3. Maintenance treatment

3.1 Objectives

The main objective of asthma management is to achieve and maintain control of the disease as quick as possible, in addition to prevent exacerbations and chronic airflow obstruction and to maximally reduce mortality. With a properly designed treatment plan, therapeutic targets (Table 3.1) can be achieved in the majority of patients in terms of daily symptom control (current control domain) and prevention of both exacerbations and excessive loss of pulmonary function (future risk domain).

C

To attain these objectives a global and individualized long-term strategy must be followed based on an optimally adjusted pharmacological treatment along with supervision measures, environmental control and asthma education activities[1]. Pharmacological treatment should be adjusted according to the degree of control, considering the most effective therapeutic options, safety and cost of the different alternatives, and taking into account the patient's satisfaction with the degree of control achieved. Patients should be periodically evaluated to determine whether objectives are being met. Clinical inertia and causative factors on the part of the patient, the physician and the healthcare system should be avoided.

Table 3.1. Asthma treatment goals

In the domain of current asthma control
• To prevent daytime, nighttime and exercise-related symptoms. • Use of short-acting β_2-agonists no more often than twice a month. • To maintain a normal or near-normal pulmonary function. • No restrictions on daily life activities and physical exercise. • To fulfil the expectations of both patients and their families.
In the domain of future risk
• To prevent exacerbations and mortality. • To minimize progressive loss of pulmonary function. • To avoid treatment-related adverse effects.
Avoid therapeutic inertia

3.2 Pharmacological treatment

Asthma treatment should follow an overall plan, established by consensus of the physician and the patient (and eventually by the patient's family), in which the goals, the interventions to achieve them and the criteria for their modification or adaptation according to changing disease circumstances must be made clear. Distinguishing between the 'current control' domain and the 'future risk' domain in the control of the disease is relevant, because it has been documented that these domains may respond differently to treatment[2,3]. For example, some patients may have a good daily control of asthma symptoms and yet experience exacerbations, and viceversa.

C

Treatment should be adjusted continuously, so that the patient remains always in a well-controlled status. This cyclic treatment adjustment means that asthma control should be objectively assessed (chapter 2.6), that the patient is being treated to achieve control and that treatment is periodically checked to maintain asthma control (Figure 3.1). That is, if a patient is not well controlled, treatment must be stepped up as needed in order to regain control, always taking into account non-pharmacological measures, treatment adherence and risk factors susceptible to be modified.

D

If asthma has been controlled for at least 3 months, maintenance therapy may be gradually decreased in order to determine minimum treatment needs that are required to maintain control[4]. A simple scoring system that includes data of different clinical (ACT, previous exacerbations) and functional (spirometric values) variables has been developed, to determine the risk after stepping down treatment in patients with controlled asthma[5].

C

Drugs used to treat asthma are classified as controller or maintenance medications and reliever medication, also called "rescue" medication. **Controller or maintenance medications** should be administered continuously during prolonged periods of time, include inhaled glucocorticoids (IGC) or systemic glucocorticoids, leukotriene receptor antagonists (LTRA), long-acting β_2-agonists (LABA), tiotropium and monoclonal antibodies (omalizumab, mepolizumab, reslizumab and dupilumab). Chromones and sustained-release theophylline have fallen into disuse because of their lower efficacy.

Reliever medications are used on-demand for rapid treatment or prevention of bronchoconstriction, and include

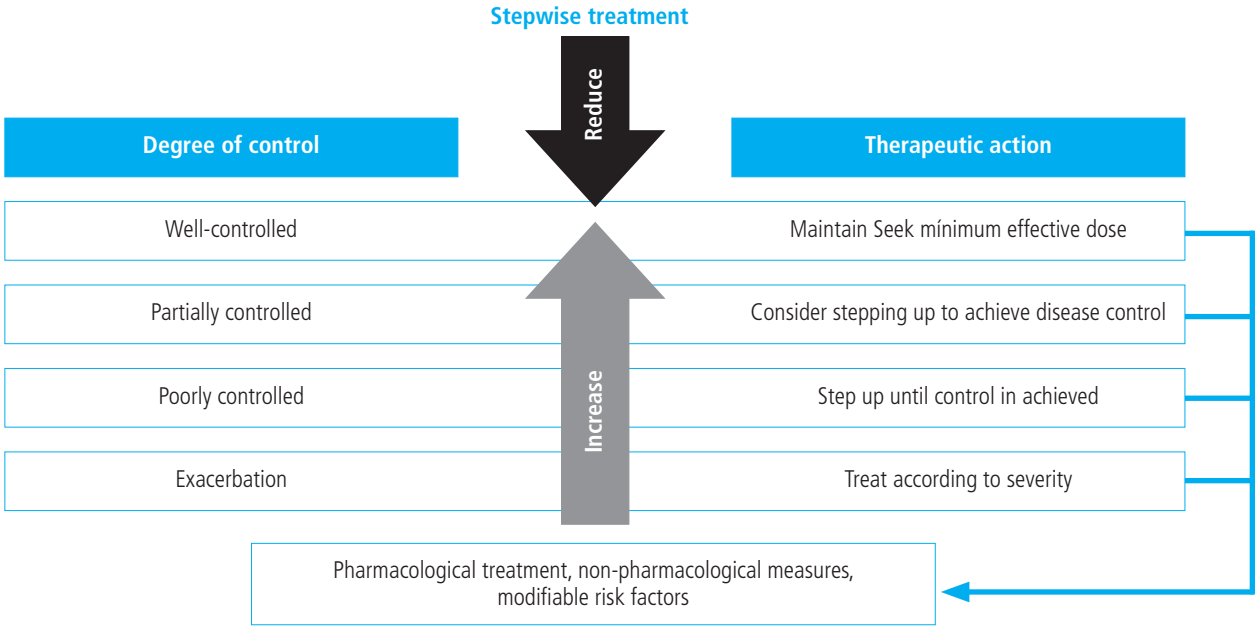


Figure 3.1. Cyclic adjustment of treatment according to periodic assessment of control of asthma.

Table 3.2. Characteristics of inhaled β_2-adrenergic agonists

	Amount per puff (µg)		Time of effect (minutes)		
Drug	**Pressurized inhaler**	**Dry powder**	**Onset**	**Maximum**	**Duration**
Short-acting					
Salbutamol	100	100	3-5	60-90	180-360
Turbutaline	-	500	3-5	60-90	180-360
Long-acting					
Formoterol	12	4.5 – 9 - 12	3-5	60-90	660-720
Salmeterol	25	50	20-45	120-240	660-720
Vilanterol	-	22	3-5	-	1440

inhaled short-acting β_2-agonists (SABA) (Table 3.2) and inhaled short-acting anticholinergics (*ipratropium bromide*). Also, the combinations *budesonide/formoterol, beclomethasone/formoterol* or *beclomethasone/salbutamol*, used on-demand can be considered reliever medications.

The six treatment steps (Figure 3.2) aimed at achieving asthma control are the following:

3.2.1 Steps

Step 1

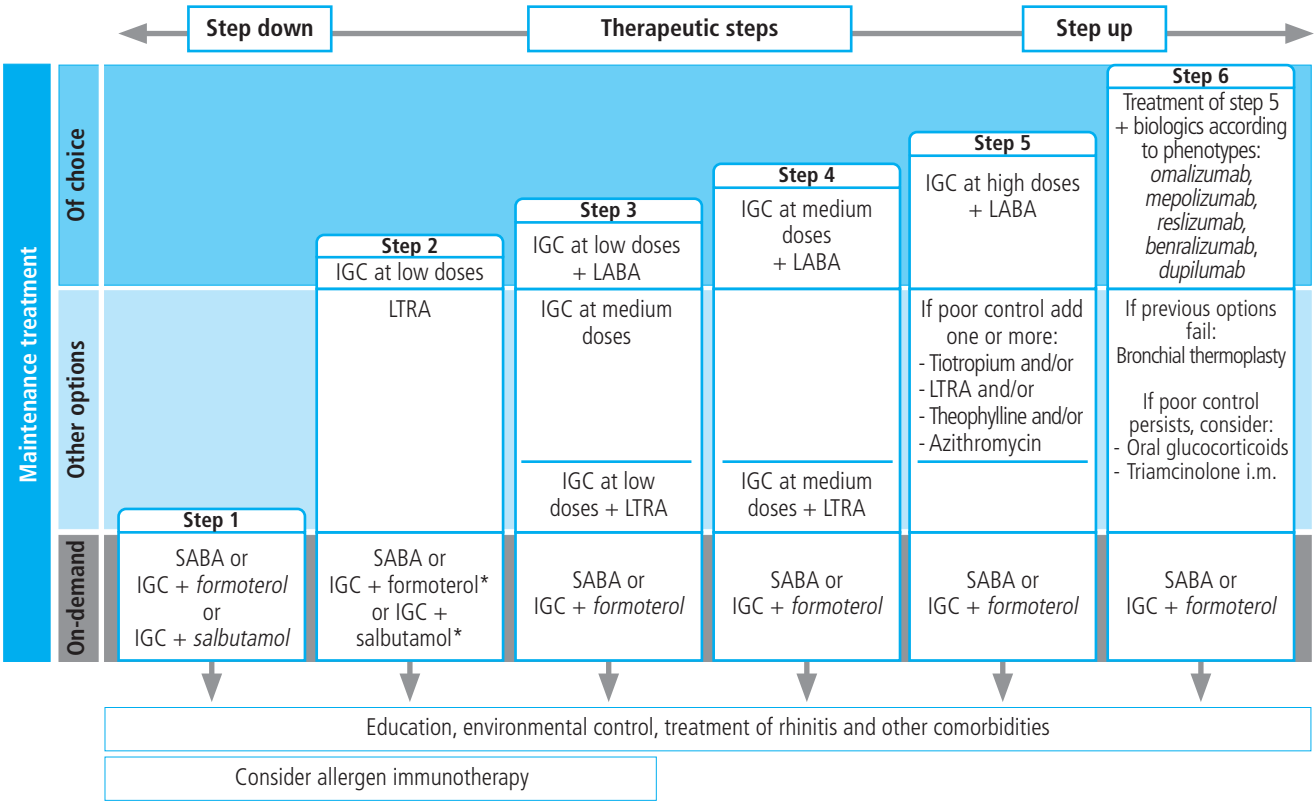
Different treatment options can currently be considered for this step. A correct clinical and functional assessment of the patient is requiered for an adequate selection of treatment.

B

Inhaled SABA (*salbutamol or terbutaline*), exclusively on-demand, can be used in those patients with mild and occasional daytime symptoms (maximum twice a month) and without nighttime symptoms[6,7]. The patient should remain asymptomatic between episodes, maintain a normal pulmonary function, and neither having had exacerbations in the previous year nor presenting risk factors for exacerbations (Table 2.7)[6].

B

The association *budesonide/formoterol* on-demand can also be used[8]. In a randomized study on adult asthma patients with approximately half of patients having intermittent asthma and in which an open-label design was used to reflect clinical practice conditions[9], the use of *budesonide/formoterol* on-demand was superior to salbutamol on-demand in the prevention of exacerbations. In a small study of patients with intermittent asthma and increased fractional exhaled nitric oxide (FE_{NO}) in which both *budesonide/formoterol* and *formoterol* on-demand were compared, the combination showed a higher reduction of FE_{NO} levels[11]. However, these indications are not included in the technical specifications of these drugs. In addition, cost-benefit studies have not been carried out.



*Without maintenance treatment.
IGC: Inhaled glucocorticoid; LABA: Long-acting β_2-agonist; LTRA: Leukotriene receptor antagonist; SABA: Short-acting β_2-agonist

Figure 3.2. Therapeutic steps for maintenence treatment in adult asthma.

Table 3.3. Equipotent doses of inhaled glucocorticoids

	Low dose (mg/day)	Medium dose (mg/day)	High dose (mg/day)
Budesonide	200-400	401-800	801-1..600
Beclomethasone dipropionate	200-500	501-1000	1001-2000
Extrafine beclomethasone*	100-200	201-400	> 400
Ciclesonide	80-160	161-320	321-1280
Fluticasone propionate	100-250	251-500	501-1000
Fluticasone furoate	-	92	184
Mometasone furoate	100-200	201-400	401-800

*Extrafine beclomethasone dipropionate.

A The use of an inhaled SABA on-demand, more than twice a month, for the treatment of symptoms (excluding its preventive use before exercise), or having had exacerbations in the previous year, or a FEV_1 value < 80 % indicates an inadequate asthma control and prompts the initiation of maintenance therapy[12-14].

A Inhaled SABAs administered 10-15 minutes before exercise are the drugs of choice to prevent exercise-induced bronchoconstriction[15].

D An inhaled anticholinergic is only recommended as a reliever medication in those rare cases of intolerance to SABA agents[8].

Step 2

A The treatment of choice at this step is an inhaled glucocorticoid (IGC) (*beclomethasone, budesonide, ciclesonide, fluticasone or mometasone*) at low doses and administered daily[16-19]. In general, this is the first step for most patients with persistent asthma who have not been previously treated. The usual dose ranges between 200 and 400 µg/day of budesonide or equivalent. Continuous administration of IGC is the most effective treatment for persistent asthma, both for the control of daily symptoms and to reduce the risk of exacerbations[13,19-21]. The equipotent doses of the most common IGC are shown in Table 3.3.

B Two clinical trials showed that a strategy of using a combination of *budesonide/formoterol* in a single inhaler on-demand compared to continuous IGC treatment in mild persistent asthma, was not inferior in preventing exacerbations (the rate of which was similarly low); however, it was inferior in the maintenance of asthma control and in the increase of pulmonary function[22,23]. In a randomized open-label study[9], *budesonide* twice a day plus salmoterol on-demand and *budesonide/formoterol* oin-demand were similar regarding annualized exacerbation rates.

Also, a similar result with *beclomethasona/salbutamol* has been observed.

D Results of the aforementioned studies may provide indirect evidence of a posible indication of the combinations of low dose IGC with LABA or SABA (e.g. *budesonide/formoterol, beclomethasona/formoterol* or *beclomethasona/salbutamol*), administered exclusively on-demand, in the treatment of step 2 in patients with low treatment adherence and in which specific educational interventions have been unsuccessful. However, no studies have been specifically designed to assess this therapeutic indication.

A At this level, an alternative treatment includes leukotriene receptor antagonists (LTRA) or anti-leukotrienes (*montelukast* and *zafirlukast*)[24,25], although IGC are more effective for long-term treatment[24]. Patients who are well controlled on IGC at low doses fail to maintain the same level of asthma control with montelukast[26].

B LTRA would be particularly indicated as alternative drug in patients who are unable or unwilling to receive IGC or have adverse effects with IGC, have difficulties with the inhaler technique, or suffer from concomitant allergic rhinitis[27,28].

A In patients who have not previously received maintenance treatment with IGC, the combination of IGC at low doses and LABA as initial treatment as compared with IGC at low doses, improves symptoms and pulmonary function but has a higher cost and it does not reduce the risk of exacerbations[29].

B Sustained-release *theophylline* is not recommended for use at this step since it have been shown to be modestly effective as both bronchodilator and anti-inflammatory drug[30,31] and may cause mild to serious adverse events.

A Chromones (*disodium cromoglycate* and *nedocromil sodium*) show low efficacy, although they have a good tolerability[32]. Currently, they are not commercialized in Spain for this indication.

Step 3

A First-line treatment at this step is a combined inhaled treatment with IGC at low doses and a LABA (*salmeterol* or *formoterol* or *vilanterol*)[33-38], which can be administered using a single device (preferred option) or separate inhalers. By using this combination a more pronounced reduction of symptoms, improvement of pulmonary function, and reduction of exacerbations and use of reliever medications is obtained as compared to increasing the dose of IGC. However, an appropriate individualized risk/benefit assessment for both strategies is required.

A Treatment with LABA should be always been accompanied by an IGC. LABA agents must never be used as monotherapy because of a higher risk of hospitalizations and life-threatening exacerbations[40,41]. IGC/LABA combinations commercialized in Spain include *fluticanose propionate* with *salmeterol, budesonide* with *formoterol, beclomethasone dipropionate* with *formoterol*, and *fluticasone furoate* with *vilanterol*.

A *Formoterol* is a rapid-onset LABA. For this reason, if *budesonide/formoterol* or *beclomethasone/formoterol* combinations are chosen, they can be used as both maintenance and reliever therapy (MART strategy). This strategy leads to reduced exacerbations and a better asthma control, despite requiring a lesser amount of IGC[20,42-49]. It may be assumed that other IGC combinations (*fluticasone propionate*) with formoterol may be effective as MART strategy, although there is no evidence of its use as maintenance and on-demand treatment and the indication is not included their technical specifications.

A In any case, MART therapy always should be administered using a single inhaler device.

A A further option at this step includes increasing IGC doses up to medium doses, but this approach is less effective than adding a LABA[50-52]. Alternatively, IGC at low doses associated with a LTRA may be used. This option has been found to be superior to IGS monotherapy and although it is not as effective as the IGS and LABA combination, has an excellent safety profile[53-56]. However, the addition of an LTRA does not appear allowing to reduce the IGC dose[57].

Step 4

B The first-line treatment at this step is the combination a IGC at medium doses with a LABA[29,34,36,58].

A For patients who have had at least one exacerbation in the previous year, the combination of a IGC at low doses (*budesonide* or *beclomethasone*) and formoterol, using the MART strategy, is more effective in reducing exacerbations than the same dose of an IGC and LABA in a fixed schedule, or higher doses of IGC[49,59].

B Alternatively, the combination of an IGC at medium doses with a LTRA can be used, although the addition of LABA to the IGC is more effective in preventing exacerbations, control of daily symptoms and improving pulmonary function[54].

Step 5

B The next step consists of up-titrating IGC dosage and using it in combination with LABA[34,36,60]. IGC at medium and high doses are usually administered twice daily, although a greater therapeutic efficacy can be achieved with *budesonide* by increasing the dosing frequency up to 4 times a day[61].

C Other drugs can be added for maintenance therapy, with a subgroup of patients improving with the addition of LTRA[62,63] or sustained-release *theophylline*[64].

B In patients not well controlled with the combination of an IGC at low doses and a LABA, who show post-bronchodilator $FEV_1/FVC \leq 70$ %, the addition of *tiotropium* as maintenance therapy has shown to improve pulmonary function and to reduce exacerbations[65,66].

B Macrolide antibiotics, particularly azithromycin administered 3 days/week for several months, may play a role as an add-on medication in patients with severe non-eosinophilic asthma and frequent exacerbations[67,68], as well as in eosinophilic asthma[69] (see chapter 7).

Step 6

A For asthma patients who remain uncontrolled and with frequent exacerbations, the addition of biologic drugs should

A be considered after a specialized evaluation and according to the endophenotype of the patient.

A In cases of uncontrolled severe allergic asthma (USAA), the anti-IgE monoclonal antibody (*omalizumab*) by the subcutaneous route can be added, which improves daily symptoms and decreases exacerbations[70-73], increasing the overall control of the disease (see chapter 7).

A In patients with eosinophilic USAA, independently of the presence of allergy, biologic drugs targeting interleukin-5 (IL-5) pathway can be used. Currently, anti-IL-5 monoclonal antibodies, *mepolizumab* y *reslizumab*, and the anti-IL-5 receptor α chain (IL-5Rα), *benralizumab*, are approved as additional treatment of eosinophilic USAA (severe refractory eosinophilic asthma)[74-80] (see chapter 7).

A *Dupilumab*, a human monoclonal antibody directed against the interleukin-4 receptor subunit α (IL-4Rα) of IL-4 that blocks the effects of IL-4 and IL-13 is approved as additional treatment in patients older than 12 years of age with USAA with increased eosinophils and/or FE_{NO} (see chapter 7).

B In cases in which the administration of biologic agents has failed, the indication of enbronchial thermoplasty may be considered[83] (see chapter 7).

D The last therapeutic option when all other alternatives have failed is the administration of systemic glucocorticoids (always used at the lowest effective dose and for the minimum period of time possible)[84,85] even though they are also associated with adverse effects, occasionally serious (see chapter 7).

3.2.2 Inhalers and nebulizers

B Inhaled therapy is the preferred administration route for the treatment of asthma as it acts directly on the lungs, delivers a greater amount of drug into the airways, elicits a rapid response and is associated with few or no systemic effects[86-91].

B The main disadvantage of this route is the difficulty of the inhalation technique of the different devices[92-95].

Table 3.4. Aerodynamic properties provided by inhalers (based in part on Giner 2013)[96]

	Pulmonary deposition (%)		Oropharyngeal deposition (%)		MADM (µm)
	in vivo	in vitro	in vivo	in vitro	
pMDI					
Conventional pMDI	7.8-34	-	53.9-82.2	-	1.4-8
Conventional pMDI with spacer	11.2-68.3	-	31.2	40	2-3.2
Breath-actuated pMDI	50-60	-	30	-	-
Modulite®	31-34	-	33-58	-	1-2
Alvesco®	50-52	-	32,9	-	-
BAI					
k-haler®	44.7[97]	-	23-30	-	-
SMI					
Respimat®	40-53	-	19.3-39	-	-
DPI (by alphabetaical order)					
Accuhaler®	7.6-18	15-30	-	-	3.5
Aerolizer®	13-20	21.7-28	73	-	1.9-7.9
Breezhaler®	36	39	-	45	2.8
Easyhaler®	18.5-31	29	-	-	2.2-3.0[98]
Ellipta®	-	-	-	-	2-4.8
Genuair®	30.1	-	54.7	-	-
Handihaler®	17.8	17.3-22	-	71	3.9
Ingelheim® inhaler	16	-	59	-	-
Nexthaler®	56	-	43	-	1.4-1.5
Spinhaler®	11.5	-	30.9	-	-
Turbuhaler®	14.2-38	28	53-71.6	57.3-69.3	1.7-5.4
Twisthaler®	36-37	-	-	-	2-2.2

MADM: mean aerodynamic diameter mass; BAI: breath-actuated inhaler; DPI: dry powder inhaler; pMDI: pressurized metered-dose inhaler; SMI: soft miss inhaler. The comparison of values among devices should be considered with caution because of differences in the methods and drugs used for estimating the corresponding values, as well as differences in human studies, which were performed in diverse clinical settings (healthy and ill subjects with different diseases and degrees of severity), inspiratory flows and ages.

C Currently available inhalation devices include: the conventional pressurized inhaler (pMDI) and the the Modulite® system, which can be used with or without a spacer, the breath-actuated inhaler (BAI) k-haler® and Easy-breathe®, the soft mist inhaler (SMI) Respimat®, the dry powder inhalers (DPI) (Accuhaler®, Aerolizer®, Breezhaler®, Easyhaler®, Ellipta®, Forspiro®, Genuair®, Handihaler®, Nexthaler®, Spiromax®, Turbuhaler®, Twisthaler® and Zonda®) and the nebulizers (*jet*, ultrasonic or vibrating mesh). Each of them has their own technical characteristics that should be considered when prescribed (Table 3.4)[90].

C All inhaler devices if correctly used provide en efficient deposition of the drug in the lung[88].

B The use of spacers is recommended for pMDI. Spacers circumvent coordination issues, improve the distribution and the amount of drug reaching the bronchial tree, reduce the deposition of drug particles in the oropharynx, decrease cough and the possibility of oral candidiasis (that may be associated with the use of IGC), decrease systemic bioavailability and, hence, the risk of systemic effects[99-102].

A Healthcare professionals involved in the care of patients with asthma should know the inhalation techniques of each of the devices; knowledge, however, is still insufficient[103-104].

A Given that the proper use of inhalers is a crucial aspect in the treatment of patients with asthma, all healthcare professionals involved, doctors, nurses and pharmacists especially those from the community due to their accessibility, should be involved in the instruction and review of the inhalation technique[105-112].

C The patient should be periodically trained and controlled in the use of the prescribed inhaler device, explaining its characteristics, the appropriate technique, demonstrating how it is used, then asking the patient to perform the maneuvers (with a placebo device) and correcting the possible mistakes[91,113-115].

B Whenever pharmacologically possible, a single type of inhaler device should be used[116,117].

D After the instruction in the use of the device, the patient should be given a brochure with description of the technique and receive information on how to find demonstration videos showing the correct technique[89,90,92,114,115].

D It is important to take advantage of control visits, performance of pulmonary function tests and admissions to the hospital to check the patient's inhalation technique[114].

3.3 Other treatments

3.3.1 Smoking and environmental control

C Smokers with asthma have more severe symptoms, a poorer response to IGC treatment, even in patients with mild asthma[118], and an accelerated loss of pulmonary function[119,120], so that a step-up in treatment is often required[121]. The proportion of asthmatic smokers is high and similar to that in the general population. Moreover, since longuidudinal studies have found a relationship between tobacco use and asthma in both adults and adolescents[122], the main objective in environmental control is getting the patient to stop smoking. To this end, smokers should receive full information of the most appropriate quit smoking methods[123]. Exposure to both environmental contaminants and passive smoking aggravates the course of asthma and constitute a risk factor for asthma development in childhood[124]. Administrative regulations banning smoking in public spaces are being having a highly positive impact[125,126]. Also, passive exposure to smoke of electronic cigarettes has been related with a higher risk for exacerbations and asthma symptoms[127,128], and active exposure to severe effects of respiratory health[129], so that vaping cannot be recommended as a method to quit.

C Some asthma patients, particularly those with sinonasal polyposis, may experience exacerbations when administered *acetylsalicylic acid* or other non-steroidal anti-inflammatory drugs (NSAID). Many of these reactions are serious or even fatal[130], so that it is necessary that patients are correctly diagnosed based on evident data in the medical history (several reactions to different NSAID) or by means of an oral challenge test which, in severe cases, can be replaced with bronchial or nasal inhalation challenge testing[131,132]. This issue is more comprehensively explained in chapter 8.5 (*acetylsalicylic acid*-exacerbated respiratory disease).These patients, however, among their environmental measures, should avoid the use of analgesic or anti-inflammatory treatments with drugs of the NSAID therapeutic class.

C Specific recommendations should be considered in allergic asthma, once sensitizations to different allergens had been confirmed in each patient. The most effective measures are those enabling a dramatic decrease of exposure levels, such as those applicable to many patients with occupational asthma (job change) or asthma due to animal dander (removal of animals from the patient's home) or cockroach allergy (wise use of pesticides)[133-138].

B Isolated individual interventions, such as the use of mattress covers or acaricides have not shown to be effective, not even in reducing exposure levels[139-141].

B However, in a recent randomized study, the use of impermeable bed covers was effective for preventing exacerbations in children and adolescents with allergic asthma triggered by dust mites[142].

B The use of combined specific measures has been associated with a significant reduction in the level of allergen exposure and, in consequence, of benefits in clinical efficacy[133,143,144]. In a randomized trial of 937 patients with uncontrolled moderate to severe asthma and sensitization to at least one domestic allergen, in which combined measures were applied (impermeable covers, vaccuum cleaners and air purifiers in the bedroom both with HEPA filters, cockroach disinsection plans), associated with a general education program, for one year, obtained a significant reduction in symptoms and unscheduled medical visits[133].

B Finally, the two more recent systematic reviews of the effect of combined interventions showed favorable outcomes[137,145].

3.3.2 Allergen immunotherapy

A Subcutaneous immunotherapy with allergen extracts is an effective treatment in well-controlled allergic asthma with low or medium treatment levels (steps 2 to 4), provided that a clinically relevant IgE-mediated sensitization against common aeroallergens has been demonstrated and well-characterized and standardized allergen extracts are used[146,147], avoiding complex mixtures[148,149]. However, many patients with mild intermittent asthma (step1) suffer from moderate or severe allergic rhinitis concomitantly, which would justify the

B

A prescription of immunotherapy[150]. Immunotherapy should not be prescribed to patients with uncontrolled severe asthma, because its efficacy is not well documented and entails a high risk of serious, even fatal, adverse reactions[149,151]. For this reason, subcutaneous immunotherapy should only be prescribed by specialist physicians with experience in this type of treatment and administered in centers equipped with the basic resources for the immediate treatment of a possible adverse reaction.

B The search for safer and more convenient options for the patient has led to investigate the efficacy of sublingual immunotherapy. Some systematic reviews conclude that oral immunotherapy with capsules or lyophilized extracts can significantly reduce clinical manifestations and the use of rescue medication in children, adolescents and adults with allergic asthma[147,152-154].

B Most clinical trials showing clinical efficacy were performed with well-characterized extracts at much higher doses than those usually prescribed for subcutaneous immunotherapy. The tolerability profile of sublingual immunotherapy is optimal and fatal reactions have not been reported[147,154].

B Sublingual immunotherapy with an oral lyophilized mite extract when added to regular pharmacological maintenance treatment is able to reduce the number of moderate to severe exacerbations[155] and to improve control of the disease, with a very favorable safety profile. Therefore, its use is recommendable for adult patients with moderately controlled or partially controlled asthma[150].

B No comparative studies on the cost-effectiveness of immunotherapy versus conventional pharmacotherapy are yet available, and they are not likely to be performed since their complex design makes them still unfeasible.

B However, immunotherapy is not only useful in controlling disease manifestations, but it also offers additional advantages over pharmacotherapy, such as the maintenance of clinical benefits for several years after treatment discontinuation[156,157], a decrease in the risk of developing asthma in patients with allergic rhinitis[157,158] or the occurrence of new sensitizations in monosensitive patients[159]. Finally, immunotherapy has been found to be cost-effective in comparison with pharmacotherapy alone in patients with the coexistence of allergic rhinoconjunctivitis and asthma[160-162].

3.3.3 Influenza and pneumococcal vaccinations

A Influenza[163,164] and pneumococcal[165] vaccines have not been shown to be effective in preventing asthma exacerbations.

D However, since it is a cost-effective approach, and due to the high risk of complications in patients with chronic diseases[166,167] and a higher risk of therapeutic failure in children[168], annual influenza vaccination should be considered in patients with moderate and severe asthma, both in adults and children. Similarly, and given that asthma population have a high risk of invasive pneumococcal disease[169, 170], different international[171] and national[172] consensus documents as well as the National Healthcare System[173] recommend the administration of pneumococcal vaccine in patients with severe asthma.

3.4 Education

3.4.1 Objectives

A Education of asthma patients is an essential component of treatment, because reduces the risk of exacerbations, improves quality of life and decreases healthcare costs[174], thus becoming an indispensable part of the overall management of asthma[8,175-180]. The main goal of education is to provide patients with the knowledge and skills they need to improve self-care and treatment compliance. This results in a better adherence to treatment and, in consequence, in an optimal control of the disease. In addition, education pomotes patient's self-control of asthma. Self-control is the situation in which the patient monitors their symptoms and applies self-management following a plan agreed with his/her doctor. Self-control supported by a healthcare professional reduces the number of consultations and exacerbations, and improves quality of life without increasing costs[181,182].

3.4.2 Knowledge and skills

A From a practical point of view[183], education should consider two major aspects: transmission of knowledge and acquisition of skills and competences (Table 3.5).

A Regarding the information that the patient should receive about asthma, their needs, previous knowledge, beliefs[184], age, severity of asthma, and the degree of involvement necessary in their self-control and treatment should be considered.

A These interventions should include[185]: symptom self-management or PEF monitoring, written action plans, and regular assessments of asthma control, asthma treatment and abilities of the healthcare personnel[181].

B Interventions without written action plans are less effective[185,186]. Actions that are exclusively informative are ineffective[178,185].

B Regarding the skills to be developed, patients will be trained in taking the prescribed medication, particularly in the technique of their inhalation devices[89,90,92.93,187], in the recognition of exacerbations and how to act early, and in the avoidance of allergenic triggers[188,189].

Table 3.5. Information and basic skills that should be learned by a patient with asthma

1. **To know** that asthma is a chronic disease requiring continuous treatment even if symptoms are absent.
2. **To know** the differences between inflammation and bronchoconstriction.
3. To be able to **differentiate** between inflammation "controller" drugs and obstruction "reliever" drugs.
4. **To recognize** the symptoms of the disease.
5. **To use** inhalers correctly.
6. **To identify** triggers and avoid triggering factors as much as possible.
7. **To monitor** symptoms and peak expiratory flow (PEF).
8. **To recognize** the signs and symptoms of asthma worsening (loss of control).
9. **To act** in case of asthma worsening in order to prevent an attack or exacerbation.

Table 3.6. Asthma action plan

A. Standard

I. USUAL TREATMENT

1.- Take daily _____

2.- Before Exercise, take _____

II. WHEN SHOULD YOUR TREATMENT BE INCREASED

1. Assessment of the degree of asthma control

Do your asthma symtoms occur more than twice a day?	No/Yes
Do your activity of physucal exercise is limited by asthma?	No/Yes
Do you wake up at night because of asthma?	No/Yes
Do you need to take your bronchodilator more than twice a day?	No/Yes
If you use a peak flow meter (PEF), are PEF values lower than _____?	No/Yes

If your answers have been Yes to three or more questions, your asthma is not well controlled and your usual treatment needs to be increased.

2. How to increase treatment

Increase your treatment as follows and assess your improvement daily:

_____ (Write down the increase of your new treatment)

Maintain this treatment for _____days (specify the number).

3. When should I call the doctor/hospital for help

Call your doctor/hospital _____ (Provide phone numbers)

If your asthma does not improve _____ days (specify the number)

_____ (lines for Complementary instructions)

4. EMERGENCY: severe loss of asthma control

If your have a severe breathleness attack that your can only speak short sentences.

If you have a severe breathlessness or asthma attack.

If you have to use your reliever or rescue bronchodilator every 4 hours without any improvement.

1. Take 2 to 4 puffs _____ (rescue bronchodilator)
2. Take ___ mg of _____ (oral glucocorticoids)
3. Ask for medical assistance: go to _____: Address _____: Call phone number _____
4. Continue using your _____ (rescue bronchodilator) until you get medical help

B. REDUCED (mini-action plan), based in part on Plaza 2015[190]

FRONT

Name _____

Date _____

If your asthma has worsened in the last 24 hours due to having:

- Difficult breath or whistling more than twice or
- Difficult breath or whistling in the last night or
- Need to take your rescue inhaler more than twice

Increase treatment as follows:

1. Increase_____ and maintain for __days
2. If no improvement star _____ (prednisone) 30 mg. 1 tablet a day, and maintain for ___ days (maximum 3-5).*
3. If no improvement, ask for a visit with your doctor.

BACK

The 4 basic advices

1. **Asthma is a chronic inflammatory disease**. For this reason, do not stop taking daily your maintenance or usual treatment. It is the best way to prevent crisis or asthma attacks.
2. **Do not smoke,** or be in the presence of other people smoking.
3. **If you lose control of your athma, take action!** If your have an action plan, implement it; if not, seek for medical help.
4. If you have allergy (mites, pets, pollens, etc..), **avoid exposure.**
5. **If you repeat the use of cortisone*…**

*Review and put notes to avoid overdosing or uncontrolled repeated treatment.

C Minimal educational interventions reduced to the essentials (mini-action plan, avoidance behaviors and revision of inhalation technique) have shown efficacy if they are administered repeatedly at follow-up visits[190].

3.4.3 Action plan

B The education program should consider setting up an action plan, which consists of a set of individualized written instructions in which asthma severity, disease control and the usually prescribed treatment are taken into account. The main objective of the education program is the early detection of asthma worsening and the rapid adoption of measures to achieve quick remission. Depending on the patient's and the physician's preferences[191-193], the level of control on which the action plan should be based can be assessed in terms of severity and frequency of asthma symptoms, as well as through daily home recording of PEF. This plan should include two basic components[194-196]: usual treatment in situation of clinical stability and actions to be implemented in case of asthma worsening (Table 3.6). This action plan will be reviewed at every visit, either scheduled or unscheduled, as well as on hospital admissions or at visits to the emergency department.

B Action plans improve the patient's quality of life, but a systematic review did not find other beneficial or detrimental effects of using a written action plan[197].

3.4.4 Treatment adherence

B Patient's adherence to treatment is a critical factor for achieving and maintaining disease control. It is estimated that adherence in asthma patients is lower than 50%[198,199]. Low adherence is associated with increased morbimortality as well as with a greater use of healthcare resources[200,201].

D Three types of patients with low adherence or non-adherence have been described: erratic (due to forgetfulness to take medication), deliberated (or intentionally non-adherence where the patient decides not to take medications) and involuntary or unwitting (due to failure in understanding the disease and/or its treatment)[202,203].

B Treatment adherence should be evaluated at each medical visit using a reasonably validated method, such as the Test of Adherence to Inhalers (TAI), pharmacy dispending medication, or the combination of both[204-206].

B The education program should include the assessment of the level of adherence, promoting the appropriate corrective measures in case of low adherence and adapting them to the patient's pattern of non-adherence.

D Participation of the patient in the choice of the inhaler provides greater therapeutic adherence and control of the disease. Therefore, patients should be involved in the selection of the inhaler device[102,104,116,117,207-210].

B Non-adherence to control medication in severe asthma can be detected by the FE_{NO} suppression test[211].

3.4.5 Other aspects to be considered

D For education to be effective, a confidence relationship between the healthcare team and the patients should be established, so that patients can raise their doubts, concerns and fears. The healthcare provider should use a simple and understandable language towards both the patients and their relatives, ensure that all concepts have been understood and encourage the patients to put forward their doubts and queries.

B Also, written personalized goals shared by patients and physicians must be established.

C An appropriate agreement between the patient's opinions and expectations and his/her physician is one of the factors related to asthma control[212].

Patients and their families should be encouraged to raise doubts and queries regarding the information received or emerging from the medical interview, and sufficient time should be allocated so that they can be sorted out at the next visit[8].

B Since education is a continuous process and not an isolated event, each visit should give the opportunity to review, strengthen and increase patients' knowledge and skills; hence, it is indispensable that education should be agreed on and accepted by the whole team[178].

B Table 3.7 describes the educational tasks that should be undertaken at each visit. Once properly trained, the nursing and pharmacy staff should actively participate in the organization and management of education programs[106,213-215].

Table 3.7. Educational tasks to be implemented at each visit

	Communication	Information	Instruction
Initial visit	Assess expectations Agree on common targets Discuss adherence issues	Basic concepts on asthma and its treatment	Inhalation technique Self-monitoring
Control visits	Evaluate achievements concerning expectations and objectives Discuss adherence issues	Reinforce information provided at the initial visit. Inform about environmental avoidance measures	Reinforce inhalation technique How to avoid triggers Interpretation of records Self-management plan
Reviews	Evaluate achievements concerning expectations and objectives Discuss adherence to treatment and environmental avoidance measures	Reinforce the whole information	Review and reinforce inhalation technique Review and reinforce self-monitoring and the self-management plan

A Individualized discharge programs assisted by trained nursing personnel prevent readmissions for exacerbations[216].

C Educational interventions carriet out in the primary care setting reduce unscheduled visits and the inappropriate use of drugs, such as antibiotics[217].

A In the interventions to potentiate self-care, sociocultural differences of the patients should be considered[184].

B Educational interventiones cannot exclusively develop in the clinical setting. Interventions of self-care in schools or by other patients with asthma provide a better control, a reduction of exacerbations and a better quality of life. Also, they can positively influence on adolescents to quit smoking[218,219].

B The use of telemedicine improved adherence to treatment[220] through inhaler monitorizing devices[221] or reminder alarms[222].

A It also improves symptoms and decreases the use of medical care[223]. Teleconsultation improves asthma control and quality of life[224] (see section 9.4).

A The effectiveness of the patient's self-control in asthma is very positive. For interventions on the patient's self-management to be effective, it is necessary to combine the active participation of the patient, with training and motivation of professionals integrated into a healthcare system that values the self-control in asthma patients[225].

C Educational workshops are a useful tool as a complement to individualized care, being more profitable when performed during the periods of time when patients present more symptoms[226].

A The community pharmacist, due to its accessibility and frequent use by the patient, can identify poorly controlled patients especially those who abuse SABA agents or have low adherence to anti-inflammatory maintenance treatment. The community pharmacist can offer health education improving adherence, asthma control and obtaining better clinical and economic outcomes. If necessary, he/she can refer the patient to medical consultation[112,227-230].

RECOMMENDATIONS

3.1.	SABAs, when administered 10-15 min before the exercise, are the drugs of choice to prevent exercise-induced bronchoconstriction.	R1
3.2.	In **step 1** *budesonide/formoterol*, *beclomethasona/formoterol* or *beclomethasona/salbutamol* on-demand can be used, although this strategy is not approved in technical specifications and the cost-effectiveness is unknown.	R2
3.3.	First-choice treatment **(step 2)** is an IGC at low doses used on a daily basis. LTRA can be considered as alternative treatment.	R1
3.4.	In **step 2**, an alternative could be the use of IGC at low doses with LABA or SABA (e.g. *budesonide/formoterol*, *beclomethasona/formoterol*, or *beclomethasone/salbutamol*) on-demand in patients with low adherence to treatment in whom a specific education had previously failed. However, this strategy is not approved in the products technical specifications and the cost-effectiveness is unknown.	R2
3.5.	For moderate persistent asthma, the first-line treatment is the combination of an IGC at low doses **(step 3)** or medium doses **(step 4)** with inhaled LABA.	R1
3.6.	For moderate persistent asthma, an IGC at low doses **(step 3)** or medium doses **(step 4)** asociated with an LTRA can be considered as an alternative treatment.	R1
3.7.	The combination of *budesonide/formoterol* or *beclomethasona/formoterol* can be used as maintenance and on-deman (reliever) treatment.	R1
3.8.	In severe persistent asthma **(step 5)** first-line treatment is an IGC at high doses in combination with a LABA.	R1
3.9.	In patients with severe *persistent asthma* **(step 5 or 6)** uncontrolled with the combination of an IGC at high doses and a LABA, with post-bronchodilation $FEV_1/FVC \leq 70$ %, the addition of tiotropium has shown to improve pulmonary function and reduce exacerbations.	R2
3.10.	SABA, *budesinode/formoterol* or *beclomethasone/formoterol* combinations and, in selected cases, short-acting anticholinergics (ipratropium bromide), are the drugs that can be used as reliever medications (in all therapeutic steps).	R1
3.11.	Inhalation is the route of choice in the management of asthma.	R1
3.12.	All healthcare professionals taking care of asthma patients should be involved in the instruction and control of inhaled therapy.	R1
3.13.	The patient should participate in the selection of the inhaler device.	R1
3.14.	It is recomendable the use of a single type of inhaler or at least similar inhalers.	R2
3.15.	Patients should be trained on the inhalation technique of inhaler devices and their technique should be periodically supervised.	R1
3.16.	Smoking cessation is recommended in smokers with asthma.	R1
3.17.	In allergic asthma, specific combined measures of **environmental control according to sensitization of the patient** are recommended.	R2
3.18.	In well-controlled allergic asthma with low or medium treatment levels **(steps 1 to 4)**, **allergen immunotherapy** is recommended when clinically relevant IgE-mediated sensitization against common aeroallergens has been demonstrate, and well standardized extracts are used.	R1
3.19.	**Allergen immunotherapy** should be prescribed by experienced specialized physicians. All administration of subcutaneous immunotherapy and the first of sublingual immunotherapy should be carried out in centers with available basic resources for immediate treatment of a possible adverse reaction.	R2
3.20.	When differente alternatives of **immunotherapy** are available, the use of those that have the consideration of registered medicines with well established efficacy, safety and quality should be priorized.	R2
3.21.	Patients with asthma should follow a **fomal education program** of their disease. Informative actions alone have not been shown to be effective.	R1
3.22.	Patients with asthma should be provided with a **written action plan** in order to detect early asthma worsening and to be able to implement actions for rapid remission.	R1
3.23.	It is indispensable to determine the level of adherence to treatment in each individual patient. To this purpose, the use of validated methods such as the TAI questionnaire or electronic registry of pharmacy dispensing medicines is recommended.	R2
3.24.	Sel-control interventions to be effective should combine the active participation of the patient, the healthcare profesional and the healthcare system.	R1

References

1. Boulet LP, Becker A, Berubé D, Beveridge R, Ernst P; on behalf of the Canadian Asthma Consensus Group. Summary of recommendations from the Canadian Asthma Consensus report 1999. CMAJ. 1999; 161(11 Supl): S1-S12.
2. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting beta-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. J Allergy ClinImmunol. 2007; 119: 344-50.
3. Blakey JD, Woolnough K, Fellows J, Walker S, Thomas M, Pavord ID. Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm. Prim Care Respir J. 2013; 22: 344-52.
4. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006; 117: 563-70.
5. Pérez de Llano L, García-Rivero JL, Urrutia I, Martínez-Moragón E, Ramos J, Cebollero P, et al. A Simple Score for Future Risk Prediction in Patients with Controlled Asthma Who Undergo a Guidelines-Based Step-Down Strategy. J Allergy Clin Immunol Pract. 2019; 7: 1214-21.e3.
6. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention 2018. Disponible en: www.ginasthma.org
7. SIGN-158-british-guideline-on-the-management-of-asthma.html Disponible en https://www.sign.ac.uk/sign-158-british-guideline-on-the-management-of-asthma
8. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (2019 update). Disponible en: https://ginasthma.org/wp-content/uploads/ 2019/06/GINA-2019-main-report-June-2019-wms.pdf
9. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al.; Novel START Study Team. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med. 2019; 380: 2020-30.
10. Haahtela T, Tamminen K, Malmberg LP, Zetterström O, Karjalainen J, Ylä-Outinen H, et al. Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study. Eur Respir J. 2006; 28: 748-55.
11. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, et al.; BEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007; 356: 2040-52.
12. Cockcroft DW. As-needed inhaled beta2-adrenoceptor agonists in moderate-to-severe asthma: current recommendations. Treat Respir Med. 2005; 4: 169-74.
13. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, OhlssonSV, et al; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003; 361(9363): 1071-6.
14. Zeiger RS, Baker JW, Kaplan MS, Pearlman DS, Schatz M, Bird S, et al. Variability of symptoms in mild persistent asthma: baseline data from the MIAMI study. Respir Med. 2004; 98: 898-905.
15. Tan RA, Spector SL. Exercise-induced asthma: diagnosis and management. Ann Allergy Asthma Immunol. 2002; 89: 226-35.
16. Adams NP, Bestall JC, LassersonTJ, Jones PW, Cates C. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev. 2005;(4):CD003135.
17. Adams NP, Bestall JB, Malouf R, LassersonTJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev. 2005;(1):CD002738.
18. Koh MS, Irving LB. Evidence-based pharmacologic treatment for mild asthma. Int J ClinPract. 2007; 61: 1375-9.
19. Reddel HK, BelousovaEG, Marks GB, Jenkins CR. Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A double-blind randomised controlled trial. Prim Care Respir J. 2008; 17: 39-45.
20. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005; 171: 129-36.
21. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. J Allergy Clin Immunol. 2001; 107: 937-44.
22. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018; 378: 1865-76.
23. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med. 2018; 378: 1877-87.
24. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. Am J Med. 2005; 118: 649-57.

25. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev. 2012;(5):CD002314.
26. Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al. ALA. American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med. 2007; 356: 2027-39.
27. Busse WW, Casale TB, Dykewicz MS, Meltzer EO, Bird SR, Hustad CM, et al. Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity. Ann Allergy Asthma Immunol. 2006; 96: 60-8.
28. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. Allergy. 2006; 61: 737-42.
29. Ni Chroinin M, Greenstone I, LassersonTJ, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database Syst Rev. 2009;(4):CD005307.
30. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. Respir Med. 2002; 96: 432-8.
31. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. Lancet. 1994; 343(8904): 1006-8.
32. Dudley T, Parker S, Baldwin R. Clinical inquiries. Is nedocromil effective in preventing asthmatic attacks in patients with asthma? J FamPract. 2004; 53: 927-8.
33. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J RespirCrit Care Med. 1996; 153: 1481-8.
34. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997; 337: 1405-11.
35. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000; 320: 1368-73.
36. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al.; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004; 170: 836-44.
37. Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database Syst Rev. 2005;(4):CD005533.
38. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax. 2005; 60: 730-4.
39. Barnes PJ, Nicolini G, Bizzi A, Spinola M, Singh D. Do inhaled corticosteroid/long-acting beta2-agonist fixed combinations provide superior clinical benefits compared with separate inhalers? A literature reappraisal. Allergy Asthma Proc. 2012; 33: 140-4.
40. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med. 2006; 144: 904-12.
41. Weatherall M, Wijesinghe M, Perrin K, Harwood M, Beasley R. Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. Thorax. 2010; 65(1): 39-43.
42. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006; 368(9537): 744-53.
43. Rabe KF, Pizzichini E, Ställberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006; 129: 246-56.
44. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? EurRespir J. 2005; 26: 819-28.
45. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007; 101: 2437-46.
46. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martínez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007; 61: 725-36.
47. Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013;(12):CD009019.
48. Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med. 2013; 1: 23-31.
49. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: A systematic review and reta-analysis. JAMA. 2018; 319: 1485-96.
50. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002; 109: 410-8.
51. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. Med J Aust. 2003; 178: 223-5.
52. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children

with persistent asthma. Cochrane Database Syst Rev. 2010;(4):CD005533.
53. Pieters WR, Wilson KK, Smith HC, Tamminga JJ, Sondhi S. Salmeterol/fluticasone propionate versus fluticasone propionate plus montelukast: a cost-effective comparison for asthma. Treat Respir Med. 2005; 4: 129-38.
54. Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax. 2008; 63: 453-62.
55. Ram FS, Cates CJ, Ducharme FM. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev. 2005;(1):CD003137.
56. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus antileukotrienes for chronic asthma. Cochrane Database Syst Rev. 2014;(1): CD003137.
57. Chauhan BF, Jeyaraman MM, Singh A, Lys J, Abou-Setta AM, Zarychanski R, et al. Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma. Cochrane Database Syst Rev. 2017;(3):CD010347.
58. Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, et al.; Salford Lung Study Investigators. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet. 2017; 18; 390(10109): 2247-55.
59. Bateman ED, Harrison TW, Quirce S, Reddel HK, Buhl R, Humbert M, et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. Respir Res. 2011; 12: 38.
60. Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev. 2005;(4):CD005535.
61. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. J Allergy ClinImmunol. 1982; 70: 288-98.
62. Tonelli M, Zingoni M, Bacci E, Dente FL, Di Franco A, Giannini D, et al. Short-term effect of the addition of leukotriene receptor antagonists to the current therapy in severe asthmatics. Pulm Pharmacol Ther. 2003; 16: 237-40.
63. Virchow JC Jr, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. Am J RespirCrit Care Med. 2000; 162(2 Pt 1): 578-85.
64. Inoue H, Komori M, Matsumoto T, Fukuyama S, Matsumura M, Nakano T, et al. Effects of salmeterol in patients with persistent asthma receiving inhaled corticosteroid plus theophylline. Respiration. 2007; 74: 611-6.
65. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012; 367: 1198-207.
66. Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. J Asthma Allergy. 2014; 7: 11-21.
67. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax. 2013; 68: 322-9.
68. Wong EH, Porter JD, Edwards MR, Johnston SL. The role of macrolides in asthma: current evidence and future directions. Lancet Respir Med. 2014; 2: 657-70.
69. Hiles SA, McDonald VM, Guilhermino M, Brusselle GG, Gibson PG. Does maintenance azithromycin reduce asthma exacerbations? An individual participant data meta-analysis. Eur Respir J. 2019 Sep 12. pii:1901381. doi: 10.1183/13993003.01381-2019. [Epub ahead of print]).
70. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005; 60: 309-16.
71. Humbert M, Berger W, Rapatz G, Turk F. Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma. Allergy. 2008; 63: 592-6.
72. Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis. Curr Med Res Opin. 2007; 23: 2379-86.
73. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane database of systematc reviews. 2014;(1): CD003559.
74. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012; 380: 651-9.
75. Ortega H, Chupp G, Bardin P, Bourdin A, Garcia G, Hartley B, et al. The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. Eur Respir J. 2014; 44: 239-41.
76. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371: 1198-207.
77. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: result from two multicenter, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015; 3: 355-66.
78. Bleecker ER, Fitzgerald JM, Chanez P, Papi A, Weinstein SF, Braker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta-2agonists (SIROCCO): a randomized, multicenter, placebo-controlled, phase 3 trial. Lancet. 2016; 88: 2115-27.
79. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014; 371: 1189-97.
80. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017; 376: 2448-58.

81. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018; 378: 2486-96.
82. Rabe JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018; 378: 2475-85.
83. Torrego A, Solá I, Muñoz AM, Roqué I Figuls M, Yepes-Nuñez JJ; Alonso-Coello P, et al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database of Systematic Reviews. 2014;(3):D009910.
84. Mash B, Bheekie A, Jones PW. Inhaled vs oral steroids for adults with chronic asthma. Cochrane Database Syst Rev. 2000;(2):CD002160.
85. Pavord ID. Oral corticosteroid-dependent asthma: current knowledge and future needs. Curr Opin Pulm Med. 2019; 25: 51-58.
86. Newman SP, Clarke SW. Therapeutic aerosols 1-physical and practical considerations. Thorax. 1983; 38: 881-6.
87. Clarke SW, Newman SP. Therapeutic aerosols 2-Drugs available by the inhaled route. Thorax. 1984; 39: 1-7.
88. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. Lancet. 2011; 377: 1032-45
89. Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al.; European Respiratory Society; International Society for Aerosols in Medicine. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011; 37: 1308-31.
90. Consenso SEPAR-ALAT sobre terapia inhalada. Arch Bronconeumol. 2013; 49(Supl.1): 1-14.
91. GEMA Inhaladores. Madrid: Luzán 5; 2018. Disponible en www.gemasma.com
92. Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G, et al. Inhaler Error Steering Committee. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. Respir Med. 2013; 107: 37-46
93. Sanchis J, Corrigan C, Levy ML, ViejoJL; ADMIT Group. Inhaler devices-from theory to practice. Respir Med. 2013; 107: 495-502.
94. Sanchis J, Gich I, Pedersen S. Aerosol Drug Management Improvement Team (ADMIT). Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? Chest. 2016; 150: 394-406.
95. Plaza V, Giner J, Rodrigo JG, Dolovich M, Sanchis J. Errors in the use of inhalers by health care professionals: A Systematic Review. J Allergy Clin Immunol Pract. 2018; 6: 987-95.
96. Giner J, Roura P, Hernández C, Torrejón M, Peiró M, Fernández MJ, de Santa María EL, Gimeno MA, Macian V, Tarragona E, Plaza V. Knowledge and Attitudes of Nurses in Spain about Inhaled Therapy: Results of a National Survey. J Aerosol Med Pulm Drug Deliv. 2016; 29: 86-93.
97. Kappeler D, Sommerer K, Kietzig C, Huber B, Woodward J, Lomax M, et al. Pulmonary deposi- tion of fluticasone propionate/formoterol in healthy volunteers, asthmatics and COPD patients with a novel breath-triggered inhaler. Respir Med. 2018; 138: 107-14.
98. Haikarainen J, Selroos O, Löytänä T, Metsärinne S, Happonen A, Rytila P. Pulm Ther. 2017; 3: 125.
99. Brown PH, Greening AP, Crompton GK. Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. Thorax. 1993; 48: 233-8.
100. Newman SP, Newhouse MT. Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. J Aerosol Med. 1996; 9: 55-70.
101. Newman SP. Spacer devices for metered dose inhalers. Clin Pharmacokinet. 2004; 43: 349-60.
102. Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res [Internet]. 2018; 4(2). pii: 00065-2018. doi: 10.1183/23120541.00065-2018. eCollection 2018 Apr.
103. Plaza V, Sanchis J. Medical personnel and patient skill in the use of metered dose inhalers: a multicentric study. CESEA Group. Respiration. 1998; 65: 195-8.
104. Plaza V, Giner J, Calle M, Rytilä P, Campo C, Ribó P, et al. Impact of patient satisfaction with his or her inhaler on adherence and asthma control. Allergy Asthma Proc. 2018; 39: 437-44.
105. Armour C, Bosnic-Anticevich S, Brillant M, Burton D, Emmerton L, Krass I, et al. Pharmacy Asthma Care Program (PACP) improves outcomes for patients in the community. Thorax. 2007; 62: 496-592.
106. Armour CL, Reddel HK, Lemay KS, Saini B, Smith LD, Bosnic-Anticevich SZ, et al. Feasibility and Effectiveness of an Evidence-Based Asthma Service in Australian Community Pharmacies: A Pragmatic Cluster Randomized Trial. Journal of Asthma. 2013; 50: 302-9.
107. Basheti IA, Reddel HK, Armour CL, Bosnic-Anticevich SZ. Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists. J Allergy Clin Immunol. 2007; 119: 1537-8.
108. García-Cárdenas V, Sabater-Hernández D, Kenny P, Martínez-Martínez F, Faus MJ, Benrimoj SI. Effect of a pharmacist intervention on asthma control. A cluster randomised trial. Respiratory Medicine. 2013; 107: 1346-55.
109. Giraud V, Allaert F-A, Roche N. Inhaler technique and asthma: Feasability and acceptability of training by pharmacists. Respir Med. 2011; 105: 1815-22.
110. Hämmerlein A, Müller U, Schulz M. Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients: Improvement of inhalation technique. J Evaluation Clinical Practice. 2011; 17: 61-70.
111. Mehuys E, van Bortel L, de Bolle L, van Tongelen I, Annemans L, Remon JP, et al. Effectiveness of pharmacist intervention for asthma control improvement. Eur Respir J. 2008; 31: 790-9.
112. Wong L-Y, Chua S-S, Husin A-R, Arshad H. A pharmacy management service for adults with asthma: a cluster randomised controlled trial. Family Practice. 2017; 34: 564-73.
113. Giner J, Macián V, Hernández C; Grupo EDEN. Multicenter prospective study of respiratory patient education and instruction in the use of inhalers (EDEN study). Arch Bronconeumol. 2002; 38: 300-5.
114. Takaku Y, Kurashima K, Ohta C, Ishiguro T, Kagiyama N, Yanagisawa T, et al. How many instructions are required to correct inhalation errors in patients with asthma and chronic obstructive pulmonary disease? Respir Med. 2017; 123: 110-5.
115. Basheti IA, Obeidat NM, Reddel HK. Effect of novel inhaler technique reminder labels on the retention of inhaler technique

skills in asthma: a single-blind randomized controlled trial. NPJ Prim Care Respir Med. 2017; 27: 9.
116. Van del Palen J, Klein JJ, van Hervaarden CL, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. Eur Respir J. 1999; 14: 1034-7.
117. Dekhuijzen PNR, Vincken W, Virchow JC, Roche N, Agusti A, Lavorini F, et al. Prescription of inhalers in asthma and COPD: Towards a rational, rapid and effective approach. Respir Med. 2013; 107: 1817-21.
118. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med. 2007; 175: 783-90.
119. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med. 1998; 339: 1194-200.
120. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. Am J Respir Crit Care Med. 2005; 171: 109-14.
121. Clearie KL, McKinlay L, Williamson PA, Lipworth BJ. Fluticasone/Salmeterol Combination Confers Benefits in People With Asthma Who Smoke. Chest. 2012; 141: 330-8.
122. Hedman L, Bjerg A, Sundberg S, Forsberg B, Rönmark E. Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. Thorax. 2011; 66: 20-5.
123. Jiménez CA, Barrueco M, Solano S, Torrecilla M, Domínguez M, Díaz-Maroto JL, et al. Recomendaciones en el abordaje diagnóstico y terapéutico del tabaquismo. Documento de consenso. Arch Bronconeumol. 2003; 39: 35-41.
124. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995; 332: 133-8.
125. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. N Engl J Med. 2010; 363: 1139-45.
126. Sims M, Maxwell R, Gilmore A. Short-term impact of the smokefree legislation in England on emergency hospital admissions for asthma among adults: a population-based study. Thorax. 2013; 68: 619-24.
127. Bayly JE, Bernat D, Porter L, Choi K. Secondhand Exposure to Aerosols From Electronic nicotine delivery systems and asthma exacerbations among youth with asthma. Chest. 2018; 155: 88-93.
128. Bals R, Boyd J, Esposito S, Foronjy R, Hiemstra PS, Jiménez-Ruiz CA, et al. Electronic cigarettes: a task force report from the European Respiratory Society. Eur Respir J. 2019; 31; 53(2). doi: 10.1183/13993003.01151-2018. Print 2019 Feb.
129. Christiani DC. Vaping-Induced Lung Injury. N Engl J Med. 2019 Sep 6. doi: 10.1056/NEJMe1912032. [Epub ahead of print]
130. Plaza V, Serrano J, Picado C, Sanchis J; High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J. 2002; 19: 846-52.
131. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. Allergy. 2007; 62: 1111-8.
132. Izquierdo AD, Bobolea I, Doña I, Campo P, Segura C, Ortega N, et al. Position statement of the Spanish Society of Allergology and Clinical Immunology on provocation tests with aspirin/nonsteroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol. 2020; 30(1): 1-13.
133. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med. 2004; 351: 1068-80.
134. Phipatanakul W, Cronin B, Wood RA, Eggleston PA, Shih MC, Song L, et al. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. Ann Allergy Asthma Immunol. 2004; 92: 420-5.
135. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. Chest. 2005; 127: 1565-71.
136. Orriols R, Abu K, Alday E, Cruz MJ, Gáldiz JB, Isidro I, et al. Normativa del asma ocupacional. Arch Bronconeumol. 2006; 42: 457-74.
137. Portnoy J, Chew GL, Phipatanakul W, Williams PB, Grimes C, Kennedy K, et al. Environmental assessment and exposure reduction of cockroaches: a practice parameter. J Allergy Clin Immunol. 2013; 132: 802-8.
138. Rabito FA, Carlson JC, He H, Werthmann D, Schal C. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. Journal of Allergy and Clinical Immunology. 2017; 140: 565-70.
139. Luczynska C, Tredwell E, Smeeton N, Burney P. A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics. Clin Exp Allergy. 2003; 33: 1648-53.
140. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. N Engl J Med. 2003; 349: 225-36.
141. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. Allergy. 2008; 63: 646-59
142. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children. A randomized trial of mite-impermeable bed covers. Am J Respir Crit Care Med. 2017; 196: 150-8.
143. Htut T, Higenbottam TW, Gill GW, Darwin R, Anderson PB, Syed N. Eradication of house dust mite from homes of atopic asthmatic subjects: a double-blind trial. J Allergy Clin Immunol. 2001; 107: 55-60.
144. Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. J Allergy ClinImmunol. 2003; 111: 169-76.
145. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, et al. Effectiveness of indoor allergen reduction in asthma management: A systematic review. Journal of Allergy and Clinical Immunology. 2018; 141: 1854-69.
146. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews. 2010;(8):CD001186.
147. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. Allergy. 2017; 72: 1825-48.

148. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med. 1997; 336: 324-31.
149. Pitsios C, Demoly P, Bilo MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy. 2015; 70: 897-909.
150. Agache I, Lau S, Akdis CA, Smolinska S, Bonini M, Cavkaytar O, et al. EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma. Allergy. 2019; 74: 855-73.
151. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal rereactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol. 2004; 113: 1129-36.
152. Olaguibel JM, Álvarez MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. J Investig Allergol Clin Immunol. 2005; 15: 9-16.
153. Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy. 2008; 63: 1280-91.
154. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: A systematic review. JAMA. 2013; 309: 1278-88.
155. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: A randomized clinical trial. JAMA. 2016; 315(16): 1715-25.
156. Durham SR, Walker SM, VargaEM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999; 341: 468-75.
157. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al.; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007; 62: 943-8.
158. Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G, et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. Pediatr Allergy Immunol. 2017; 28: 18-29.
159. Pajno GB, Barberio G, de Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy. 2001; 31: 1392-7.
160. Nasser S, Vestenbæk U, Beriot-Mathiot A, Poulsen P. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. Allergy. 2008; 63: 1624-9.
161. Hankin CS, Cox L, Bronstone A, Wang Z. Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis. J Allergy Clin Immunol. 2013; 131: 1084-91.
162. Asaria M, Dhami S, van Ree R, Gerth van Wijk R, Muraro A, Roberts G, et al. Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: A systematic overview. Allergy. 2018; 73: 269-83.
163. Abadoglu O, Mungan D, Pasaoglu G, Celik G, Misirligil Z. Influenza vaccination in patients with asthma: effect on the frequency of upper respiratory tract infections and exacerbations. J Asthma. 2004; 41: 279-83.
164. Christy C, Aligne CA, Auinger P, Pulcino T, Weitzman M. Effectiveness of influenza vaccine for the prevention of asthma exacerbations. Arch Dis Child. 2004; 89: 734-5.
165. Sheikh A, Alves A, Dhami S. Pneumococcal vaccine for asthma. Cochrane Database Syst. Rev. 2002;(1):CD002165.
166. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Eng J Med. 2000; 342: 232-9.
167. Jain VK, Rivera L, Zaman K, Espos RA Jr, Sirivichayakul C, Quiambao BP, et al. Vaccine for Prevention of Mild and Moderate-to-Severe Influenza in Children. N Eng J Med. 2013; 369: 2481-91.
168. Merckx J, Ducharme FM, Martineau C, Zemek R, Gravel J, Chalut D, et al. Respiratory viruses and treatment failure in children with asthma exacerbation. Pediattrics. 2018; 142(1): e20174105
169. Talbot TR, Hartert TV, Mitchel E, Halasa NB, Arbogast PG, Poehling KA, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med. 2005; 352: 2082-90.
170. Klemets P, Lyytikainen O, Ruutu P, Ollgren J, Kaijalainen T, Leinonen M, et al. Risk of invasive pneumococcal infections among working age adults with asthma. Thorax. 2010; 65: 698-702.
171. Kim DK, Bridges CB, Harriman KH, Advisory Committee on Immunization Practices. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older: United States, 2016. Ann Intern Med. 2016; 164: 184-94.
172. Picazo JJ, González-Romo F, García A, Peréz-Trallero E, Gil P, de la Cámara R, et al. Consenso sobre la vacunación anti-neumocócica en el adulto con patología de base. Rev Esp Quimioter. 2013; 26: 232-52.
173. Grupo de trabajo vacunación frente a neumococo en grupos de riesgo 2015 de la Ponencia de Programas y Registro de Vacunaciones. Utilización de la vacuna frente a neumococo en grupos de riesgo. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministerio de Sanidad, Servicios Sociales e Igualdad. 2015. Disponible en: http://www.msssi.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/Neumococo_Gruposriesgo.pdf
174. Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. Thorax 2006; 61: 722-8.
175. Hughes DM, McLeod M, Garner B, Goldbloom RB. Controlled trial of a home and ambulatory program for asthmatic children. Pediatrics. 1991; 87: 54-61.
176. Colland VT. Learning to cope with asthma: a behavioural self-management program for children. Patient Educ Couns. 1993; 22: 141-52.
177. Van Der Palen J, Klein JJ, Zielhuis GA, Van Herwaarden CLA, Seydel ER. Behavioural effect of self-treatment guidelines in a self-management program for adults with asthma. Patient Educ Couns. 2001; 43: 161-9.

178. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood Bauman A, et al. Educación para el autocuidado y examen médico regular para adultos con asma (Revisión Cochrane traducida). En: La Biblioteca Cochrane Plus, 2008 Número 1. Oxford: Update Software Ltd. Disponible en: http://www.update-software.com
179. Powell H, Gibson PG. Opciones para la educación sobre el autocuidado para los adultos con asma (Revisión Cochrane traducida). En: La Biblioteca Cochrane Plus, 2008 Número 1. Oxford: Update Software Ltd. Disponible en: http://www.update-software.com
180. British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax. 2014; 69(Suppl 1):1-192.
181. Pinnock H, Parke HL, Panagioti M, Daines L, Pearce G, Epiphaniou E, et al. Systematic meta-review of supported self-management for asthma: A healthcare perspective. BMC Med. 2017; 15: 64.
182. Kuhn L, Reeves K, Taylor Y, Tapp H, McWilliams A, Gunter A, et al. Planning for Action: The impact of an asthma action plan decision support tool integrated into an electronic health record (EHR) at a large health care system. J Am Board Fam Med. 2015; 28: 382-93.
183. Partridge MR. Patient education. En: O'Byrne P, Thomsen NC, eds. Manual of asthma management. WB Saunders; 1995: 378-92.
184. Ahmed S, Steed L, Harris K, Taylor SJC, Pinnock H. Interventions to enhance the adoption of asthma self-management behaviour in the South Asian and African American population: A systematic review. NPJ Prim Care Respir Med. 2018; 28: 5.
185. Gibson PG, Powell H, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, et al. Limited (information only) patient education programs for adults with asthma. Cochrane Database Syst Rev. 2002;(2):CD001005.
186. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2003;CD001117.
187. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011; 105: 930-8.
188 Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002;(2):CD000011.
189. Creer TL. Medication compliance and childhood asthma. En: Krasnegor NA, Epstein L, Johnson SB, YaffeSJ, editors. Developmental aspects of health compliance behavior. Hittsdale, NS: Lawrence Associate; 1993. pp. 303-33.
190. Plaza V, Peiró M, Torrejón M, Fletcher M, López-Viña A, Ignacio JM, Quintano JA, Bardagí S, Gich I; PROMETHEUS Study Group. A repeated short educational intervention improves asthma control and quality of life. Eur Respir J. 2015: 46; 1298-1307.
191. Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, et al. Are asthma medications and management related to deaths from asthma? Am J Respir Crit Care Med. 2001; 163: 12-18.
192. Douglass J, Aroni R, Goeman D, Stewart K, Sawyer S, Thien F, et al. A qualitative study of action plans for asthma. BMJ. 2002; 324(7344): 1003.
193. Reddel HK, Marks GB, Jenkins CR. When can personal best peak flow be determined for asthma action plans? Thorax. 2004; 59: 922-924.
194. Lahdensuo A. Guided self management of asthma-how to do it. BMJ.1999; 319(7212): 759.
195. Côté J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet, LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. Am J Respir Crit Care Med. 2001; 163: 1415-9.
196. Gibson PG, Powell H. Written action plans for asthma: An evidence-based review of the key components. Thorax. 2004; 59: 94-9.
197. Gatheral TL, Rushton A, Evans DJ, Mulvaney CA, Halcovitch NR, Whiteley G, et al. Personalised asthma action plans for adults with asthma. Cochrane Database Syst Rev. 2017;(4):CD011859.
198. Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled asthma medication in preschool children. Thorax. 1995; 50: 1274-9.
199. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. J Asthma. 2010; 47: 162-5.
200. Horn CR, Clark TJH, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. Respir Med. 1990; 84: 67-70.
201. Jentzsch NS, Camargos P, Sarinho ESC, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. Respir Med. 2012; 106: 338-43.
202. Rand CS. Adherence to asthma therapy in the preschool child. Allergy. 2002; Supplement 57(74): 48-57.
203. Hyland M. Types of noncompliance. Eur Respir Rev. 1998; 8: 255-9.
204. Plaza V, Fernández-Rodríguez C, Melero C, Cosío BG, Entrenas LM, de Llano LP, et al. Validation of "Test of the Adherence to Inhalers" (TAI) for asthma and COPD patients. J Aerosol Med Pulm Dug Deliv. 2016; 29: 142-52.
205. De Lano LP, Pallares A, González-Barcala FJ, Mosteiro-Añón M, Corbacho D, Dacal R, et al. Assessing adherence to inhaled medication in asthma: impact of once-daily versus twice-daily dosing frequency. The ATAUD study. J Asthma. 2018; 55: 933-938.
206. Plaza V, Giner J, Curto E, Alonso-Ortiz MB, Orue MI, Vega JM, et al.; the group of investigators of the RE-TAI study. Assessing adherence by combining the Test of Adherence to Inhalers with pharmacy prescription records. J Investig Allergol Clin Immunol. 2019 Oct 10:0. doi: 10.18176/jiaci.0461. [Epub ahead of print]
207. Taylor YJ, Tapp H, Shade LE, Liu TL, Mowrer JL, Dulin MF. Impact of shared decision making on asthma quality of life and asthma control among children. J Asthma. 2018; 55: 675-83.
208. Toy EL, Beaulieu NU, McHale JM, Welland TR, Plauschinat CA, Swensen A, Duh MS. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med. 2011; 105: 435-41.
209. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasona furoate administered via a dry powder inhaler: a randomized open-label study. BMC Pulm Med. 2010; 510: 1.
210. Osman LM. Patient preferences and inhaler use in chronic obstructive pulmonary disease. Int J Resp Care. 2006; 2: 95-9.

211. Heaney LG, Busby J, Bradding P, Chaudhuri R, Mansur AH, Niven R, et al. Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma. Am J Respir Crit Care Med. 2019; 199: 454-64.
212. Urrutia I, Plaza V, Pascual S, Cisneros C, Entrenas LM, Luengo MT, et al. Asthma control and concordance of opinions between patients and pulmonologists. J Asthma. 2013; 50: 877-83.
213. Castro M, Zimmermann NA, Crocker S, Bradley J, Leven C, Schechtman KB. Asthma Intervention Program Prevents Readmissions in High Healthcare Users. Am J Respir Crit Care Med. 2003; 168: 1095-9.
214. Borgmeyer A, Gyr PM, Jamerson PA, Henry LD. Evaluation of the role of the pediatric nurse practitioner in an inpatient asthma program. J Pediatr Health Care. 2008; 22: 273-81.
215. Kuethe MC, Vaessen-Verberne AA, Elbers RG, van Aalderen WM. Nurse versus physician-led care for the management of asthma. Cochrane Database Syst Rev. 2013;(2):CD009296.
216. Hall KK, Petsky HL, Chang AB, O'Grady KF. Caseworker-assigned discharge plans to prevent hospital readmission for acute exacerbations in children with chronic respiratory illness. Cochrane Database Syst Rev. 2018;(11):CD012315.
217. Boulet LP, Boulay MÈ, Gauthier G, Battisti L, Chabot V, Beauchesne MF, et al. Benefits of an asthma education program provided at primary care sites on asthma outcomes. Respir Med. 2015; 109: 991-1000.
218. Kew KM, Carr R, Crossingham I. Lay-led and peer support interventions for adolescents with asthma. Cochrane Database Syst Rev. 2017;(4):CD012331.
219. Harris K, Kneale D, Lasserson TJ, McDonald VM, Grigg J, Thomas J. School-based self-management interventions for asthma in children and adolescents: a mixed methods systematic review. Cochrane Database Syst Rev. 2019;(1):CD011651.
220. Bender BG, Cvietusa PJ, Goodrich GK, Lowe R, Nuanes HA, Rand C, et al. Pragmatic trial of health care technologies to improve adherence to pediatric asthma treatment: a randomized clinical trial. JAMA Pediatr. 2015; 169: 317-23.
221. Chan AHY, Harrison J, Black PN, Mitchell EA, Foster JM. Using electronic monitoring devices to measure inhaler adherence: A practical guide for clinicians. J Allergy Clin Immunol Pract. 2015; 3: 335-49.e5.
222. Morton RW, Elphick HE, Rigby AS, Daw WJ, King DA, Smith LJ, et al. STAAR: A randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax. 2017; 72: 347-54.
223. Halterman J, Fagnano M, Tajon R, Tremblay P, Wang H, Butz A, et al. Effect of the School-Based Telemedicine Enhanced Asthma Management (SB-TEAM) Program on Asthma Morbidity: A Randomized Clinical Trial. JAMA Pediatrics. 2018; 172(3): e174938-e174938.
224. Chongmelaxme B, Lee S, Dhippayom T, Saokaew S, Chaiyakunapruk N, Dilokthornsakul P. The Effects of Telemedicine on Asthma Control and Patients' Quality of Life in Adults: A Systematic Review and Meta-analysis. J Allergy Clin Immunol Pract. 2019; 7: 199-216.e11.
225. Pinnock H, Epiphaniou E, Pearce G, Parke H, Greenhalgh T, Sheikh A, et al. Implementing supported self-management for asthma: a systematic review and suggested hierarchy of evidence of implementation studies. BMC Med. 2015; 13: 127.
226. Cano Fuentes G, Dastis C, Morales I, Manzanares ML, Fernández A, Martín L. Ensayo clínico aleatorio para evaluar la eficacia de una intervención educativa desarrollada en atención primaria sobre asmáticos adultos. Atencion Primaria. 2014; 46; 117-39.
227. Dokbua S, Dilokthornsakul P, Chaiyakunapruk N, Saini B, Krass I, Dhippayom T. Effects of an Asthma Self-Management Support Service Provided by Community Pharmacists: A Systematic Review and Meta-Analysis. J Manag Care Spec Pharm. 2018; 24: 1184-96.
228. Manfrin A, Tinelli M, Thomas T, Krska J. A cluster randomised control trial to evaluate the effectiveness and cost-effectiveness of the Italian medicines use review (I-MUR) for asthma patients. BMC Health Services Research [Internet]. 2017 Dec [cited 2019 Sep 2]; 17(1). Disponible en: http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-017-2245-9
229. LeMay KS, Armour CL, Reddel HK. Performance of a brief asthma control screening tool in community pharmacy: a cross-sectional and prospective longitudinal analysis. Primary Care Respiratory Journal. 2014; 23: 79-84.
230. Van Boven JF, Hiddink EG, Stuurman-Bieze AG, Schuiling-Veninga CC, Postma MJ, Vegter S. The pharmacists' potential to provide targets for interventions to optimize pharmacotherapy in patients with asthma. Int J Clin Pharm. 2013; 35: 1075-82.