices with HEPA filters], cockroach disinfection plans), together with a year-long general educational programme, led to a significant reduction in symptoms and unscheduled medical visits [149].

On the other hand, two systematic reviews with a meta-analysis concluded that the efficacy of environmental control measures against mites is minimal in rhinitis patients [158] and totally ineffective in asthma patients [155]. Nevertheless, this meta-analysis has been questioned, due to the inappropriate selection of the studies it includes [159].

Various factors, such as climatic conditions, building types, furniture and bed clothing, or lifestyle habits, can have a marked influence on the efficacy of these measures. Consequently, the generalization of the results of a particular program may be questionable.

Some asthma patients, especially those who develop naso-sinusal polyps, may have asthma attacks when they are given aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). Many of these reactions are serious or an even fatal [160], so patients must be correctly diagnosed, either on the basis of an obvious clinical history (various reactions to different NSAIDs) or an oral challenge, which can be substituted in serious cases by bronchial or nasal inhalatory challenge [161,162]. The best alternative analgesic agent in these patients (Table 3.4) is paracetamol administered at less than 650 mg per individual dose, given that some patients may have bronchospastic crises and these occur more often if high doses are used. Opiates, such as tramadol or codeine, are also regarded as safe alternative painkillers. Glucocorticoids can be employed as anti-inflammatory drugs. Selective (meloxicam) or specific (celecoxib, etoricoxib) COX-2 inhibitors could be another alternative, although, before recommending them, it is advisable to confirm patient tolerance [163]. This type of test should be conducted in centers with experience in this field.

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Table 3.4. Painkillers and anti-inflammatory agents which can be used in NSAID-intolerant Patients

Painkillers

- Paracetamol taken in ≤ 650 mg doses
- Opiates: tramadol, codeine, dextropropoxifene

Anti-inflammatory drugs

- Glucocorticoids
- Selective COX₁ inhibitors: meloxicam
- Specific COX₂ inhibitors: celecoxib, etoricoxib

3.3.2 Allergen Immunotherapy

A Immunotherapy involving subcutaneous administration of allergen vaccines is an effective treatment for well controlled allergic asthma with low or moderate treatment levels (therapeutic stages 2-4), as long as a clinically relevant IgE-mediated sensitization to common Aeroallergens has been demonstrated, well characterized [164,165] and standardized extracts are used and the use of complex mixtures is avoided [166].

B Immunotherapy must not be prescribed for patients with severe or uncontrolled asthma because it is ineffective and due to the high risk of severe, even fatal, reactions [167,168]. This is why subcutaneous immunotherapy should be prescribed by specialists with experience in using this treatment and administered in centers with basic measures for the immediate treatment of a possible reaction.

B The search for safer and more convenient alternatives for patients has stimulated research on the efficacy of sublingual immunotherapy. Two systematic reviews conclude that it is capable of significantly reducing bronchial manifestations in children and adolescents with allergic asthma [169,170]. Most clinical trials that have demonstrated its clinical efficacy have done so with well characterized extracts at much higher doses than those routinely used in subcutaneous immunotherapy. The tolerance profile of sublingual immunotherapy is optimal and fatal reactions have not been reported.

Currently there are no cost-efficacy studies that compare immunotherapy with conventional pharmacotherapy. Nevertheless, immunotherapy has additional advantages, including maintenance of the clinical benefits obtained, even several years after treatment has been withdrawn [171,172]. It also curtails the progression of rhinoconjunctivitis caused by pollen allergies to asthma [172] or the appearance of new sensitizations in monosensitized patients [173].

3.3.3 Influenza and pneumococcal vaccination

A Influenza [174,175] and pneumonia vaccinations [176] have shown no efficacy in preventing asthma exacerbations.

RECOMMENDATIONS

- In **allergic asthma** an evaluation of possible sensitizations of the patient to different allergens is recommended. **R1**
- In allergic asthma due to mites isolated environmental **control measures** are not recommended. **R2**
- In well controlled allergic asthma with low or moderate treatment levels (**stages 2-4**), as long as a clinically relevant IgE-mediated sensitization to common Aeroallergens has been demonstrated and well **standardized** extracts are used, allergen immunotherapy is recommended. **R1**
- Allergen **immunotherapy** should be prescribed by experienced medical specialists and administered at centres which can provide basic measures for the immediate treatment of a possible adverse reaction. **R2**

Table 3.6. Action plan

I. USUAL TREATMENT		
1. Take on a daily basis		
2. Before doing exercising, take		
II. WHEN YOUR TREATMENT MUST BE INCREASED?		
1. Assessment of the level of control of your asthma:		
Do you have asthma symptoms more than twice a day?	No	Yes
Is your activity or physical exercise limited by your asthma?	No	Yes
Does your asthma wake you up at night?	No	Yes
Do you need to use your bronchodilator more than twice a day?	No	Yes
If you use a flow (PEF) meter, are the values lower than? (If you have replied "Yes" to three or more questions, your asthma is not well-controlled and your usual treatment needs to be increased.	No	Yes
2. How to increase the treatment:		
Increase your treatment in the following way and assess your improvement daily: (write down the increase in your new treatment)		
Maintain this treatment for days (specify the number).		
3. When you need to ask your doctor/hospital for help:		
Telephone your doctor/hospital (provide telephone numbers)		
If your asthma fails to improve in days (specify the number) (complementary instructions)		
4. Emergency. Serious lack of control of your asthma:		
If you have intense bouts of breathlessness and you can only utter short phrases.		
If you have intense and severe asthma attacks.		
If you have to use your rescue or relief bronchodilator every 4 hours and there is no improvement.		
1. Take 2 to 4 puffs (rescue bronchodilator).		
2. Take mg of (oral glucocorticoids).		
3. Request medical help: go to: address Call number		
4. Continue using your (rescue bronchodilator) until you get medical help		

Table 3.7. Educational Tasks which must be Performed at Each Visit

	Communication	Information	Instruction
Initial visit	Investigate expectations. Agree on targets. Discuss compliance.	Basic asthma concepts and treatment.	Inhalation technique. Self-monitorization.
Second visit	Evaluate achievements in terms of targets and expectations. Discuss compliance.	Reinforce the information received at the first visit. Inform the patient about environmental avoidance measures.	Reinforce inhalation technique. How to avoid triggers factors. Interpretation of readings. Action plan.
Check-ups	Evaluate achievements in terms of targets and expectations. Discuss therapeutic compliance and environmental avoidance measures.	Reinforce all information.	Revise and reinforce the inhalation technique. Revise and reinforce self-monitoring and the treatment plan.

For education to be effective it is important to establish trust between the medical team and the patient, so that patients can voice any doubts, concerns or fears. Medical personnel will need to use a language that is comprehensible to patients and/or their relatives, clarifying any concepts which have been presented but not fully understood and inviting them to express any doubts or questions. Furthermore, shared objectives must be set with patients, which will always require individualized plans to be drawn up in writing.

The educational program must include the preparation of asthma action plans. Plans consist of a set of written instructions tailored to each patient, taking into account the severity and control of asthma and the usual treatment prescribed. The main aim of asthma action plans is the early detection of exacerbations and the rapid implementation of interventions designed to achieve rapid remission. The level of control, on which the intervention plan will be based, can be assessed either in terms of the severity and frequency of asthma symptoms or on the basis of the daily PEF measurements the

patient takes in his own home, depending on the preferences of patients or their doctor [186-189]. This plan should consist of two basic parts [190,192]: the usual treatment for situations of clinical stability and the steps to be taken if the patient's asthma deteriorates (Table 3.6). It must be reviewed at each appointment, whether the visit is scheduled or not, as well as during any hospital admissions or ED visits.

Since education is a continuous process and not an isolated event, each visit is an opportunity for review, reinforcement and an expansion of patient knowledge and skills, so it is essential for the entire team to agree upon and be consistent about [181]. We need to remember that, during the educational process, when the intensity of intervention is reduced, its efficacy also decreases, given that purely informative interventions are not effective [182]. The educational tasks for each visit are described in Table 3.7 [71]. After receiving training, nursing personnel must participate actively in the administration and management of this type of educational program [193,194].

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RECOMMENDATIONS

- Asthma patients should follow a formal asthma educational programme. Actions which are purely informative have not been shown themselves to be effective.R1
- Asthma patients should be provided with a written action plan to ensure the early detection of asthma exacerbations and to enable interventions to achieve rapid remission.R1