5. Treatment of childhood asthma

5.1 Education

A The education of the child with asthma and his/her family increases the quality of life, reduces the risk of exacerbations and the cost of healthcare, the reasons for which education is one the fundamental pillars of treatment. Its objective is for the child to achieve a normal life for his/her age including physical exercise and sport activities[1].

A Education is essential to improve treatment adherence and to achieve control of the disease[2,3].

Table 5.1. Key aspects of the education of a child with asthma

Topic area	Key aspects
Asthma	– Concept of asthma (chronic disease, variability) – Symptoms exacerbation/between exacerbations – Bronchoconstriction – Inflammation
Environmental measures	– Counseling against smoking – Triggering factors (allergens, virus, exercise, etc.) – How to identify and avoidance mesures
Treatment	– Bronchodilators (rescue treatment) – Anti-inflammatory drugs (maintenance treatment) – Side-effects – Exacerbation (how to recognize initial symptoms and early action) – Inmunotherapy
Inhalers	– Importance of inhaled medication – Inhalation technique – Maintenance of the system – Errors/forgetfulness
Self-control	– PEF. Best personal value – Symptoms registry – Personalized written action plan
Lifestyle	– School attendance – Practice of sports – Autonomy

PEF: peak expiratory flow.

B Education should be developed in all healthcare settings in which children with asthma are attended[4].

B Education will be primary addressed to the family during early childhood and, from 8-9 years, should be especially addressed to the child, in order to promote personal autonomy and to achieve the maximum degree of self-care[5].

B Home education programs may be beneficial for children with poorly controlled asthma and are potentially profitable[6].

C For education to be effective, it is essential to identify the educational needs and the factors that affect the behavior of the patient and/or his/her family[7].

C Key aspects of education are shown in Table 5.1[1].

A The education of children with asthma is more effective when accompanied by personalized written action plans (Table 5.2)[8,9], which addresses maintenance treatment (Table 5.3)[10] and the management of asthma exacerbations (Table 5.4)[11]. Every educational plan must be associated with periodic reviews.

A In children, written action plans based on measurement of PEF do not provide benefits as compared with plans based on monitoring of symptioms, so that PEF-based plans are not generally recommended[8,12]. However, on an individual basis, children and adolescents with severe asthma and low perception of symptoms could benefit from plans based on PEF monitoring[13,14].

D

5.2 Maintenance treatment

5.2.1 Drugs

A ***Inhaled glucocorticoids (IGC).*** ICG are the first-line of treatment. In children older than 3 years of age, the efficacy of daily IGC is well established, with improvement of clinical and functional parameters, bronchial inflammation, better quality of life, and decrease in the risk of both exacerbations and hospitalizations[15,16].

A Infants and preschool children treated with IGC daily experience fewer asthma/wheezing episodes[17,18] a better treatment response being obtained by those showing risk factors of developing persistent asthma (Asthma Predictive Index [API])[19,22], while viral-induced episodic wheezing shows limited response[23]. A treatment trial followed by evaluation of response is recommended[24].

B Treatment with IGC, either continuously or intermittently, does not modify the natural history of the disease[21-25].

B In preschool and children, the use of controller drugs (IGC or montelukast) at regular doses or intermittently at the onset of symptoms is not recommended[26-28].

B Early intermittent therapy with IGC at high doses given to infants and preschool children with moderate-severe episodic wheezing and risk factors (API +) at the onset of symptoms have shown to be effective in reducing severity and duration of exacerbations[16,29,30], but further studies are needed to establish the recommendation of this therapy. B

B When administered at usual doses, IGC are safe drugs for the management of childhood asthma. There is usually a decrease in the growth rate at the beginning of treatment (1-3 years), although this is a transient effect and does not influence final growth or final height. However, the final height of children treated with IGC over prolonged periods is lower, an effect proved to be dose-dependent[31,32].

Table 5.2. Components of a personalized action plan

Action plan for treating asthma exacerbation at home
– Recognize asthma symptoms and the onset of an exacerbation for using early short-acting bronchodilators and on-demand when symptoms appear.
– Recognize alarm signs and when to seek help from the doctor or go to the emergency department.
Salf-controlled/family-controlled action plan
– Rules for avoiding specific asthma triggers in children.
– Daily use of preventive medication: doses, frequency and route of administration.
– Changes of preventive medication according to severity and frequency of symptoms **(symptom diary)** and/or measurement of peak expiratory flow **(home PEF recording)**.
– When to go to his/her pediatrician because asthma is not controlled.
– Prevention and treatment of exertional asthma.

PEF: peak expiratory flow.

Table 5.3. Written action plan to maintain asthma control

Your usual treatment (preventive):

Every day I take: _____

Before exercise I take _____

When to Increase Preventive Treatment

Assess your level of asthma control:

In the last week you have had:

Asthma symptoms more than twice a day?	No	Yes
Activity or physican excersise limited by your asthma?	No	Yes
Night awakenings due to asthma?	No	Yes
Need of rescue medication more than twice a day?	No	Yes
If you measure (PEF), your PEF is lower than	No	Yes

If you have answered **"Yes" to 3 or more questions**, your asthma is not well controlled and **to increase a step in your treatment may be necessary**

How to Increase Treatment

Increase treatment from _____

to _____

and assess improvement every day. Maintain this treatment for _____days.

In case of an exacerbation, **treatment in the action plan for the management of exacerbations** will be started and will attend a medical consultation for a new assessment.

Modified from GINA www.ginasthma.com

D It is difficult to establish the equivalent doses of the IGC mostly used in pediatric age[33]. Comparable doses of IGC drugs for use in the pediatric age are tentatively shown in Table 5.5, taking into account that the lowest dose that maintains control of the patient should be sought.

Table 5.4. Action plan for treating an asthma exacerbation at home

What is an ASTHMA EXACERBATION EPISODE and HOW TO ACT AT HOME?

An asthma exacerbation episode is a sudden or progressive worsening of symptoms:
- Increased cough (continuous, nocturnal or with exercise).
- Whistling sound.
- Fatigue (difficult breathing).
- Feeling of chest tightness.
- Decrease of PEF (if you use the pek-flow meter).

There are **symptoms** that warn us that **an exacerbation can be severe** (warning signs):
- Bluish color of the lips.
- Ribs sink when breathing.
- Dificulty speaking.
- Numbness.

Warning signs indicate that medical assistance should be immediately requested!

What to do at home in the presence of an exacerbation?
- Keep calm.
- Treat symptoms as early as possible.
- Start medication at home.
- Never wait to see if symptoms disappear spontaneously.
- After starting medication, observe for 1 hour and assess response.

USE OF MEDICATION:

Take your rapid rescue medication: salbutamol _____ with spacer, 2-4 puffs, separated by 30-60 seconds. This dose can be repeated every 20 minutes, up to a maximum of 3 times. If symptoms does not improve in 1 hour, start taking oral corticoids _____ (1 mg/kg/day, maximum 40 mg/day), for 3-5 days.

Take your anti-inflammatory medication_____ times a day, all days, according to the indications given by your pediatrician

ASSESS RESPONSE TO TREATMENT

If you improve in one hour and improvement is maintained for 4 hours, continue with salbutamol: 2-4 puffs every 4-6 hours (depending on symptoms) and visit your pediatrician in 24-48 hours.

If you do not improve or the improvement is not maintained and you relapse again: go to an emergency department

If you know how to control excerbations, the duration of symptoms will be lower and your quality of life will improve.

D A D A B B B A B A

Leukotriene receptor antagonists (LTRA). In preschool children with virus-induced asthma/weezing, LTRA are associated with a modest reduction of symptoms and need of oral glucocorticoids as compared with placebo[27,34,35]. Although a definite beneficial effect remains unclear, a clinical trial to assess response to LTRA may be conducted, which could be stopped if the expected response is not obtained[34]. More evidence is needed to determine whether there is a responder phenotype to *montelukast*[36].

If asthma symptom cannot be controlled with IGC at low doses, increasing IGC at medium doses is more effective than the association with *montelukast*[37].

Association of long-acting β_2-adrenergic agonists (LABA) and IGC. It has been approved for use in children over 4 years of age. LABAs are safe when administered with an IGCs, but never as monotherapy[38,39].

A decrease in the number of exacerbations and the need for systemic glucocorticoids was observed in a study of children treated with *formoterol/budesonide* in a single inhaler as both maintenance and reliever therapy (MART approach)[40], although some authors consider that there is limited evidence for this age segment[41].

In children aged between 6 and 11 years with persistent asthma not controlled with low doses of IGC, doubling the IGC dose has a similar effect to adding a LABA on clinical control and lung function[42]. However, the clinical phenotype and the heterogeneity of the individual response to IGC, LTRA and LABA should be assessed[43,44], therefore, it is necessary to closely monitor the response to treatment in children with asthma not controlled using IGC.

Tiotropium. It is a long-acting muscarinic antagonist. It can be used in children from 6 years of age with poorly controlled severe asthma treated with IGC at high doses plus LABA. The dose is 5 µg once a day[45]. A study in children aged 1 to 5 years concluded that tolerability of tiotropium is good in preschool children and can reduce the number of exacerbations[46].

Theophyllines. These drugs are less effective than IGCs as maintenance monotherapy, even though their anti-inflammatory activity enables their use in association with IGC in individual cases of severe asthma[47].

Anti-IgE monoclonal antibody (omalizumab). Omalizumab has shown therapeutic efficacy (decrease in the doses of IGC, quality of life improvement, reduction of exacerbations and hospitalizations) in children over 6 years of age with moderate or severe persistent allergic asthma inadequately controlled with IGC at high doses and LABA[48-50]. It is administered subcutaneously every 2-4 weeks at doses tailored to total IgE levels and body weight. A number of studies carried out in daily practice conditions in children with

Table 5.5. Comparable doses of inhaled glucocorticoids commony used in pediatric age (mg/day)

Children under 12 years of age			
	Low doses	Medium doses	High doses
Budesonide	100-200	> 200-400	> 400
Fluticasone propionate	50-100	> 100-250	> 250

A severe allergic asthma, omalizumab was found to improve asthma control, reduce exacerbation and hospital admission rates, and decrease IGC doses at the fifth month of treatment[50].

C ***Anti-IL5 monoclonal antibody (mepolizumab).*** It is recommended in children from 6 years of age with severe eosinophilic asthma insufficiently controlled with high doses of IGC and LABA[51,52]. In children 6 to 11 years of age, the recommended dose is 40 mg subcutaneously every 4 weeks and 100 mg every 4 weeks from 12 years of age.

A ***Immunotherapy (IT).*** When biologically standardized extracts are used and sensitized patients are appropriately selected, immunotherapy has been shown to provide a beneficial effect by reducing symptoms, the need of reliever and maintenance medication, and decreasing bronchial hyperresponsiveness (both specific and non-specific)[53].

B Also, IT prevents the development of new sensitizations and asthma in children with rhinitis[54,55].

5.2.2 Treatment according to the level of severity, control and future risk

D In naïve patients, the choice of treatment is determined by the initial severity. Subsequently, modifications will be carried out in a stepwise approach, adjusting the medication according to the current degree of control, assessing future risk and taking into account the child's age (Figure 5.1).

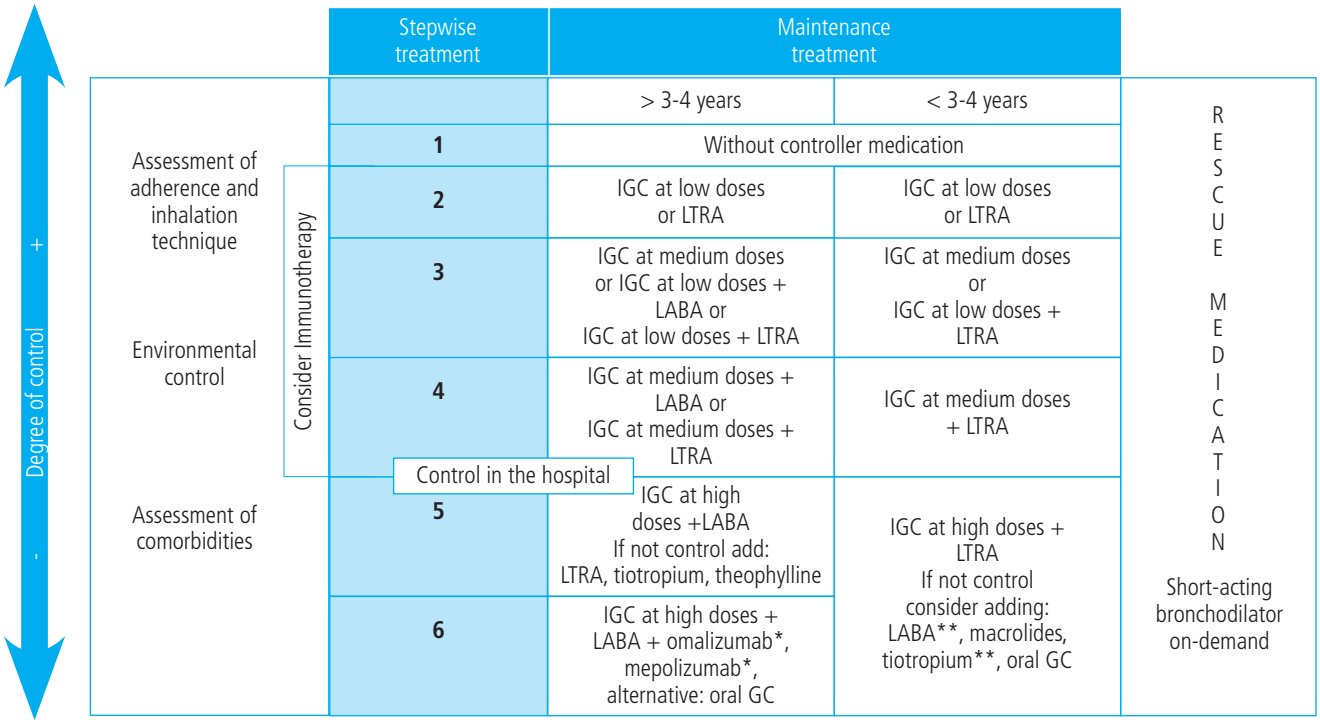
B Children with occasional episodic asthma should be prescribed bronchodilators on-demand without any maintenance treatment. Children with frequent episodic asthma should start treatment at step 2, whereas children with persistent symptoms and/or impairment of pulmonary function should start treatment at step 3 or 4. For children with severe asthma, treatment should preferably be started at step 5 with a further decrease to a lower step (step down) when control is reached and trying to find the minimum effective dose[38,56]. The degree of control and the treatment step should be assessed every three months. B

5.3 Evaluation and treatment of exacerbations

5.3.1 Evaluation of severity

D The following factors should be considered: time course of the exacerbation episode, pharmacological treatment administered, presence of associated diseases and possible risk factors (previous intubation or ICU admission, hospitalizations in the preceding year, frequent need of admission to the emergency department in the previous year and/or use of oral glucocorticoids, excessive use of SABA in the preceding weeks).

C Severity assessment is mainly based on clinical criteria (respiratory rate, presence of wheezing and sternocleidomastoid retractions). Although no clinical scale is considered to be well validated[57,58], the Pulmonary Score (Table 5.6)[59] has been found



IGC: inhaled glococorticoids; LRAT: leukotriene receptor antagonist; LABA: long-acting β_2-adrenergic agonist; GC: glucocorticoid; *: from 6 years of age; **: Off-label.

Figure 5.1. Stepwise treatment of asthma in the pediatric age according to the level of control.

Table 5.6. Pulmonary Score for the clinical assessment of asthma exacerbation in children*

Score	Respiratory rate		Wheezing	Use of sternocleidomastoid muscle
	< 6 years	≥ 6 years		
0	< 30	< 20	No	No
1	31-45	21-35	End of expiration	Slight increase
2	46-60	36-50	Throughout expiration (stethoscope)	Increased
3	> 60	> 50	Inspiration and expiration without stethoscope**	Maximum activity

*It is scored from 0 to 3 in each of the sections (minimum 0, maximum 9)
**If wheezing is absent and the sternocleidomastoid activity is increased, the wheezing section should be scored 3.

Table 5.7. Overall evaluation of the severity of asthma exacerbation in children by integrating the Pulmonary Score and the arterial oxygen saturation

	Pulmonary Score	SaO_2
Mild	0-3	>94%
Moderate	4-6	91-94 %
Severe	7-9	<91%

SaO_2: arterial oxygen saturation. In case of disagreement between clinical score and arterial oxygen saturation, the score indicating higher degree of severity will be used.

C to be easy-to-use and applicable to all ages. The combination of symptoms and arterial oxygen saturation (SaO_2) allows completing an estimation of the severity of the exacerbation episode (Table 5.7).

5.3.2 Drugs

A ***Inhaled short-acting β_2-adrenergic agonists (SABA).*** These agents constitute the first-line treatment due to their higher effectiveness and lower incidence of side effects[60]. They should preferably be administered via a pressurized inhaler with a spacer chamber, since this way of administration is as effective as nebulizers for treating an acute asthma episode[61-64].

A Recommended doses and dosing intervals depend on the severity of the exacerbation episode and the response to the initial doses[65]. The most commonly used drug is *salbutamol*, which is available as a solution for use with a nebulizer and a pressurized inhaler. The latter must be administered in sequences of 2-10 puffs of 100 µg until response is obtained. For mild attacks, a series of 2-4 puffs may be sufficient, although up to 10 puffs may be necessary for severe exacerbations.

B Nebulized SABA should be restricted to those cases in which the patient requires oxygen supply for SaO_2 normalization, although a recent randomized clinical trial showed that even in severe exacerbations, the administration of salbutamol and ipratropium bromide with spacer chamber and facil mask with oxygen by means of a nasal cannula was more effective than using a nebulizer[66].

B Continuous nebulization does not offer greater advantages compared to intermittent nebulization at the same total administered doses[67,68].

A ***Ipratropium bromide.*** The use of frequent doses, every 20 minutes, of ipratropium bromide for the first 2 hours in case of severe asthma exacerbations or moderate exacerbations not responding to initial treatment with SABA, has been shown to be effective and safe[69,70]. The nebulized dose is 250 µg for children weighing less than 30 kg y 500 µg for those weighing more than 30 kg. The dose for inhaled use with a spacer chamber is 40-80 µg (2-4 puffs). The maximum effect, which tends to decrease gradually, is observed with the first doses, so this agent should only be used during the initial 24-48 hours[71].

B In infants, the use of ipratropium bromide combined use with inhaled SABA has been shown to be effective in treating more severe exacerbations[72]. The effect of this association using an inhaler seems to be be superior than that administered by nebulization[66].

A **Systemic glucocorticoids.** The efficacy of systemic glucocorticoids in preschool children with mild to moderate acute episodes of wheezing induced by viral infections has been questioned; hence, its use should be restricted to more severe exacerbations (1-2 mg/kg/day)[35,73,74]. In children aged over 5 years, these agents have shown benefit after early use[75], with the oral route being preferred over intravenous or intramuscular routes, except for circumstances in which oral intake may be inappropriate[76,77]. Systemic glucocorticoids should be administered in moderate-severe exacerbations, and may be considered for mild exacerbations when sufficient improvement with bronchodilators has not been achieved or the child has a history of severe attacks. Prednisolone at doses of 1-2 mg/kg/day (maximum 40 mg) for 3 to 5 days until resolution is commonly administered[78,79].

B *Dexamethasone* is being used as an alternative. The effect of administering a single dose of dexamethasone orally (at 0.3 mg/kg) is not inferior to that of administering prednisolone orally (at 1 mg/kg/day) during 3 days of treatment[80-83].

B **Inhaled glucocorticoids.** There is insufficient evidence to recommend the use of IGC as an alternative[84] or additional treatment to systemic glucocorticoids[85,86] in the management of asthma exacerbations. Larger studies are required, with better methodological quality and cost-effectiveness analysis[87], as well as safety studies[84].

A **Magnesium sulfate.** It can be used in severe exacerbations failing to respond to initial treatment[88,89]. The drug is administered intravenously as a single dose of 40 mg/kg (up to 2 g) over 20 minutes.

C Nebulized magnesium sulfate together with a ß2-adrenergic agonist in the treatment of an asthma exacerbation seems to have benefits in the improvement of pulmonary function[90,91].

5.3.3 Therapeutic regimens

C Treatment of an asthma exacerbation episode depends on its severity and follows the scheme shown in Figure 5.2. Doses of drugs and duration of administration should be modified according to the severity of the exacerbation and the response to treatment.

A When SaO_2 is below 94%, oxygen therapy is required to maintain SaO_2 between 94-98%[92,93]. An SaO_2 < 92 % after initial treatment with inhaled bronchodilators can be used as a marker to select the more severely ill patients who should be hospitalized for starting intensive treatment[92,94].

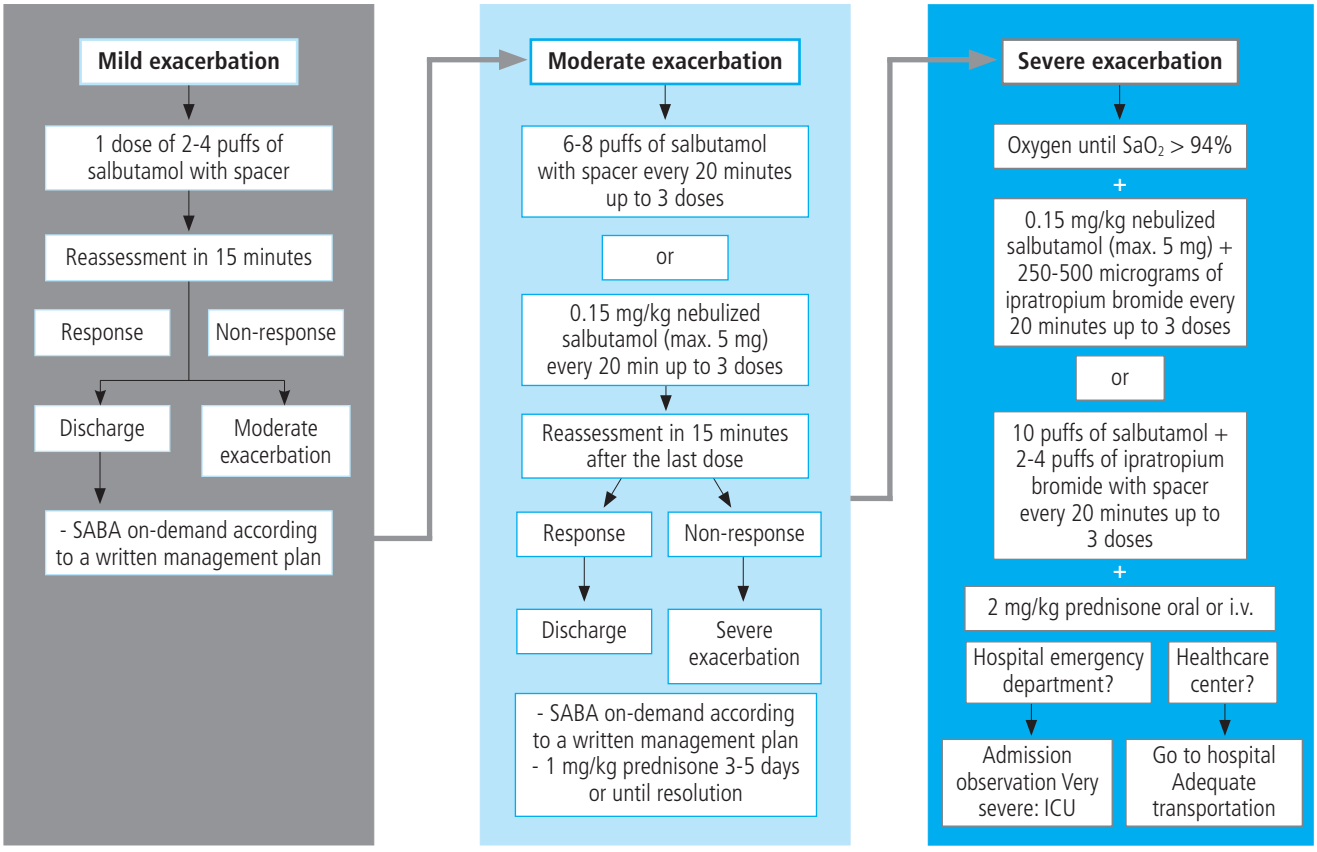
C In children with with moderate/severe exacerbations refractory to first-line treatment, high-flow nasal cannula oxygen therapy appears to be superior to conventiobal oxygen therapy to reduce breathing difficulty[95,96]. However, more studies are needed to show its general efficacy for treating asthma and respiratory failure in the emergency setting[97].

C Regarding non-invasive ventilation (NIV), the current available evidence does not allow us to confirm or exclude its use inexacerbation episores refractory to the usual treatment[98].

B Mild and moderate exacerbations can be treated in the primary care setting.

D In the presence of severe exacerbation or suspicion of complications, history of high-risk exacerbations or lack of response to treatment, patients should be referred to the hospital in a medicalized ambulance.

D **Follow-up.** It is necessary to evaluate the degree of the control of symptoms in the previous weeks, the presence of risk factors, possible triggering factors and previous treatment. Also, it is important to assess the level of therapeutic adherence and to supervise that the inhalation technique is correct. A written action plan must be reviewed or provided and a follow-up visit arranged[10].



kg: kilogram; mg: milligram; SaO_2: oxyhemoglobin saturation; max: maximum; SABA: short-acting $ß_2$-adrenergic agonist.

Figure 5.2. Treatmen of asthma exacerbation in children.

RECOMMENDATIONS

5.1.	The education of the child with asthma and his/her family is recommended because increases the quality of life and reduces the risk of exacerbations and healthcare costs.	R1
5.2.	In the education of children with asthma, it is recommended to include written personalized management action plans, addressing maintenance treatment and how to treat exacerbations.	R1
5.3.	Inhaled IGC is recommended as first-line treatment for the control of persistent asthma in children of all ages.	R1
5.4.	Montelukast can be tried as an alternative to IGC for maintenance therapy.	R2
5.5.	Treatment with LABA can be considered in children older than 4 years of age but always combined with IGC. LABA monotherapy should never be administered.	R1
5.6.	In the treatment of children with allergic asthma, immunotherapy should be considered provided that biologically strandardized extracts are used and patients are appropriately selected.	R1
5.7.	In children aged 6 years or older with insufficiently controlled severe persistent asthma with high doses of IGC and LABA and/or LTRA and/or tiotropium, the use of biological agents or monoclonal antibodies is recommended.	R1
5.8.	Before considering that an asthma patient is poorly controlled and stepping up treatment, the diagnosis of asthma should be confirmed, treatment adherence and inhalation technique should be evaluated, and other comorbidities excluded.	R1
5.9.	Early and repeated administration of SABA at high doses is the first-line of treatment of asthma exacerbations in children.	R1
5.10.	It is recommended to indidualize drug doses according to severity of exacerbations and the response to treatment.	R2
5.11.	Early use of systemic glucocorticoids is recommended in moderate and severe exacerbations; in mild exacerbation, an individualized assessment is recommended.	R1
5.12.	In the presence of $SaO_2 < 92$ % after an initial treatment with inhaled bronchodilators, admission to the hospital to start intensive therapy is recommended.	R2
5.13.	A pMDI with spacer chamber is recommended for the administration of bronchodilators, particularly in mild-moderate exacerbations.	R1
5.14.	It is necessary to evaluate the degree of control, risk factors, adherence to treatment and inhalation technique, as well as to offer a written action plan and guarantee the follow-up of children with exacerbations.	R2

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