5. Treatment of childhood asthma

5.1 Maintenance therapy

5.1.1 Drugs

A ***Inhaled glucocorticoids (IGC).*** In children older than 3 years old, the efficacy of IGCs is well established, and are considered the first-line treatment as they improve clinical and functional parameters, bronchial inflammation and quality of life, and reduce the risk of both exacerbations and hospitalizations[162].

A Inhaled glucocorticoid-treated infants and preschool children experience fewer episodes of asthma/wheezing than those receiving placebo (NNT = 7)[350], a better treatment response being obtained by those showing risk factors of developing persistent asthma (Asthma Predictive Index [API])[351,352], while viral-induced episodic wheezing shows limited response[353]. A treatment trial followed by evaluation of response is recommended[354].

B Treatment with IGC, either continuous or intermittent, does not modify the natural history of the disease[353,355].

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, but further studies to assess drug safety are required[356,357],

B When administered at usual doses, IGCs are safe drugs for the management of childhood asthma, although the final height of children treated with IGCs over prolonged periods is lower, an effect proved to be dose-dependent[358].

A 5-year treatment with 200 µg fluticasone propionate does not have any negative effects on bone mineral density[359].

D The equipotent doses of IGCs are shown in table 5.1

A ***Leukotriene receptor antagonists (LTRA).*** Their efficacy in the control of childhood asthma has been demonstrated, and although the anti-inflammatory activity and efficacy in clinical trials is lower than those of IGC[170,360], the effectiveness of these drugs has been reported to improve in real-world studies because of their good profile of treatment adherence[361].

C In atopic children with recurrent wheezing aged less than 3 years, LTRAs have been found to be effective in reducing the number of episodes, improving pulmonary function and decreasing exhaled nitric oxide[362].

B The association of LTRA with IGC improves the control of symptoms, without the need of increasing the doses of IGC[363,364]. In addition, LTRAs may be useful in reducing the number of virus-induced exacerbations in children with intermittent asthma[365].

A Montelukast, either as monotherapy or in combination with IGC, is more effective than IGC alone or combined with long-acting β_2-agonists (LABAs) to prevent exercise-induced bronchoconstriction in children aged 6 to 18 years[366].

Chromones. The efficacy of the long-term treatment with these drugs is not superior to that of placebo, so they should not be used in the childhood population[367].

B ***Association of 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[199,368].

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)[369].

In two studies of children with persistent uncontrolled asthma with IGC at low doses, the addition of a LABA led to a more effective control of both clinical manifestations and lung function than doubling the IGC dose[370,371]. However, heterogeneity of the individual response to an IGC, LTRA and LABA should be evaluated[190,372,373], so that it is necessary to monitor response to treatment in children whose asthma is not controlled with an IGC.

B ***Teophyllines.*** These drugs are less effective than IGCs as maintenance monotherapy, even though their anti-inflammatory activity enables their use in association with ICG in cases of severe persistent asthma[374].

B ***Anti-IgE monoclonal antibodies.*** A number of studies have demonstrated the therapeutic efficacy of these drugs (need for lower doses of IGCs, quality of life improvement, reduction of exacerbations and fewer hospitalizations) in children over 6 years of age with moderate-to-severe persistent allergic asthma, inadequately controlled with IGCs at high doses and LABA[210].

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Table 5.1. Equipotent doses of inhaled glucocorticoids commonly used in children (µg/day)

	Low doses	Medium doses	High doses
Budesonide	≤ 200	201-400	> 401
Fluticasone propionate	≤ 100	101-250	> 251

Table 5.2. Stepwise asthma management based on the control level in children under 3 years of age

Degree of control		Stepwise treatment	Controller medication	Rescue medication
	Assessment of adherence and inhalation technique	1	No controller medication	Short-acting bronchodilator on-demand
		2	IGC at low doses or LTRA	
		3	IGC at medium doses or IGC at low doses + LTRA	
		4	IGC at medium doses + LTRA	
	Environmental control	5	IGC at high doses + LTRA if no control is achieved add LABA*	
		6	GC oral	

GC: glucocorticoid; IGC: inhaled glucocorticoid; LABA: long-acting β2-agonist; LTRA: anti-leukotrienes. *off-label.

Table 5.3. Stepwise asthma management based on the control level in children over 3 years of age

Degree of control (− / +)			Stepwise treatment	Controller medication	Rescue medication
	Assessment of adherence and inhalation technique	Consider immunotherapy	1	No controller medication	Short-acting bronchodilator on-demand
			2	IGC at low doses or LTRA	
			3	IGC at medium doses or IGC at low doses + LABA or IGC at low doses + LTRA	
	Environmental control		4	IGC at medium doses + LABA or IGC at medium doses + LTRA	
			5	IGC at high doses + LTRA If no control is achieved, add: LTRA, theophylline	
			6	Oral GC Omalizumab	

GC: glucocorticoid; IGC: inhaled glucocorticoid; LABA: long-acting β2-agonist; LTRA: anti-leukotrienes.

A In a real-world study of children with 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[375].

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)[251].

B Also, IT prevents the development of new sensitizations and asthma in children with rhinitis[376].

5.1.2 Treatment according to the level of severity and the degree of control

D Classification of asthma based on severity (table 2.13) is applied to untreated patients in order to choose the initial maintenance treatment. Then, further changes can be introduced following a stepwise strategy by adjusting medication according to the current control of asthma symptoms, assessing future risk and considering the age of the child (tables 5.2 y 5.3). In children older than 3 years of age, clinical questionnaires such as the Asthma Control Questionnaire in Children (CAN [table 2.14] or the C-ACT (Childhood Asthma Control Test) can be used to facilitate the evaluation of symptoms. D

D 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 (IGC at low doses or LTRA) with subsequent increase in treatment until control is achieved. Children with moderate persistent asthma should start treatment at step 3. 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, trying to find the minimum effective dose[377-379]. The degree of control and the treatment step must be reassessed every three months. D

Table 5.4. Pulmonary Score for the clinical evaluation of asthma attacks in children*[382]

Score	Respiratory rate < 6 years	Respiratory rate ≥ 6 years	Wheezing	Use of sternocleidomastoid muscle
0	< 30	< 20	No	No
1	31-54	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.

5.2 Evaluation and treatment of exacerbations

5.2.1 Evaluation of severity

D The following factors should be considered: time course of the exacerbation episode, prior treatment, current maintenance therapy, and the concomitant presence of associated diseases and risk factors comorbidities and risk factors (previous intubation, hospitalizations in the preceding year, use of oral glucocorticoids, etc.).

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[380], the Pulmonary Score (table 5.4)[381] has been found to be easy-to-use and applicable to all ages. The combination of symptoms and arterial oxygen saturation (SaO_2) allow completing an estimation of the severity of the exacerbation episode (table 5.5).

Table 5.5. 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%

SaO2: arterial oxygen saturation.
In case of disagreement between clinical score and arterial oxygen saturation, the score indicating higher degree of severity will be used.

5.2.2 Drugs

A ***Inhaled short-acting β_2-agonists (SABA).*** These agents constitute the first-line of treatment due to their higher effectiveness and lower incidence of side effecs[382]. 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[323,383,384].

A Recommended doses and dosing intervals depend on the severity of the attack and the response to initial doses[308]. 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 enough, although up to 10 puffs may be necessary for severe attacks.

B Nebulized SABA should be restricted to those instances where the patient requires oxygen supply for SaO_2 normalization. Continuous nebulization does not offer great advantages over intermittent nebulization when similar total doses are compared[323,385].

A ***Ipratropium bromide.*** The addition of frequent doses, every 20 minutes, of ipratropium bromide for the first 2 hours, in case of severe asthma attacks or moderate attacks not responding to initial treatment with SABA, has been shown to be effective and safe[328,386]. 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.

B In infants, the use of ipratropium bromide combined use with inhaled SABA has been shown to be effective in treating more severe attacks[387].

A ***Systemic glucocorticoids.*** The efficacy of systemic glucocorticoids in preschool children with mild to moderate acute episodes of virus-induced wheezing has been challenged; hence, its use should be restricted to more severe attacks (1-2 mg/kg/day)[354,388]. In children aged over 5 years, these agents have shown benefit after early use[318], with oral route being preferred over intravenous or intramuscular routes[389,390]. Systemic glucocorticoids should be administered in severe attacks, and may be considered for moderate attacks when sufficient improvement with bronchodilators is not achieved or the child has a history of severe attacks. The recommended dose is 1-2 mg/kg/day (maximum 40 mg) for 3 to 5 days until resolution[319,391].

B ***Inhaled glucocorticoids (IGC).*** Although in a review study it was found that early use of IGC at high doses reduced the need for hospitalizations in patients who had not been treated with systemic glucocorticoids350, there is insufficient scientific evidence to recommend the use of IGC as an

B alternative or additional treatment of systemic glucocorticoids for the treatment of asthma exacerbation, and studies with larger sample sizes and adequate methodology, also including cost-efficacy analysis, are warranted[350,392].

A ***Magnesium sulfate.*** It can be used in severe attacks failing to respond to initial treatment[393]. The drug is administered intravenously at a single dose of 40 mg/kg (up to 2 g) in 20 minutes.

5.2.3 Therapeutic regimens

C Treatment of an asthma attack depends on its severity and may follow the scheme shown in figure 5.1. Doses of drugs and duration of administration should be modified according to the severity of the attack and the response to treatment. When arterial oxygen saturation is below 94%, oxygen therapy is required to maintain SaO_2 between 94-98%[394,395]. 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 to start intensive treatment[394,396]. Mild and moderate attacks can be treated in the primary care setting. Patients with severe attacks and/or suspected complications, history of high-risk exacerbations or treatment failure should be referred to the hospital in a medicalized ambulance, with the administration of oxygen, bronchodilators and systemic glucocorticoids during transfer.

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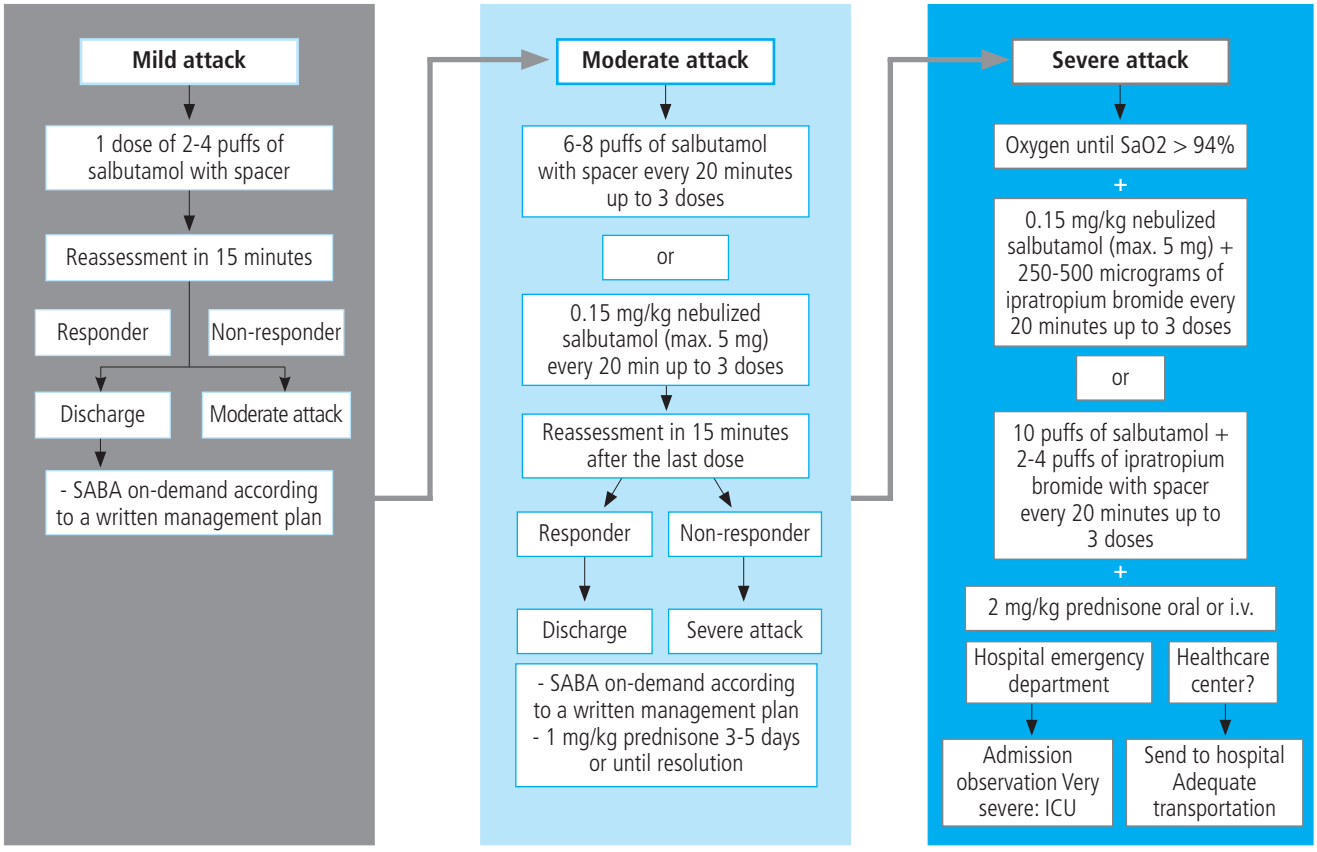

kg: kilogram; mg: milligram; SaO_2: arterial oxygen saturation; max: maximum; SABA: short-acting $ß_2$-adrenergic agonist; i.v.: intravenous.

Figure 5.1. Treatment of an asthma attack in children

RECOMMENDATIONS

5.1.	Inhaled glucocorticoids are recommended as first-line therapy for persistent asthma control in children of all ages.	R1
5.2.	Montelukast can be tried as an alternative to inhaled glucocorticoids for maintenance therapy in childhood asthma. It can be useful to prevent virus-induced exacerbations in preschoolers.	R2
5.3.	Long-acting β_2-agonists (LABAs) are the treatment to be considered for children over 4 years of age if combined with an IGC. They should never be used as monotherapy.	R1
5.4.	Immunotherapy may be considered in children with allergic asthma, provided biologically standardized extracts are used and patients have been properly selected.	R1
5.5.	Omalizumab is recommended in children over 6 years of age with severe allergic asthma inadequately controlled with IGCs and a LABA and/or an LTRA.	R1
5.6.	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 should be excluded.	R1
5.7.	Short-acting β_2-agonists (SABAs) at high doses and administered early and repeatedly are recommended as first-line treatment in the management of asthma attacks in childhood.	R1
5.8.	It is recommended to individualize drug doses according to the severity of exacerbation and the response to treatment.	R2
5.9.	A pressurized inhaler with a spacer chamber is recommended for treating mild-moderate asthma attacks in children.	R1
5.10.	Early use of a systemic glucocorticoid is recommended for the treatment of moderate and severe asthma attacks.	R1