ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Practical Update Guide on the treatment of asthma exacerbation in children and adolescents – Joint position of the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics

Guia Prático de Atualização no tratamento da exacerbação de asma na criança e no adolescente – Posicionamento conjunto da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria

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ABSTRACT

Acute exacerbation of asthma is a frequent condition in children and adolescents and one of the most common causes of seeking emergency care and hospitalization. It can occur in patients who have not yet been diagnosed with asthma, and even in those whose disease control is not adequate. Recognizing the exacerbation and starting its treatment from home until proper initial management in a hospital environment is essential to avoid its evolution to complications that put the patient at risk of life. Treatment comprises the recognition and treatment of hypoxemia, obstruction, and the inflammatory process, in addition to providing guidance at hospital discharge and referrals for continued treatment.

Keywords: Acute asthma, asthma exacerbation, child, adolescent, treatment.

RESUMO

Exacerbação aguda de asma é uma condição frequente na criança e no adolescente e uma das causas mais comuns de procura aos pronto atendimentos e de internações. Pode ocorrer em pacientes que ainda não foram diagnosticados como asmáticos, e mesmo naqueles cujo controle da doença não se encontre adequado. Reconhecer a exacerbação e iniciar seu tratamento desde o domicílio até o adequado manejo inicial em ambiente hospitalar é fundamental para evitar sua evolução para complicações que coloquem o paciente em risco de vida. O tratamento compreende o reconhecimento e tratamento da hipoxemia, da obstrução e do processo inflamatório, além de fornecer orientações na alta hospitalar e encaminhamentos para continuidade do tratamento.

Descritores: Asma aguda, exacerbação da asma, criança, adolescente, tratamento.

Definition of exacerbation

Asthma exacerbation is defined as an acute or subacute worsening of asthma symptoms and lung function. It is characterized by a progressive increase in shortness of breath, coughing, wheezing, or a feeling of tightness in the chest, representing a change in the patient's usual symptoms, sufficient to require

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a change in treatment.[1,2] Exacerbations may occur in patients with a pre-existing diagnosis of asthma, or occasionally as the first presentation of the disease.

The academic term "exacerbation", however, is more used in the scientific and clinical literature, while hospital studies refer more to "severe acute asthma". During care, using the term "exacerbation" is not always appropriate, as it is difficult for many patients to pronounce and remember. The term “asthma exacerbation” is easier to understand and conveys the sense that asthma is present even when symptoms are not persistent. The term “attack” is used by many patients and health professionals, but with widely varying meanings, and may not be perceived as a gradual worsening factor. In pediatric literature, the term “episode” is commonly used, but the understanding of this term by parents/caregivers is also unknown.[1]

In the United States, asthma exacerbations led to 1.7 million emergency room visits and 200,000 hospitalizations in 2016. Emergency asthma exacerbation care costs five times more than office-based care. In this context, the US Government has encouraged asthma care, intending to reduce emergency room visits and hospitalizations, as key health measures.[2]

Asthma exacerbation can be triggered by a viral infection, exposure to external agents (smoke, pollutants, inhaled allergens), medications, physical activity, psychosocial disorders, poor adherence to control treatment, among others.[1,3] However, a subset of patients has exacerbations without exposure to known risk factors. Additionally, severe exacerbations may occur in patients with mild or well-controlled asthma symptoms.

The list of most common factors (“triggers”) that increase a patient's risk of having exacerbations, regardless of their level of symptom control, includes:

– viral respiratory infections;
– exposure to allergens such as grass pollen, bean or soy dust, fungal spores;
– food allergy with systemic manifestations;
– air pollution;[3]
– seasonal changes and/or return to the school environment;
– poor adherence to inhaled corticosteroids.

Severe exacerbations that occur in an epidemic manner have been linked to storms, with high levels of airborne pollen or fungi.[4]

Epidemics of severe asthma exacerbations can occur suddenly and put high pressure on the local health care system. Such epidemics have been reported in association with spring storms with ryegrass pollen[4] or fungal spores, and with environmental exposure to soybean dust.

Treatment goals in asthma exacerbation

The main goals of the treatment of asthma exacerbations are the clinical stabilization of the child, with the suppression or reduction of its symptoms, and the prevention of complications such as hospitalization and death. During the treatment of exacerbations, the following goals should be pursued:[1,5]

– reverting airflow obstruction;
– correct hypoxemia;
– minimize the risk of recurrence of symptoms;
– prevent new exacerbations.

Patients at increased risk of severe exacerbations and even death should be identified and treated early, preferably in emergency departments. These patients include those with:[1]

– history of near-fatal asthma – need for intensive care unit (ICU) treatment, intubation with mechanical ventilation;
– hospitalization or emergency service for asthma exacerbation in the last year;
– excessive use of short-acting beta-2 agonist (SABA), especially with consumption greater than one bottle per month;
– the absence of inhaled corticosteroid use;
– The poor adherence to control treatment and no action plan;
– history of psychiatric illnesses or psychological problems;
– food allergy associated with asthma;
– lack of gravity perception;
– comorbidities such as pneumonia and heart disease.

Classification of exacerbation by severity - scores

It is important during the assessment of asthma exacerbation, to perform a brief history and physical examination while providing initial treatment according to the assessment of the condition, paying attention to the classification of the severity of the asthma exacerbation. This can be done by looking at the intensity of dyspnea, respiratory and heart rates, transcutaneous oxygen saturation (O_2 saturation), and lung function.

The assessment of severity is essential to define the best therapeutic approach, as well as to assess the risk of hospital admission, stay in emergency services, in addition to being useful in monitoring the patient during the treatment of the exacerbation. For this, the use of standardized severity scores contributes to a better follow-up of this process.

The parameters used for this assessment must take into account the age range and cognitive capacity of the child and adolescent. The objective of treating the exacerbation is to maintain O_2 saturation above 94% in room air, the presence of minimal or absent symptoms, and pulmonary function close to normal. The inability to speak sentences, agitation, presence of O_2 saturation below 90% (below 92% in children under 5 years) in room air, and peak expiratory flow (PEF) below 50% of the provided for the patient is considered a severe exacerbation.[1]

Table 1 highlights the aspects that are taken into account to assess the severity of asthma exacerbation in children under 5 years of age.

In more detail, Table 2 presents the parameters for assessing the severity of asthma exacerbation.[6]

Other instruments can be used to assess the severity of the exacerbation, some of which are described below.

Pediatric Asthma Severity Score - PASS [7,8]

Intended for patients under 18 years of age, the PASS is useful for assessing the possibility of hospital admission or prolonged stay in emergencies (Table 3).

Takes into account wheezing, respiratory effort, and prolonged expiration using the sum of all components (0 to 6); the larger the sum, the more intense the exacerbation.

Preschool Respiratory Assessment Measure - PRAM [8,9]

The PRAM was developed through a prospective study of children aged between 3 and 6 years, treated in emergency care and, after logistic regression analysis, included five variables: suprasternal retractions, scalene muscle contraction, air intake, wheezing, and O_2 saturation (Table 4). The sum of all components gives the severity, and the greater, the more intense the exacerbation.

Table 1
Initial assessment of asthma attacks in children under 5 years old.

Symptoms	Mild	Severe[a]
Altered consciousness	No	Restless, confused, or sleepy
O_2 saturation on admissions[b]	> 95%	< 92%
Speak[c]	Sentences	Words
Heart rate	< 100 bpm	> 200 bpm (0 to 3 years) > 180 bpm (4 to 5 years)
Central cyanosis	Absent	Probably present
Intensity of wheezing	Variable	Chest may be silent

[a] Any of these changes indicate severe asthma exacerbation.
[b] Oximetry before administering bronchodilators or installing O_2.
[c] The child's age and normal developmental capacity must be taken into account.
Source: adapted from GINA (2021)[1].

Table 2
Formal assessment of the severity of the asthma crisis in an urgent and emergency setting[6].

Crisis classification	Mild	Moderate	Severe	Imminent respiratory arrest
Symptoms				
Shortness of breath	While walking	At rest (infant – softer and shorter crying, difficulty feeding)	At rest (infant – stop breastfeeding)	
	Can lie down	Prefer sitting position	Sit back	
Difficulty speaking	Sentences	Phrases	Words	
Alert state	May be agitated	Usually agitated [a]	Usually agitated [a]	Sleepy or confused
Signals				
Respiratory frequency	Augmented	Augmented	Always > 30 go/minute	Poor expiratory effort, appears to be exhausted
		Normal RR values in awake children:		
		Age	Normal values	
		< 2 months	< 60/minute	
		2 to 12 months	< 50/minute	
		1 to 5 years	< 40/minute	
		6 to 8 years	< 30/minute	
Use of accessory muscles; suprasternal retraction	Usually absent	Occasionally	Generally	Paradoxical thoracoabdominal movement
Wheezing	Moderate, usually at the end of expiration	High during expiration	Usually high, during ins and exhalations	Absence of wheezing (silent chest)
Pulse/minute	< 100	100 to 120	> 120	Bradycardia
		Normal values for HR in children:		
		Age	Normal values	
		2 to 12 months	< 160/minute	
		1 to 2 years	< 120/minute	
		2 to 8 years	< 110/minute	

[a] Some children with severe acute exacerbation of asthma do not appear to be agitated.

PaO_2 = arterial oxygen pressure, PCO_2 = carbon dioxide partial pressure, PEF = peak expiratory flow, SpO_2 = oxygen saturation, BP = arterial pressure, RR = respiratory rate, HR = heart rate.

Notes:
– The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
– Many of these parameters have not been studied systematically, especially how they correlate with one another. Therefore, they only serve as general guides.
– The emotional impact of asthma symptoms on patients and family members varies, but they must be recognized and addressed and may interfere with treatment and follow-up.

Table 2 *(continuation)*
Formal assessment of the severity of the asthma crisis in an urgent and emergency setting[6].

Crisis classification	Mild	Moderate	Severe	Imminent respiratory arrest
Signals				
Paradoxical pulse	Absent at < 10 mmHg	Can be present 10 to 25 mmHg	Generally present > 25 mmHg (adult) 20 to 40 mmHg (child)	Absence suggests respiratory muscle fatigue
Others				Cyanosis
Functional assessment				
PEF predicted percentage or best personal percentage	≥ 70%	Between 40 to 69% or response to inhaled beta-2 after < 2 hours	< 40%	< 25% Note: PEF may not be needed in severe attacks
PaO_2 (in ambient air)	Normal (usually unnecessary test)	≥ 60 mmHg (usually unnecessary test)	< 60 mmHg: possible cyanosis	
PCO_2	< 42 mmHg (usually unnecessary test)	< 42 mmHg (usually unnecessary test)	≥ 42 mmHg: possible respiratory failure	
SpO_2 % (in ambient air) at sea level	> 95% (usually unnecessary test)	90 to 95% (usually unnecessary test)	< 90%	
		Hypercapnia (hypoventilation) Develops faster in younger children than in adults and adolescents		
PAN		Hypotension		

[a] Some children with severe acute exacerbation of asthma do not appear to be agitated.

PaO_2 = arterial oxygen pressure, PCO_2 = carbon dioxide partial pressure, PEF = peak expiratory flow, SpO_2 = oxygen saturation, BP = arterial pressure, RR = respiratory rate, HR = heart rate.

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Table 3
Pediatric Asthma Severity Score (PASS).

Wheezing		
(expiratory sounds heard on auscultation)	Absent or mild	0
	Moderate	+1
	Intense or absent due to little air movement	+ 2
Respiratory effort		
(use of accessory muscles or retraction)	Normal or diminished	0
	Moderate	+1
	Intense	+ 2
Prolonged expiration		
(expiration/inspiration time ratio)	Normal or slightly prolonged	0
	Moderately prolonged	+1
	Intensely prolonged	+ 2

Severity-based treatment of exacerbation

1. Hypoxia

Children, and especially infants, are at greater risk of respiratory failure during asthma exacerbations and develop hypoxemia more quickly than adults.[10] In children, O_2 saturation below 92% is a predictor of hospitalization, and below 90% signals the need for more aggressive treatment.[1]

Hypoxemia in exacerbations is correlated with the degree of airway obstruction, and consequently with the change in the ventilation-perfusion (V/Q) ratio.[11] At the beginning of treatment with bronchodilators, vasodilation may be greater than bronchodilation, resulting in an imbalance in the V/Q ratio, which may worsen the O_2 saturation by 5% or more in the first 30 minutes after administration of salbutamol.[12,13]

Most exacerbations are mild and do not require the provision of supplemental oxygen. When necessary, the offer must be titrated according to oximetry (if available) to keep it ≥ 94%. The administration of 1 to 3 L/min of O_2 is usually sufficient, and it may be through a nasal catheter or face mask.[11] The use of non-invasive ventilation should be considered in patients with severe exacerbations when initial treatments fail.[14] High-flow nasal cannulas (2-2.5 L/kg/min) have not yet demonstrated efficacy and safety in children with acute asthma exacerbations. Orotracheal intubation should be considered when there is a reduction in the level of consciousness, refractory hypoxemia, and respiratory acidosis, in addition to respiratory depression or bradycardia.[10,16]

2. Bronchospasm

Airflow obstruction resulting from bronchial smooth muscle contraction, whose main clinical expression is wheezing, is considered a central pathophysiological event in asthma exacerbation. The assessment of children with acute wheezing comprises a careful anamnesis covering the different differential diagnoses for each age group and physical examination, capable of determining the site of origin of the symptom (Table 5).[1]

However, clinical estimates of asthma exacerbation severity based solely on the presence of wheezing may result in an inaccurate assessment of the disease. For example, audible wheezing is usually a sign of moderate asthma, while the absence of this symptom can be a sign of severe airflow obstruction.[17]

Thus, in addition to pulmonary auscultation, different clinical symptoms and signs can help pediatricians to determine the severity of acute asthma. Signs of a severe exacerbation include the use of accessory muscles of breathing, chest hyperinflation, tachypnea, tachycardia, diaphoresis,

Table 4
Preschool Respiratory Assessment Measure (PRAM).

Suprasternal retractions	Absent	0
	Present	+ 2
Scalene muscle contraction	Absent	0
	Present	+ 2
Air entrance	Normal	0
	Decreased in the bases	+1
	Diffusely reduced/extended	+ 2
	Absent/minimum	+ 3
Wheezing	Absent	0
	Expiratory only	+1
	Ins and expiratory	+ 2
	Audible without stethoscope/minimal or absent air intake	+ 3
O_2 Saturation	≥ 95%	0
	92 to 94%	+1
	< 92%	+ 2

obnubilation, anxiety, inability to complete sentences, and difficulty lying down. Altered mental status, with or without cyanosis, is a warning sign for immediate emergency care and hospitalization[18] (see Tables 1 to 4).

Serial objective measurements of lung function facilitate quantification of the severity of airflow obstruction and response to treatment. The forced expiratory volume in one second (FEV_1) measured by spirometry is more sensitive and less variable than the PEF rate measurement.[19] However, the latter method provides a quick, simple, and cost-effective assessment of airflow obstruction. The evaluation of PEF before and after administration of a bronchodilator can indicate the degree of improvement in lung function that can be achieved by the instituted therapy. PEF values between 50% to 79% of predicted, or gives the personal best brand, signifying the need for immediate treatment with an inhaled short-acting beta-2 agonist (SABA) agent. Values below 50% indicate the need for immediate medical care, while values below 35% are associated with a possible serious episode with risk of life.[20,21]

When available, data related to the effectiveness of previous treatments are useful for instituting the most appropriate therapy. An exacerbation of allergic asthma is more likely to respond immediately to a SABA and inhaled corticosteroid dose adjustment, whereas a patient with an exacerbation triggered by viral infection is more likely to require systemic corticosteroids. Patients with excessive use of SABA may become refractory to inhaled beta-2 agonists and require systemic corticosteroids.[17]

Main medications used for bronchospasm reversal

Short-acting beta-2 agonists (SABA)

Inhaled SABAs are the first-line drugs for the treatment of acute asthma exacerbations in children.[1]

When administered by inhalation, these bronchodilator agents improve clinical scores, decrease respiratory rate, improve lung function and O_2 saturation, and present adverse effects comparable to those treated with placebo.[22]

Salbutamol, a selective SABA available free of charge by the Ministry of Health of Brazil, can be used in children of all ages. It is usually administered at a dose ranging from 2 to 10 jets (each jet contains 100 µg) every 20 minutes within the first hour of treatment.[23,24] According to the weight, the following can be administered: 5 to 10 kg - 4 jets; 10 to 20 kg - 6 jets; and >20 kg - 8 jets.

In a meta-analysis of 39 studies that included 1,897 children and 729 adults, the use of spacer-coupled metered-dose inhalers (MDI+ESP) was the preferred option for the administration of beta-2 agonists in children with mild and moderate asthma exacerbations. Treatment with a nebulizer may be preferred in patients who are unable to cooperate, using an MDI due to acute asthma severity or agitation.[25]

Ipratropium bromide

Ipratropium bromide (IB) is a quaternary derivative of atropine sulfate available as a nebulizer solution. It acts by competitively inhibiting acetylcholine at the muscarinic cholinergic receptor, thus relaxing smooth muscle in the large central airways.[26] A meta-analysis including four trials with 173 children concluded that it is not suitable for use as a single agent in children with asthma exacerbations, but combination therapy with SABA in more severe asthma exacerbations in children reduced the risk of hospital admission by up to 25%.[27,28]

The recommended nebulizer dose is 125-250 µg/dose (in children under 4 years of age, which corresponds to 10-20 drops) to 250-500 µg/dose (in children 4 years and older, which corresponds 20-40

Table 5
Differential diagnosis of wheezing and asthma in childhood.

Congenital diseases	Infectious diseases
Cystic fibrosis	Epiglottitis/tracheitis
Primary ciliary dyskinesia	Bronchiolitis
Immunodeficiency prhyme	Diphtheria/Pertussis
Diaphragmatic hernia	Bronchiectasis
	Abscess retropharyngeal
	Löffler's syndrome
Upper airway disorders	**Compressive syndromes**
Foreign body	Tuberculosis
Laryngotracheomalacia	Lymphadenopathy
Dysfunction of vocal chords	Vascular ring
	Pastas mediastinal
	Aspiration syndromes
Lower airway disorders	**Others**
Emphysema lobar	Gastroesophageal reflux
Bronchomalacia	
Foreign body	

Source: adapted from GINA (2021)[1].

drops) in combination with salbutamol. It should be administered up to three times every 20 minutes, for the first hour, then its dose should be reduced in 4 to 6 hours or discontinued[23] (each drop contains 0.0125 mg or 12.5 µg).

Magnesium sulfate

Magnesium sulfate ($MgSO_4$) is a bronchodilator that can be administered by nebulization or intravenously. It acts by direct relaxation of the bronchial muscles, but it has a slight additional anti-inflammatory property related to blocking the influx of calcium ions into muscle cells, thus modulating the release of histamine from mast cells and cholinergic neural transmission.[29] Its intravenous use is not routinely recommended for asthma exacerbations and may be indicated for severe exacerbations that have not responded to initial treatment in children older than 2 years of age. A recent meta-analysis showed that its intravenous administration seems to reduce the time and risk of hospitalization for asthma, and it can be considered in patients with severe, life-threatening exacerbations,

The use of inhaled isotonic magnesium sulfate at a dose of 150 mg in three doses in the first hour in children aged 2 years or older in severe exacerbations remains an option in GINA 2021, on the other hand, to date, there is no evidence of any substantial benefit of $MgSO_4$ nebulized in acute asthma.[1,30]

3. Inflammation

Systemic corticosteroids

Corticosteroids have been used to treat asthma for over 50 years, and their significant benefits are documented by several studies.[31,32] In a Cochrane review, short courses of steroids contributed to improved symptom scores, lower relapse rates, fewer hospitalizations, and less need to use beta-2 agonists.[28,32] In addition to bronchodilators, systemic corticosteroids are essential for successful therapy in asthma exacerbations, as it reduces inflammation and mucus production, as well as increasing the effectiveness of bronchodilators.[33] Although corticosteroids are routinely administered by inhalation for asthma control, during a severe exacerbation, systemic corticosteroids are preferred.[34] Regarding the mode of administration, the intravenous or intramuscular routes do not offer significant advantages over the oral route, which is preferred if the patient is able to tolerate the ingestion of oral medication and there is no concern about abnormal intestinal absorption.[35] Oral administration is as effective as intravenous, being faster, less invasive, and less costly.[1] In children, the oral solution should be preferred. The intravenous route can be used in patients with difficulty in swallowing, vomiting, or when orotracheal intubation or non-invasive ventilation is necessary.[1]

Current guidelines recommend early administration of systemic corticosteroids, preferably within the first hour of treatment[1,36], as an effective measure to control exacerbation and prevent relapse for all moderate to severe exacerbations in adults, adolescents, and children aged 6 to 11 years of age.[1] Its indication is particularly important in cases where there was no clinical improvement with the use of bronchodilators, when the exacerbation was accentuated, or when the patient has a history of exacerbations requiring the use of corticosteroids for resolution. These drugs need about 4 hours to impact clinical improvement.[1] The recommended dose is 1-2 mg/kg of prednisone or equivalent in a single dose in the morning, maximum 40 mg/day, for 3 to 5 days. Oral dexamethasone 0,6 mg/kg for 1 or 2 days has similar benefits, with a lower risk of oral intolerance, and should not be used any longer due to its metabolic effects. For still symptomatic cases, consider switching to prednisolone.[1,33] Potential side effects are a concern with the use of oral corticosteroids. However, short courses of prednisone 1-2 mg/kg per day for 5 days have been shown to not affect bone mineral density, height, and adrenal function 30 days after therapy.[37]

Inhaled corticosteroids

The use of inhaled corticosteroids (ICS) in high doses reduces hospital admissions in patients with acute asthma who are not treated with oral or intravenous corticosteroids.[38] That was the conclusion of a study that analyzed the benefit of ICS for emergency-treated asthma in 32 randomized controlled trials (RCTs: 21 RCTs evaluated 1,403 children aged 6 months to 18 years; 13 RCTs compared ICS versus placebo, and eight RCTs compared ICS versus systemic corticosteroids). The dose and frequency of use of ICS varied widely; however, in all cases, ICS was administered early in the exacerbation treatment course, usually at the time of the first bronchodilator treatment, and by nebulizer or MDI with spacer. There was a significant reduction in hospital admissions

(primary outcome) for children (n = 583) treated with ICS when compared to those treated with placebo (OR = 0.52, 95%CI: 0.33-0.80; p = 0.003; I^2 = 59%). No grouped data is available for secondary outcomes (eg, pulmonary function or clinical score) based exclusively on pediatric patients.[22] In conclusion, its use in combination with systemic corticosteroids in the emergency room seems to reduce the number of hospitalizations in children (evidence B). However, its cost can be a limiting factor and its use is still not consensual, especially regarding the choice of drug, dose, and treatment time, the latest evidence being conflicting.[1] For children aged 12 years and over, it is recommended to start ICS before discharge, if the patient has not previously used any ICS. Those who already use ICS should have their treatment intensified (up to 4 times the basal dose) for 2 to 4 weeks, and should be reminded about the importance of daily use, and the isolated use of bronchodilators is no longer indicated.[1]

Figures 1 and 2 show a suggested flowchart for managing exacerbation in children younger than 6 years and aged 6 years or more.

4. Other therapeutic alternatives

Second-line therapy for the treatment of asthma exacerbation in children/adolescents

Most children have mild or moderate asthma exacerbations and respond well to first-line therapy. Only a minority will have severe exacerbation that is unresponsive to conventional measures, requiring therapy escalation and the use of second-line medications.

There is great variability in the criteria that define second-line drugs, and the choice may vary depending on the clinical picture, the child's age, but especially regarding product availability and service experience.

Didactically we can group the second-line treatments in:[28]

– *additional inhaled bronchodilator treatment:* continuous inhaled beta-2 agonists, inhaled anticholinergics such as ipratropium bromide and nebulized magnesium sulfate;
– *parenteral bronchodilator treatment:* selective beta-2 agonists such as salbutamol and terbutaline; adrenaline (α and β receptor agonist), intravenous magnesium sulfate; methylxanthines such as theophylline and aminophylline and ketamine;
– *other treatments:* heliox, antibiotics, inhalational anesthetics, and ventilatory support.

Many of these drugs have already been discussed above, and the others will be detailed below.

Magnesium sulfate ($MgSO_4$)

First described as an adjunct to the treatment of severe asthma exacerbations in 1994, the mechanism by which the $MgSO_4$ causes bronchial smooth muscle relaxation and consequent bronchodilation is still not fully understood.[39] It is believed to act by increasing calcium uptake in the endoplasmic reticulum and/or blocking the influx of calcium ions into smooth muscle cells, acting as an antagonist.

In addition, it acts as a cofactor of adenyl cyclase and sodium-potassium ATPase, potentiating the effects of beta-2 agonist drugs.[39-41] Secondary mechanisms include inhibition of acetylcholine release by cholinergic nerves and reduction of histamine release by mast cells.[42] $MgSO_4$ has already been described for inhaled and parenteral use in children older than 2 years, and intravenous use, in a single administration, in 20 minutes, at doses ranging from 25 to 75 mg/kg/dose (maximum dose 2-2.5 g/dose) or in prolonged infusions for 4 hours, with higher doses 200 mg/kg/4 hours, presents more robust evidence than inhaled use.[40,41] Studies conclude that intravenous $MgSO_4$ reduces the chances of hospital admissions, is cost-effective, and, even in emergency care, is not associated with significant side effects or damage[40]. When pulmonary function parameters were evaluated, there was a significant improvement in FEV_1 and the FEV_1/FVC ratio in children with mild and moderate asthma, treated with intravenous MgSO4, with no adverse effects recorded.[39] Evidence suggests that the simultaneous administration of magnesium sulfate and a beta-2 agonist agent potentiates the bronchodilator effect by increasing the beta-receptor response.[30,41]

Inhaled beta-2 agonist in continuous use

For patients with severe exacerbations and who do not respond to the intermittent administration of inhaled short-acting beta-2 agonist, administration in continuous inhalation can be chosen, in this case using a nebulizer, in order to saturate all beta-2 receptors respiratory tract and reach maximum bronchodilation.[42] A meta-analysis that evaluated two

Figure 1
Asthma exacerbation management flowchart in children under 6 years old.

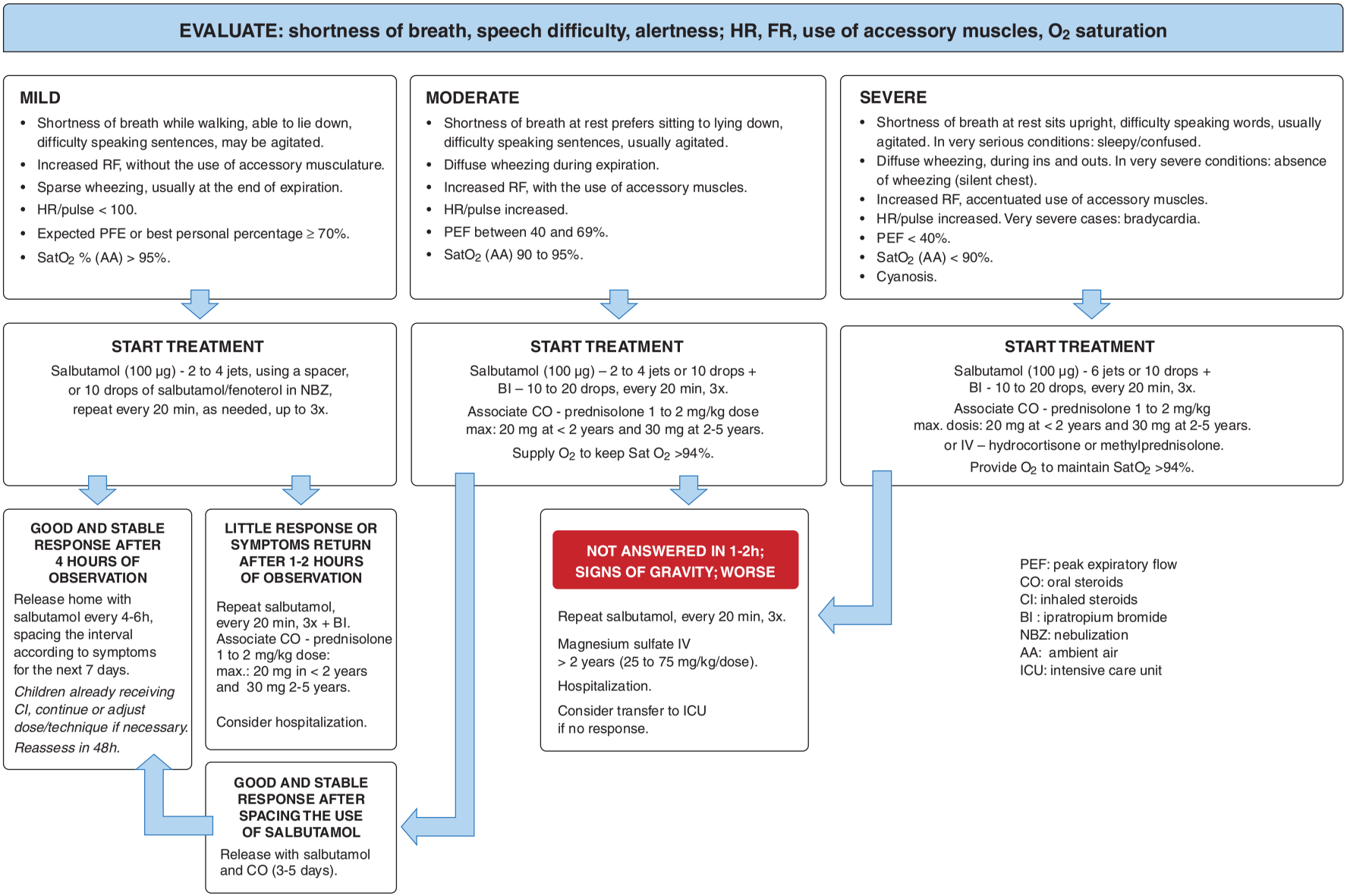
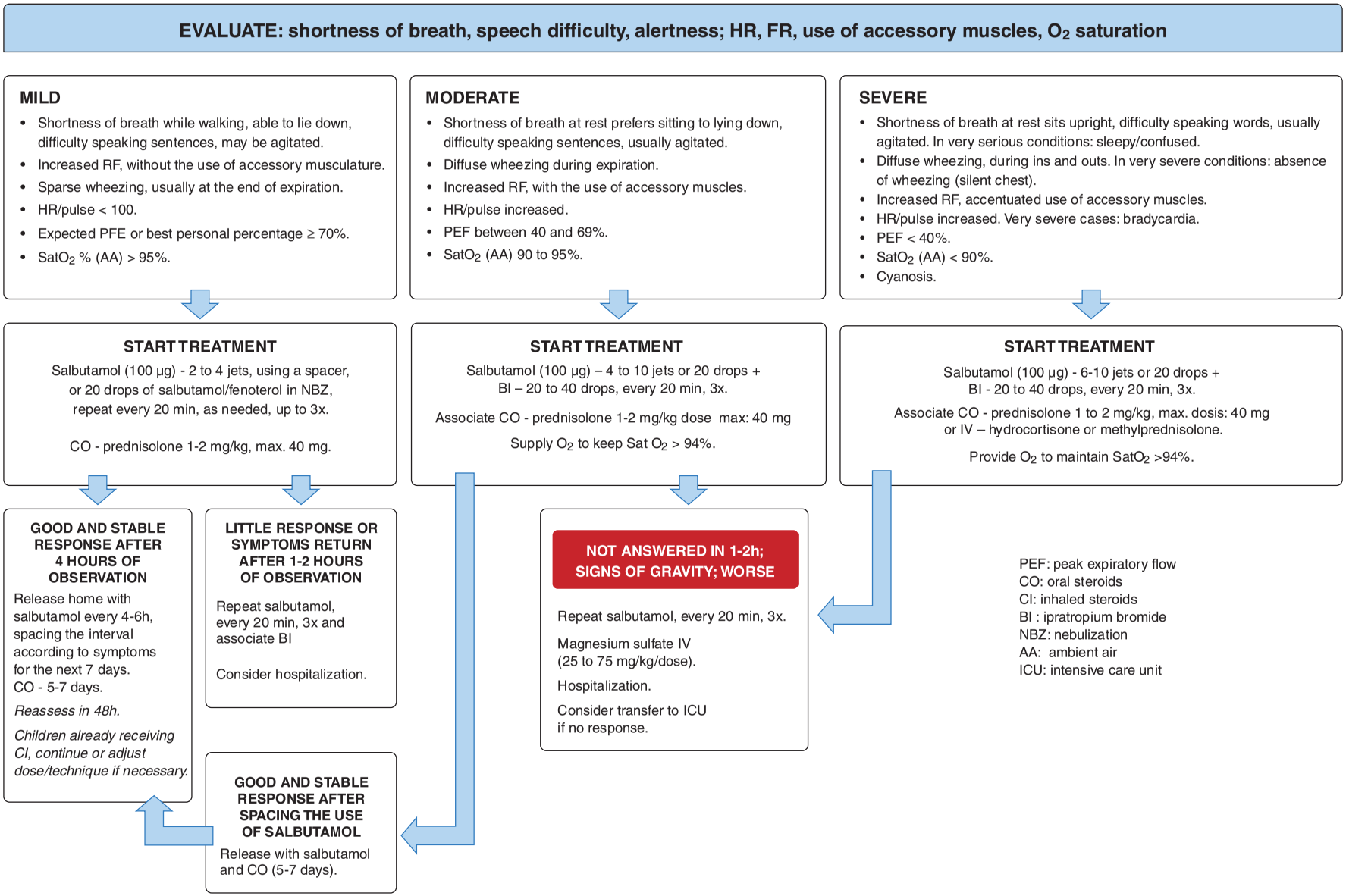


Figure 2
Asthma exacerbation management flowchart in children aged 6 years and over.



reviews showed weak evidence and no superiority of continuous use compared to intermittent (every 15/20 minutes). There was no difference in the length of stay in the emergency room and the number of hospitalizations in children, unlike what was observed in studies in adults, in which continuous nebulization was superior, especially in patients with more severe obstruction. No significant differences were observed in the side effects of the two forms of administration of bronchodilators.[43] Another fact observed was among children and adolescents hospitalized with severe asthma and submitted to continuous nebulizations with albuterol stored in bottles with benzalkonium chloride (preservative). For these patients, the duration of continuous nebulization was longer compared to those who received nebulization without the preservative (9 vs. 6 hours; RR: 1.79; 95%CI: 1.45-2.22; p < 0.001). Thus, it was concluded that benzalkonium chloride acts as a functional antagonist of salbutamol and that presentations without this product are safer for use in continuous nebulization.[44] Another fact observed was among children and adolescents hospitalized with severe asthma and submitted to continuous nebulizations with albuterol stored in bottles with benzalkonium chloride (preservative). For these patients, the duration of continuous nebulization was longer compared to those who received nebulization without the preservative (9 vs. 6 hours; RR: 1.79; 95%CI: 1.45-2.22; p < 0.001). Thus, it was concluded that benzalkonium chloride acts as a functional antagonist of salbutamol and that presentations without this product are safer for use in continuous nebulization.[44]

Intravenous beta-2 agonist

The classic idea of using intravenous beta-2 agonists in addition to or replacing inhaled beta-2 agonists stems from the concept that during a severe exacerbation, severe bronchial constriction can prevent the delivery of the inhaled drug to the distal airways.[45] On the other hand, when used systemically, they also have more adverse effects related to the interaction with beta-1 receptors outside the airways, especially tachycardia and agitation. Since the 1990s, an attempt has been made to prove the efficacy of intravenous albuterol in children with severe asthma that would refuse conventional therapy.[45] A study that compared it to placebo showed weaning from inhaled therapy and early discharge from the emergency department.

A comparative study of intravenous terbutaline with saline solution + nebulized albuterol showed a significant improvement in clinical scores, but four individuals had cardiac toxicity to terbutaline, one case of cardiac arrhythmia, and three with high levels of troponin.[46] Cochrane reviews in 2001 and 2012, including children and adults, found no significant benefit from adding intravenous beta-2 agonists to inhaled beta-2 agonists.[45,47] The route of choice for administering beta-2 agonists remains inhaled. If it is impossible to use this route, intravenous therapy must be considered, and if there is a combination of therapies, the monitoring of adverse effects must be rigorous.[45-47]

Adrenaline (epinephrine)

It is a drug with potent beta-adrenergic action and a bronchodilator effect similar to that of beta-2 agonists, but less selective. Historically, parenteral epinephrine was considered the standard therapy for asthma exacerbations in the 1970s and 1980s, but with similar clinical efficacy and the ease of use of inhaled bronchodilators proven, epinephrine was reserved as an option for critically ill patients who do not respond to first-rate inhaled therapy line.[28,48]

Methylxanthines – theophylline, and aminophylline

The bronchodilator effect of these drugs is due to the inhibition of phosphodiesterase, which leads to an accumulation of cyclic adenosine monophosphate (cAMP) in smooth muscle cells, adenosine antagonism, and catecholamine release. With proof of effectiveness and safety of beta-2 agonists of short action, the absence of additional clinical benefit of methylxanthines and, especially, the risk of side effects given the small therapeutic safety margin in the last two decades, discouraged the use of these drugs in acute exacerbations of asthma in children and adults.[28]

A systematic review from the early 2000s evaluated seven studies (380 hospitalized children with severe asthma exacerbation) and concluded that the use of aminophylline resulted in an improvement in lung function, but without a corresponding clinical improvement. In addition, there was no reduction in hospitalization time and the need for inhaled medication, with more episodes of vomiting in the groups that received aminophylline.[49]

When compared to intravenous salbutamol, in the exacerbation of severe asthma in children, a trend towards longer O_2 use (17.8 hours vs. 7.0 hours) was observed, as well as a significant increase in the length of hospital stay in the salbutamol group (85.4 hours vs. 57.3 hours), although no differences were found in the clinical score with 2 hours of treatment.[50]

It is worth remembering that aminophylline has a narrow safety margin and can cause the side effects already described. Studies have shown the occurrence of nausea, vomiting, headache, abdominal pain, and palpitations.[49,50] When considering the adverse and therapeutic effects of methylxanthines, compared to other safer classes, it is understood why methylxanthines are in the group of not recommended in most international guidelines. Currently, its use is only justified in the ICU environment, where the ability to closely monitor serum levels could mitigate the potential adverse effects of this drug.[47]

Ketamine

A drug widely used in ICU. It is a dissociative anesthetic also used for its sedative and analgesic properties.[51] The effect of inducing bronchodilation is due to sympathomimetic action or as a direct effect on bronchial smooth muscle. Other suggested effects include immunomodulation and anticholinergic action. Increased bronchial secretion and delirium are common adverse effects with prolonged use of ketamine.[28,51] For patients on mechanical ventilation, administration of ketamine was associated with an increase in dynamic compliance and a reduction in peak inspiratory pressure and $PaCO_2$[52]. There are few studies with favorable results for the use of ketamine in asthma exacerbation, and others already show little difference in the improvement of the clinical score and evolution, which places it as a drug with weak evidence compared to other adjuvant therapies. There is rational for use of ketamine in association with bronchodilators in intubated patients with respiratory failure, promoting sedation and analgesia.[28,51,52]

Heliox

It is the helium-oxygen mixture, where nitrogen (which represents approximately 79% of atmospheric air molecules) is replaced by helium. Since helium is a gas seven times lighter than nitrogen, the resulting gas is less dense and, therefore, better managed in situations of turbulent respiratory flows (as in the case of asthma), favoring a more adequate supply of oxygen. When laminar flow is achieved (when wheezing has subsided) the maximum benefit is achieved. Some studies indicate that the usefulness of heliox decreases when the need for FIO_2 falls below 0.5.[53] Heliox poses few risks, however, monitoring of the supply is recommended, as flowmeters may not accurately match the gas supply, and prolonged use of heliox may prevent turbulent flow during coughing, making pulmonary clearance difficult. Despite the relevant physical characteristic, clinical studies are controversial as to the real benefit of heliox in severe asthma exacerbation, with a tendency to show little clinical improvement and dyspnea scores, and no increase in pulmonary function values, despite gas administration have avoided intubation in a small number of patients.[53,54] The use of heliox-guided bronchodilators has been studied in children and adults with asthma,[55] and a systematic review reported increased expiratory flows and reduced hospital admissions, shorter hospital stays, and greater benefit in more severe individuals.[55,56] The use of heliox can be considered in patients who have not responded to conventional therapy, as the cost is low and the adverse event is negligible. The treatment should be discontinued if there is no clinical response.[53-56]

Non-invasive ventilatory support

Noninvasive ventilatory support (NIV) and high-flow nasal cannula (CNAF) have been increasingly used in cases of respiratory failure, including severe acute asthma. Positive pressure reduces the work of breathing by assisting the respiratory muscles and improving oxygenation by increasing mean airway pressure. With this, there is an increase in gas exchange. The use of NIV in children and adults with asthmatic status was associated with a reduction in $PaCO_2$ and respiratory rate and an increase in pH and PaO_2.[57,58] CNAF, given the characteristic of offering heated and humidified gas through a nasal cannula, in a flow that exceeds the patient's inspiratory demand and a low level of positive pressure, is usually better tolerated, especially by pediatric patients.

The use of CNAF in children with asthma exacerbation goes beyond what is observed in adult obstructive pulmonary diseases and suggests a good safety profile, but studies that prove its effectiveness

in pediatric asthma are scarce.[60] A recent study evaluated children older than 2 years of age with severe exacerbation, treated at an emergency room. The institution of CNAF did not show clinical benefits or reduction in length of stay when compared to the group treated with conventional oxygen therapy.[60]

The positive effects of CPAP (Continuous Positive Airway Pressure) and BiPAP (BI-level Positive Airway Pressure – Positive airway pressure at two levels) in children with asthma include a direct bronchodilator effect, improved alveolar recruitment, increased airflow, re-expansion of areas of collapse, hyperinflation, and reduced work of breathing.[57] Overall, scientific data suggest that NIV is safe for children with severe exacerbation and contributes to an improvement in the breathing pattern. Studies in the pediatric population, especially using the CNAF, are needed.

Antibiotics

Even given the fact that asthma exacerbations, especially in children, are mainly triggered by environmental triggers or viral infections and less commonly by bacterial infections, we often observe the prescription of antibiotics to treat the exacerbation. A Cochrane review in 2001, with randomized controlled trials, showed no clinical benefit from the addition of antibiotics during acute asthma exacerbations in children or adults.[61]

The studies that evaluated the use of macrolides in asthma are mainly in adults and are aimed at the chronic management of asthma. In a systematic review, the chronic use of macrolides was shown to have some benefit on lung function, but it was not superior to placebo in preventing hospital admissions or improving quality of life measures.[62] There are no data to support the use of macrolides in asthma exacerbations.

Inhalation anesthetics

Inhaled anesthetics such as isoflurane, halothane, and sevoflurane are powerful smooth muscle relaxants and may help relieve bronchoconstriction.[63] Isoflurane and sevoflurane are most commonly used, as halothane can cause hepatotoxicity.[63] Other adverse effects described are decreased systemic vascular resistance, leading to hypotension and malignant hyperthermia. Successful applications of inhalational anesthetics in children and young adults with refractory asthma have already been described, with a reduction in $PaCO_2$ and an increase in pH after a few hours of administration.[64] Due to the high cost of this therapy and the potential for adverse effects, inhaled anesthetics can be a choice for severe asthmatics admitted to the ICU, bearing in mind that the administration of these drugs requires specialized equipment, many of them only available in surgical rooms.[63,64]

Exacerbation monitoring

As with the initial assessment, continuous monitoring of respiratory rate, heart rate, O_2 saturation, degree of alertness, use of accessory musculature, and intercostal retractions is crucial for treatment decisions. The frequency of monitoring varies depending on disease severity and response to initial therapy, but for most patients, it is typically every 20 to 30 minutes for the first hour of treatment in all patients. It is important not to use each parameter alone.[2]

O_2 saturation with pulse oximeter should be monitored frequently (value < 92% in room air indicates severe exacerbation), especially in children ≤ 5 years. Saturation levels < 90% in adults and children indicate the need for aggressive treatment for the exacerbation.[1] Hemoglobin saturation (SpO_2 < 92%), especially after the use of bronchodilators, allows the identification of the most severe patients who should receive hospital treatment.[65] Pulse oximetry has its limitations due to movement artifacts, reading difficulties with low perfusion and should not be used in isolation as an indicator of hospital admission.[66]

For older children and adults, guidelines recommend PEF measurements (percent of predicted or best PEF) and/or FEV_1 measurements. This assessment should be performed, whenever possible, before treatment, as it is difficult to be performed in younger children and patients with severe exacerbation. Values below 40% of predicted indicate severe exacerbation.[2] According to GINA 2021, the cut-off value for a severe exacerbation is ≤ 50% of predicted or personal best value.[1] After starting treatment, sequential assessment of PEF and FEV_1 values can be used as criteria to indicate the release of the patient. Pulmonary function values (PEF, FEV_1) of 60% to 80% of predicted or the best personal value, associated with improvement in symptoms, are criteria for releasing the patient for treatment at home.[65]

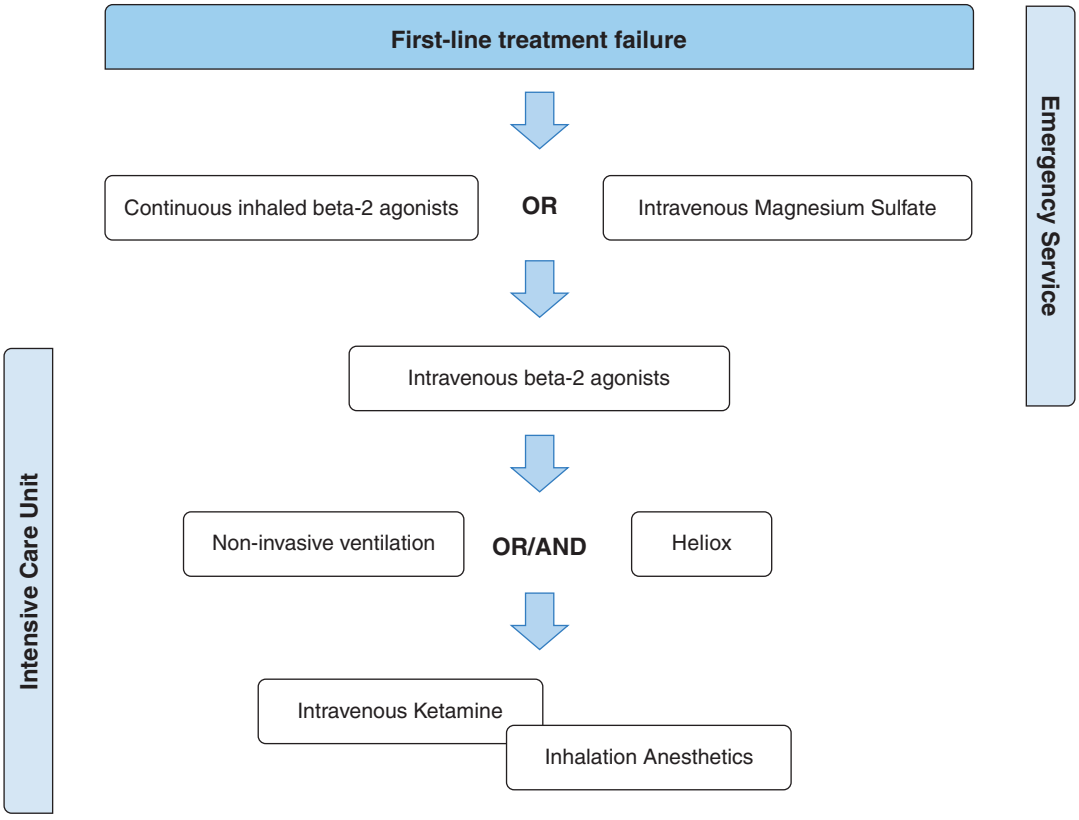


Figure 3
Suggested flowchart for asthma exacerbation management in children under 6 years old. Adapted from Rheder KJ[47].

Arterial blood gases, in general, are not routinely used and should be considered for patients with PEF or FEV_1 below 50% of predicted and/or greater personal value, or for patients who do not have a good evolution with the initial treatment,[1] or in patients with O_2 saturation below 92%. Normal or increased $PaCO_2$ levels are indicative of worsening asthma severity.[65]

Chest radiography should not be performed routinely as it rarely indicates a change in treatment. It is indicated when the patient does not respond well to treatment or when there are signs suggestive of complications, for example, pneumothorax or clinical findings of consolidation.[1,65,67]

Other laboratory tests, as well as imaging tests, are rarely useful for the treatment and are not recommended for routine assessment.[2]

Hospitalization or Intensive Care Unit – Indications

The patients who arrive at the emergency room with an acute exacerbation of asthma classified as

mild or moderate and with worsening or failure to respond to bronchodilators and corticosteroids, after two hours of initial care, will require hospitalization. Patients who arrive with an exacerbation classified as severe should be admitted to a pediatric intensive care unit (PICU).[68]

Absolute admission criteria include:[69]

– clinical deterioration observed by worsening dyspnea and/or increased respiratory effort;
– respiratory fatigue with reduced respiratory rate, reduced sternal retraction, and thoracoabdominal asynchrony;
– severe hypoventilation ("silent chest" on auscultation or the patient's inability to speak);
– need for supplemental O_2 due to low O_2 saturation on pulse oximetry for one hour or more after starting initial therapy;
– previous history of near-fatal asthma, requiring admission to the PICU, with intubation and mechanical ventilation.

Relative admission criteria include:[69]

– previous history of acute exacerbation with rapid worsening and hospitalization;
– inadequate adherence to outpatient control treatment, with frequent use of bronchodilators, especially of short duration;
– patient is in a condition of social vulnerability, and the caregiver's inability to provide necessary assistance to the patient.

The absolute criteria for admission to the PICU include:[70]

– inability to speak, confusion or drowsiness;
– hypoxemia despite O_2 additional;
– moderate to severe hypercapnia.

Intubation Indications

Absolute indications for tracheal intubation include:[71,72]

– greater severe and persistent respiratory effort, with altered mental status;
– hypoxemia (pO_2 < 60 mmHg) in the presence of high concentrations of O_2 (100%) or non-invasive positive pressure ventilation (NIV);
– progressive hypercapnia causing significant respiratory acidosis or altered mental status;
– cardiorespiratory arrest.

Treatment of asthma exacerbation outside the hospital setting

The identification of symptoms or other factors that are precursors to asthma exacerbation is essential for early treatment and prevention. The combination of increased coughing during the day, wheezing and use of beta-2 agonist at night has been shown to be a strong predictor of impending asthma exacerbation, predicting approximately 70% of exacerbations, with a low false-positive value (14%). In contrast, no individual symptom was a predictor of impending asthma exacerbation.[73]

Initial asthma exacerbation management includes an action plan that allows family members and caregivers to notice asthma worsening, initiate treatment, recognize severe exacerbations, identify when urgent care is needed, and follow recommendations for follow-up. The action plan must contain specific information about the medications, including doses and method of use.[1]

Parents and/or caregivers of children with asthma should be advised to seek medical attention immediately if:

– the child is acutely dyspneic;
– symptoms are not immediately relieved by inhaled bronchodilator;
– the period of relief after short-acting beta-2 agonist (SABA) use becomes progressively shorter;
– a child under one year of age needs SABA repeatedly.[1]

Treatment of asthma exacerbation should be started with the use of SABA (salbutamol doses ranging from 2 to 10 jets/dose or equivalent, depending on the age of the child and/or adolescent), one jet at a time, with a spacer with or without a mask. This can be repeated twice, at 20-minute intervals if necessary. The child must be watched. If there is an improvement, keep it at rest for an hour. If there is no improvement, or if more than 6 jets of SABA are needed to relieve symptoms in the first two hours, urgent medical attention should be sought.[1]

There is no evidence to support family/caregiver-initiated oral corticosteroid (OC) treatment in the home management of asthma exacerbation.[74,75] Preventive episodic treatment with high-dose nebulized inhaled corticosteroids may reduce exacerbations in children with virus-induced intermittent wheezing. However, due to side effects, especially if used inadvertently and inappropriately, this strategy should only be adopted if the physician is confident that the use will be appropriate and that the child will be monitored for adverse events.[76]

In children aged 2 to 5 years with virus-induced intermittent wheezing, a randomized controlled trial showed that a short course of leukotriene receptor antagonist (LTRA) implemented at the beginning of the exacerbation reduced symptoms, utilization of health resources, and work absenteeism of caregivers.[77] Parents should be counseled about the risk of adverse sleep and behavioral events with the use of montelukast.[78]

Asthma self-management education should include a written action plan and regular review by a health care provider of asthma control and proper use of medications. This dramatically reduces asthma morbidity in adults and children.[1] In all consultations, the technique of using inhalation devices must be re-evaluated, trained, and corrected. In young children, the focus of asthma education is on parents/caregivers, but simple measures can be taught. Asthma education is also effective when carried out by professionals from the patient's community, using understandable language and appropriate approaches.[79]

Guidance regarding the importance of long-term asthma control, side effects of repeated use of oral corticosteroids, and proper technique for the use of inhaled devices should be provided whenever possible, as they improve long-term outcomes in patients with severe asthma.[80]

Examples of action plans for children under 6 years of age or above are shown in Figures 4 and 5.

Orientation for hospital discharge

Children who experience an asthma exacerbation are at risk for future exacerbations. Studies show that caregivers have difficulty managing the instructions received at the time of hospital discharge, making medication dosage errors, in addition to poor adherence to therapy and failure to maintain an adequate outpatient follow-up.[81] Thus, we need commitment and clear strategies to modify these difficulties, taking advantage of hospitalization and guidelines given at hospital discharge to generate more impact on disease control and avoid readmissions due to exacerbations.[82]

This involves not only providing medication prescriptions but asthma education guidelines, reinforcing the importance of regular follow-up.[82,83]

Before hospital discharge, the child must be stable, that is, he has to stay out of bed without the need for supplemental O_2, with the ability to feed and ingest fluids without difficulty.

Discharge guidelines, according to GINA[1] recommendations, are described below.

Medications

1. **Short-acting bronchodilator** – should be used as needed, based on symptoms, but this daily medication requirement should be noted to assess whether the use is decreasing over the days to pre-exacerbation levels.
2. **Oral corticosteroid (CO)** – complete the treatment time, which should be 3 to 5 days in children, and 5 to 7 days in adolescents (dose of 1-2 mg/kg of prednisolone, maximum 40 mg/day).
3. **Inhaled corticosteroid (IC)** – start IC before discharge, if not previously prescribed (low dose twice a day for the first month after discharge, subsequently adjusted with the treating physician as necessary) (see Table 6). Patients who were already receiving the medication should have their treatment intensified for two to four weeks, reinforcing the importance of daily use of medication.

Education

1. **Identify risk and trigger factors that contribute to exacerbation**

   It is important to identify, before discharge, the risk factors that may have contributed to the exacerbation and establish strategies to modify them. Exacerbations severe enough to lead to hospitalization may result from exposure to allergens and irritants, respiratory viral infections, inadequate maintenance treatment, compliance

issues, and/or lack of a written asthma action plan.

2. Guide inhalation technique and action plan

Review inhalation technique and correct any errors.

Review PEF technique, if used.

Provide a written action plan or review the existing action plan (Figures 4 and 5). Patients with a plan of action and who monitor disease control using measures of PEF have better treatment outcomes after discharge.

Action plan – under 6 years old

WELL-CONTROLLED PATIENT

Breathing well
No coughing or wheezing
Sleep well at night
You can play, run

Keep medication daily

MILD SYMPTOMS

Cough or mild/moderate wheezing
Tiredness of efforts
Awakening at night by coughing
Attention!

Assess whether symptoms improve with salbutamol. If yes:

ATTITUDE:

Rescue medication: _____

Inhale _____ jets, if symptoms.

Maintain or start inhaled corticosteroids: _____

Inhale _____ jets twice a day.

Look for a health unit to make an appointment for a review, if there is no improvement within 24 hours.

MORE INTENSE SYMPTOMS

Cough/moderate/severe wheezing
Very fast breathing
Sleep interrupted by coughing
Relief medication every 2 or 3 hours
Can't speak a whole sentence
Showed cyanosis (turned purple)
Danger!

ATTITUDE:

Inhale_____ jets of salbutamol every 20/30 minutes and look for a **emergency room immediately**.

Nearest Emergency Service: _____

Mobile Emergency Service: _____

Figure 4
Suggested Action Plan for children under 6 years old.

Referrals

Ideally, schedule a return visit with the treating physician within 1 to 2 days (2 to 7 days for adolescents) and another 1 to 2 months after discharge, depending on the clinic, the practicality of scheduling, and social context. This is essential for the treatment to be continued, and for the symptoms to be well controlled.

Action plan for children aged 6 and over

WELL-CONTROLLED PATIENT

Breathing well
No coughing or wheezing
Sleep well at night
You can play, run

Keep medication daily

MILD SYMPTOMS

Cough or mild/moderate wheezing
Tiredness of efforts
Awakening at night by coughing
Attention!

ATTITUDE:

Start rescue medication: _____

Inhale _____ jets if symptoms.

Maintain or start inhaled corticosteroids: _____

Inhale _____ jets, twice a day

If it doesn't improve in 2-3 days:

Start oral steroids: _____ , in the morning, 3-5 days.

Search the health facility to make an appointment for a review.

MORE INTENSE SYMPTOMS

Cough/moderate/severe wheezing
Very fast breathing
Sleep interrupted by cough
Relief medication every 2 to 3 hours
Can't speak a whole sentence
Danger!

ATTITUDE:

Inhale _____ jets from _____ every 20/30 minutes.

Start oral corticosteroids: _____

and look for **emergency room immediately**.

Nearest Emergency Service: _____

Mobile Emergency Service: _____

Figure 5
Suggested Action Plan for children aged 6 and over.

Table 6
Low, medium, and high doses of inhaled corticosteroids, according to age group.

Inhaled corticosteroids for children under 6 years old - low dose	
Beclomethasone dipropionate	100
Budesonide	200
Nebulized budesonide	500
Mometasone	100
Fluticasone propionate	50

Inhaled corticosteroids for children aged 6 - 11 years			
Inhaled corticosteroid	**Low dose**	**Medium**	**High**
Beclomethasone dipropionate	100-200 (50-100)[a]	> 200-400 (> 100-200)[a]	> 400 (> 200)[a]
Budesonide (DPI)	100-200	> 200-400	> 400
Nebulized budesonide	250-500	> 500-1000	> 1000
Ciclesonide	80	> 80-160	> 160
Fluticasone propionate (DPI)	50-100	> 100-200	> 200
Fluticasone propionate (HFA)	50-100	> 100-200	> 200
Mometasone furoate	100	100	200

Inhaled corticosteroids for teenagers (> 12 years)			
Inhaled corticosteroid	**Low dose**	**Medium**	**High**
Beclomethasone dipropionate	200-500 (100-200)[a]	> 500-1000 (> 200-400)[a]	> 1000 (> 400)[a]
Budesonide (DPI)	200-400	> 400-800	> 800
Ciclesonide	80-160	> 160-320	> 320
Fluticasone propionate (DPI)	100-250	> 250-500	> 500
Fluticasone propionate (HFA)	100-250	> 250-500	> 500
Mometasone furoate	200-400	200-400	> 400

HFA: hydrofluoroalkane, DPI: inhalation powder device.
[a] Beclomethasone in extra-fine particle presentation.

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