5. Treatment of Asthma in Children

5.1 Maintenance Treatment

5.1.1 Drugs

B **Inhaled Glucocorticoids.** Persistent wheezing in children under the age of three can be controlled with inhaled glucocorticoids, but the treatment does not appear to modify the progression of the disease [229]. Pre-school children with intermittent wheezing episodes related to viral infections show a poor response to treatment [230]. Intermittent treatment with inhaled glucocorticoids does not improve control or progression of the disease [231]. Infants with risk factors for developing persistent asthma (Asthma Predictive Index or API) [31] also demonstrate a better response to glucocorticoid treatment [229,232]. In children over the age of three, the efficacy of inhaled glucocorticoids has been sufficiently demonstrated. Due to improvements in clinical, functional and bronchial inflammation parameters, so glucocorticoids constitute the first line of treatment [95-96].

A

A Equipotential doses of inhaled glucocorticoids for children are shown in Table 5.1.

A Leukotriene Receptor Antagonists. Their efficacy in controlling childhood asthma has been demonstrated, although they have less anti-inflammatory capacity and clinical efficacy than inhaled glucocorticoids [233]. Their use in conjunction with glucocorticoids improves the control of symptoms [234,235] and they may reduce the number of exacerbations induced by viruses in children with intermittent asthma [236].

B In a study involving atopic children under 3 years of age with clinical symptoms of recurrent wheezing, leukotriene receptor agonist have been shown to be effective in reducing the number of asthma episodes, improving pulmonary function and decreasing the amount of exhaled nitric oxide exhaled [237].

C Chromones. Their long-term efficacy is no greater than for placebo, so they are not used in children [238].

A

Table 5.1. Equipotential doses of inhaled glucocorticoids in children (µg/day)

	Low Doses	Moderate Doses	High doses
Budesonide	≤ 200	200-400	> 400
Fluticasone	≤ 100	100-250	> 250

B **Long-acting ß$_2$ Adrenergic Agonists and Inhaled Glucocorticoid Combinations.** Their use is authorized for patients over 4 years of age, but their efficacy in children has not been as well demonstrated in comparative studies as it has been in adults [239]. One study demonstrated a reduction in exacerbations and in the need for systemic glucocorticoids in children receiving formoterol/budesonide administered in a single inhaler, both as maintenance and relief treatment (SMART strategy) [240]. Long-acting ß$_2$ adrenergic agonists are safe as long as they are administered together with an inhaled glucocorticoid and never as rescue medication [126,241].

B **Theophyllines.** As maintenance monotherapy, they are less effective than inhaled glucocorticoids, although their antiinflammatory effect means they can be used in association with an inhaled glucocorticoid in cases of severe persistent asthma [242].

B **Monoclonal Anti-IgE Antibodies.** Various studies have demonstrated their therapeutic efficacy in children over 12 years of age with moderate persistent or severe atopic asthma [243].

A **Immunotherapy.** When biologically standardized extracts are used in properly selected sensitized patients, this treatment has been shown to reduce symptoms, rescue and maintenance medication and (specific and non-specific) bronchial hyperresponse [165].

5.1.2 Treatment in accordance with Level of Severity

D The classification of asthma according to its severity (Table 2.8) must be done when the patient is not receiving treatment and it is useful for choosing initial maintenance treatment. After that, modifications must be made in stages, depending on the level of control which is obtained for children under 3 years of age (Table 5.2) and (Table 5.3) for children over this age.

B Children with occasional episodic asthma must start their treatment at stage 1, in other words, using bronchodilators on demand and with no maintenance treatment. Children with frequent episodic asthma should start their treatment at stage 2 and, if control is not achieved, their treatment must be upstaged until it is. Children with moderate persistent asthma must start receiving treatment at stage 3. In children with severe asthma it is preferable to start at stage 5 and to scale treatment down as soon as control is achieved, always aiming to find the minimum effective dose [244-246].

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Table 5.2. Stages of asthma treatment depending on the level of control in children under 3 years of age

	Treatment Stage	Control Medication	Rescue Medication
Assessment of compliance and inhalatory technique	1	No control medication	Fast-acting bronchodilator on demand
	2	Low dose ICS or LTRA	
	3	Moderate-dose ICS or low-dose ICS + LTRA	
	4	Moderate-dose ICS + LTRA	
Environmental control	5	High-dose ICS + LTRA If control is not achieved add: LAß$_2$AA*	
	6	Oral GC	

Abbreviations: ICS: inhaled glucocorticoids; LTRA: leukotriene receptor antagonist; LAß$_2$AA: long-acting ß$_2$ adrenergic agonist; GC: glucocorticoids. The treatment alternatives included in each stage are listed in order of preference.

Table 5.3. Stages of asthma treatment depending on the level of control in children over 3 years of age

		Treatment Stage	Control Medication	Rescue Medication
Assessment of compliance and inhalatory technique	Consider immunotherapy	1	No control medication	Fast-acting bronchodilator on demand
		2	Low-dose ICS or LTRA	
		3	Moderate-dose ICS or low-dose IGC LAß$_2$AA or low-dose ICS with LTRA	
		4	Moderate-dose ICS + LAß$_2$AA or moderate-dose ICS+LTRA	
Environmental Control		5	High-dose ICS + LAß$_2$AA If control is not achieved add: LTRA, theophylline	
		6	Oral GC Omalizumab	

Abbreviations: ICS: inhaled glucocorticoids; LTRA: leukotriene receptor antagonist; LAß$_2$AA: long-acting ß$_2$ adrenergic agonist; GC: glucocorticoids. The treatment alternatives included in each stage are listed in order of preference.

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RECOMMENDATIONS

- The use of **inhaled glucocorticoids** is recommended as the first line of treatment for controlling persistent asthma in children of any age. **R1**
- **Long-acting ß$_2$ adrenergic agonists** are a form of treatment that should be considered for children if they are used in association with an inhaled glucocorticoid. **R1**
- **Long-acting ß$_2$ adrenergic agonists** must never be administered as monotherapy. **R1**
- Children with moderate persistent asthma should initiate treatment with moderate doses of inhaled glucocorticoids until control is achieved and then the dose should be reduced. As an alternative, treatment can begin with a combination of inhaled glucocorticoids at low doses and an anti-leukotriene in children under 4 years of age or a **long-acting ß$_2$ adrenergic agonist** in older children. **R1**
- For treatment of children with allergic asthma, **immunotherapy** treatment should be considered, as long as biologically standardized extracts are used and patients are carefully selected. **R1**

5.2 Assessment and Treatment of Exacerbations

5.2.1 General Considerations

D Therapeutic approaches to exacerbations will depend on their severity. Drug doses and administration times must be modified in accordance with the severity of attacks and their response to treatment.

D Moreover, how long a particular attack has taken to develop, the treatment previously administered, the maintenance treatment the patient is receiving, and concomitant diseases and risk factors (prior intubation, hospitalization in the previous year, use of oral glucocorticoids, etc.) must be considered.

Mild and moderate attacks can be treated at Primary Care centers. When attacks are severe and/or complications are suspected, or there is a history of high-risk attacks or failure to respond to treatment, patients must be referred to a hospital ED.

5.2.2 Assessment of Severity

C Assessment is essentially based on clinical criteria (respiratory rate, presence of wheezing and retractions of the sternocleidomastoid muscles), variables included in the Pulmonary Score (Table 5.4) [247]. This stage is simple and applicable to all ages. The symptoms, together with the oxygen saturation level determined by pulsioximetry (SaO_2), enable estimation of the severity of an episode (Table 5.5).

C An SaO_2 level below 92% following initial inhaled bronchodilator treatment identifies the most serious patients and they must be hospitalized to commence intensive treatment [248].

Table 5.4. Pulmonary score for the clinical assessment of asthma attacks in children* [247]

Score	Respiratory Rate		Wheezing	Use of sternocleidomastoid Muscle
	< 6 years	≥ 6 years		
0	< 30	< 20	No	No
1	31-45	21-35	Final expiration	Slight increase
2	46-60	36-50	During entire expiration (stethoscopy)	Increased
3	> 60	> 50	Inspiration and expiration without stethoscopy**	Maximum activity

* Each section is scored from 0 to 3 (minimum 0, maximum 9).
** If there is no wheezing and the activity of the sternocleidomastoid muscle is increased, assign the "wheezing" section a score of 3.

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Table 5.5. General assessment of the severity of asthma exacerbations in children including the pulmonary score and oxygen saturation

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

Abbreviation: SaO_2: oxyhaemoglobin saturation.
In case of disparity between the clinical score and the oxygen saturation percentage, the most severe indicator will be used.

5.2.3 Drugs

A **Short-acting ß$_2$ Adrenergic Agonists.** These are the first line of treatment. Inhalation is the route of choice, due to its greater effectiveness and fewer side effects [249]. The pressurized inhaler system with a spacing chamber is at least as effective as nebulizers for the treatment of acute asthma episodes [206,250,251].

A The recommended doses will depend on the severity of the crisis and the response to initial doses. The most widely used drug is salbutamol, which is available as a nebulizer solution, pressurized inhaler or dry powder. Terbutaline in dry powder form can be used for the treatment of attacks in older children who use the Turbuhaler® system correctly. The bronchodilator must be administered in series of 2-10 100 µg puffs of salbutamol until a response is achieved. In mild crises a single series of 2-4 puffs may be sufficient, and in severe attacks it may be necessary to administer up to ten puffs. A

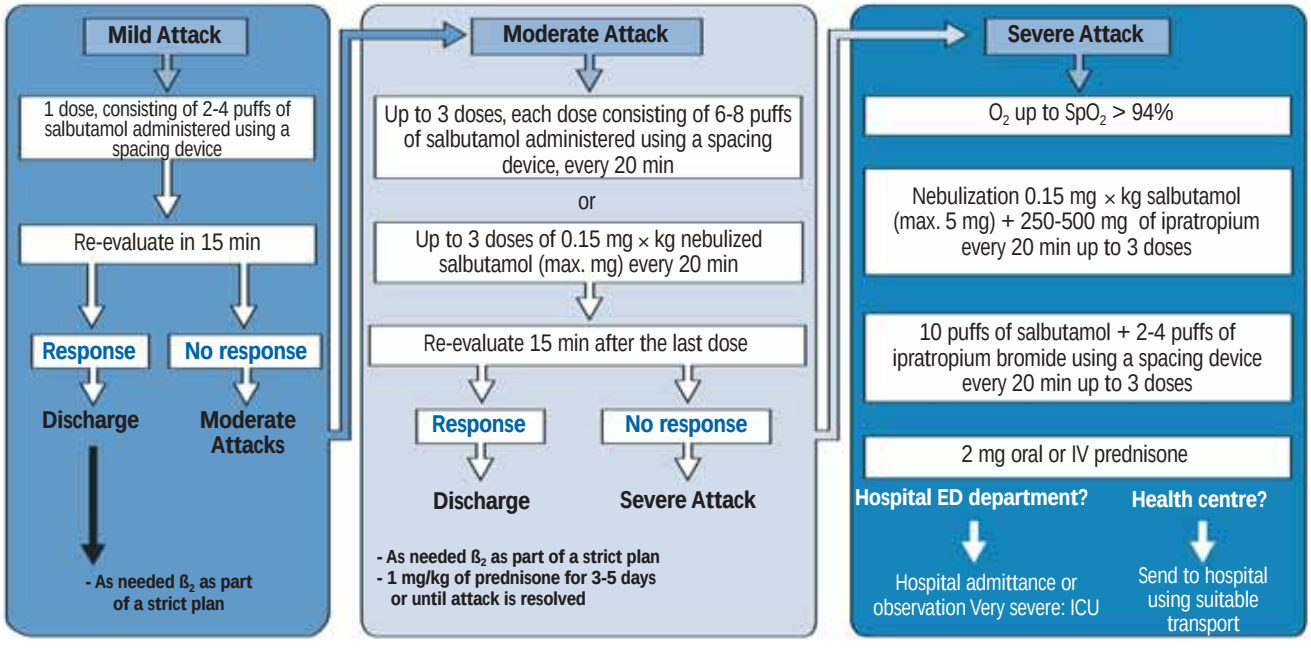
B The use of nebulized ß$_2$ adrenergic agonists must be limited exclusively to cases in which the patient requires oxygen in order to normalize his SaO_2. Continuous nebulization does not offer great advantages with respect to intermittent nebulization, when the same total doses are administered [252]. B

A **Ipratropium bromide.** Add frequent doses of ipratropium bromide, which it has shown itself to be effective and safe, during the first two hours in cases of severe asthma crisis or in moderate crises that fail to respond to initial treatment with ß$_2$ adrenergic agonists [217,253]. A

The nebulized dose is 250 µg/4-6 hours in patients who weigh less than 30 kg and 500 µg/4-6 hours in patients weighing more than 30 kg. The dose delivered using an inhalation chamber is 40-80 µg (2-4 puffs). Repeated doses must be administered every 20 or 30 minutes. The maximum effect, which is not maintained, is elicited by the initial doses, so it should only be used in the first 24-48 hours.

B In infants its use in combination with inhaled, 2 adrenergic agonists has been shown to be effective in the treatment of more severe attacks [254]. B

B **Systemic Glucocorticoids.** These have shown a beneficial effect when they are used at an early stage [209,218], with the oral route preferable to the intravenous route [255,256]. They must be administered during all moderate and severe attacks,



kg: kilogram; min: minute; mg: milligram; µg: microgram; SaO_2: oxyhaemoglobin saturation

Figure 5.1. Treatment of asthma attacks in children

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B and in mild attacks if an improvement is not maintained by the administration of bronchodilators (short-acting ß$_2$ adrenergic agonists are needed within 4 hours) or if the child has a history of severe attacks. The recommended dose is 1-2 mg/kg/day (maximum 60 mg) over a period of 3-5 days or until the attacks relents.

B **Inhaled Glucocorticoids.** Although there are various studies that do not support the use of inhaled glucocorticoids in asthma attacks in children [257-259], a meta-analysis that included 470 adults, and 663 children and adolescents, suggested that high and multiple doses of inhaled glucocorticoids (500 μg of nebulized fluticasone every 15 minutes, or 800 μg of nebulized budesonide every 15 minutes, or alternatively 500 μg of budesonide every 10 minutes using a pressurized inhaler with a spacing chamber or 400 mg of budesonide every 30 minutes using a spacing chamber) administered at intervals of 30 minutes or less over a period of at least 90 minutes has a rapid and additive effect to that of oral glucocorticoids [219]. Inhaled glucocorticoids should not serve as a substitute for systemic glucocorticoids. B

5.2.4 Therapeutic Regimes

C The treatment of an asthma attacks will depend on its severity and must follow the steps in the flow chart provided in Figure 8. In all cases in which oxygen saturation is lower than 94% oxygen must be administered [260].

A Short-acting ß$_2$ adrenergic agonists must be used as needed, preferably using a pressurized inhaler and a spacer device [249,261]. The doses and frequency of administration will depend on the severity of the attacks. In moderate and severe crises, a short cycle (3-5 days) of oral glucocorticoids must be added [262].

D Severe attacks must be referred to a hospital in a medically equipped ambulance, administering oxygen, bronchodilators and systemic glucocorticoids on the way.

RECOMMENDATIONS

- **Short-acting B$_2$ adrenergic agonists** at high doses, administered at an early stage and repeated, are recommended as the first line of treatment for an asthma crisis. **R1**
- It is advisable to tailor drug doses according to the severity of the attack and its response to treatment. **R1**
- The use of a pressurized inhaler with a spacer device system is recommended in the treatment of mild-moderate asthma attack. **R1**
- In moderate-severe attacks the early use of a **systemic glucocorticoid** is recommended. **R1**

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