4. Asthma exacerbations

C Asthma exacerbations (also called asthma attacks) are episodes of worsening of the patient's baseline condition that require treatment modifications. In a given patient, they should be clinically identified by changes in symptoms, or in the reliever medication, or in the lung function as compared to daily fluctuations. Retrospectively, exacerbations can also be identified by an increase in the dose of maintenance treatment over at least 3 days[149].

C Depending on how fast they occur two types of exacerbations are identified: **slow-onset asthma attacks** (usually developing in days or weeks) and **rapid-onset asthma attacks** (progressing in less than 3 hours), which can be distinguished by their different etiology, pathogenesis and prognosis[235,304]. Slowly progressing exacerbations (more than 80 % of those seen in emergency departments) are often caused by upper respiratory tract infections or a poor disease control resulting from non-adherence to treatment; the major pathogenetic mechanism is inflammation and treatment response is also slow. In contrast, rapid-onset attacks are caused by inhaled allergens, drugs (NSAID or ß-blockers), food (due to food allergy, particularly milk and egg in childhood, and panallergens related to lipid transfer proteins in dried fruits, fruits and vegetables; or additives and preservatives), or emotional stress; their mechanism is bronchoconstriction and, although initially more severe (a higher risk of intubation and death), treatment response is more favorable and faster.

C The intensity of exacerbations is variable with some attacks occasionally showing mild or symptoms that may be undetectable by the patient, while other episodes are very severe and life-threatening. Factors increasing the likelihood of experiencing life-threatening asthma attacks are shown in table 4.1[305-307].

Table 4.1. Factors predisposing to life-threatening asthma

1. Previous episodes requiring admission to the ICU, or intubation/mechanical ventilation.
2. Frequent hospitalizations in the previous year.
3. Multiple visits to the emergency department in the previous year.
4. Psychological traits (alexithymia) or psychological diseases (attitudes of negation) or psychiatric disorders (depression) interfering with treatment adherence.
5. Cardiovascular comorbidity.
6. Excessive use of a short-acting β2-agonist.
7. Sudden onset of attack.
8. Patients without periodic control of their disease.

ICU: intensive care unit.

4.1 Severity evaluation

D Since further treatment depends on the severity of the exacerbation, a prompt initial evaluation of the patient's clinical condition is mandatory.

D An asthma attack is evaluated in two steps[308]:

- **Initial (or static).** It is aimed at identifying patients with vital risk factors (table 4.1), detecting life-threatening signs and symptoms (table 4.2), and objectively measuring the degree of airflow obstruction by determining FEV_1 or PEF and their impact on gas exchange.
- **After response to treatment (or dynamic evaluation).** It is intended to compare changes in the degree of airflow obstruction versus initial values, and to assess the need for other diagnostic studies.

D A brief initial anamnesis will provide information on the asthmatic origin of symptoms, duration of the exacerbation episode and previous treatment. In the presence of life-threatening signs and symptoms as well as imminence of cardiorespiratory arrest (altered consciousness, bradycardia, hypotension, cyanosis, "silent" chest or psychomotor agitation), the possibility of admission to the intensive care unit (ICU) should be considered. The remaining signs and symptoms (table 4.2) are scarcely useful since they are poorly correlated with the degree of airflow obstruction and there is a large variability in their interpretation[309].

C The objective assessment of the degree of airflow obstruction by spirometry (FEV_1) or using a peak expiratory flow (PEF) meter enables to ascertain initial severity and evaluate treatment response. According to the values recorded, exacerbations are classified as **mild**, if FEV_1 or PEF are equal to or higher than 70% predicted or personal best values, respectively; moderate, if FEV_1 or PEF values range between 70 and 50%; and **severe**, if these values are lower than 50%. Functional response to treatment is estimated to be satisfactory

Table 4.2. Assessment of severity of asthma exacerbation

	Mild attack	Moderate-severe attack	Respiratory arrest
Dyspnea	Mild	Moderate-severe	Very severe
Speech	Paragraphs	Phrases-words	
Respiratory rate (/min)	Increased	> 20-30	
Heart rate (/min)	< 100	> 100-120	Bradycardia
Use of accessory muscles movement	Absent	Present	Paradoxical thoracoabdominal
Wheezing	Present	Present	Silent chest
State of consciousness	Normal	Normal	Decreased
Paradoxical pulse	Absent	> 10-25 mm Hg	Absent (muscular fatigue)
FEV_1 o PEF (reference values)	> 70 %	< 70 %	
SaO_2 (%)	> 95 %	90-95 %	< 90 %
PaO_2 mm Hg	Normal	80-60	< 60
$PaCO_2$ mm Hg	< 40	> 40	> 40

FEV_1: forced expiratory volume in one second; PaCO2: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PEF: peak expiratory flow; /min: per minute; SaO_2: arterial oxygen saturation.

C when FEV_1 or PEF exceed 40% predicted and PEF increases at least 50 l/min at 30 minutes from the beginning of treatment[310]. Initial treatment response of airflow obstruction is the major prognostic factor when assessing exacerbations.

D Measurement of oxygen saturation by pulse oximetry is required in all patients with FEV_1 or PEF values below 50 % predicted in order to exclude hypoxemia and to assess the need for oxygen therapy. Arterial gases are useful in patients whose saturation cannot be maintained above 90% despite oxygen therapy[311].

D Other complementary studies at the beginning of an asthma attack, such as chest X-rays and an electrocardiogram, are indicated in case of symptoms, such as fever, pain or intense breathlessness that may suggest the presence of complications like pneumothorax or lower respiratory tract infection or when therapeutic response, as shown by objective parameters, is not appropriate[312].

4.2. Treatment

The immediate **objective** when treating an asthma attack is to preserve the patient's life, reverting airflow obstruction and hypoxemia as soon as possible, and thereafter to set up or review the therapeutic plan to prevent further attacks. The pharmacological treatment that should be used according to severity of exacerbation and the usually recommended doses are shown in the algorithm of figure 4.1 and in table 4.3.

4.2.1. Mild exacerbation

D In clinical practice, it is difficult to differentiate a mild exacerbation from a transient loss of asthma control, since changes observed will be close to the normal range of variation for a given patient[149].

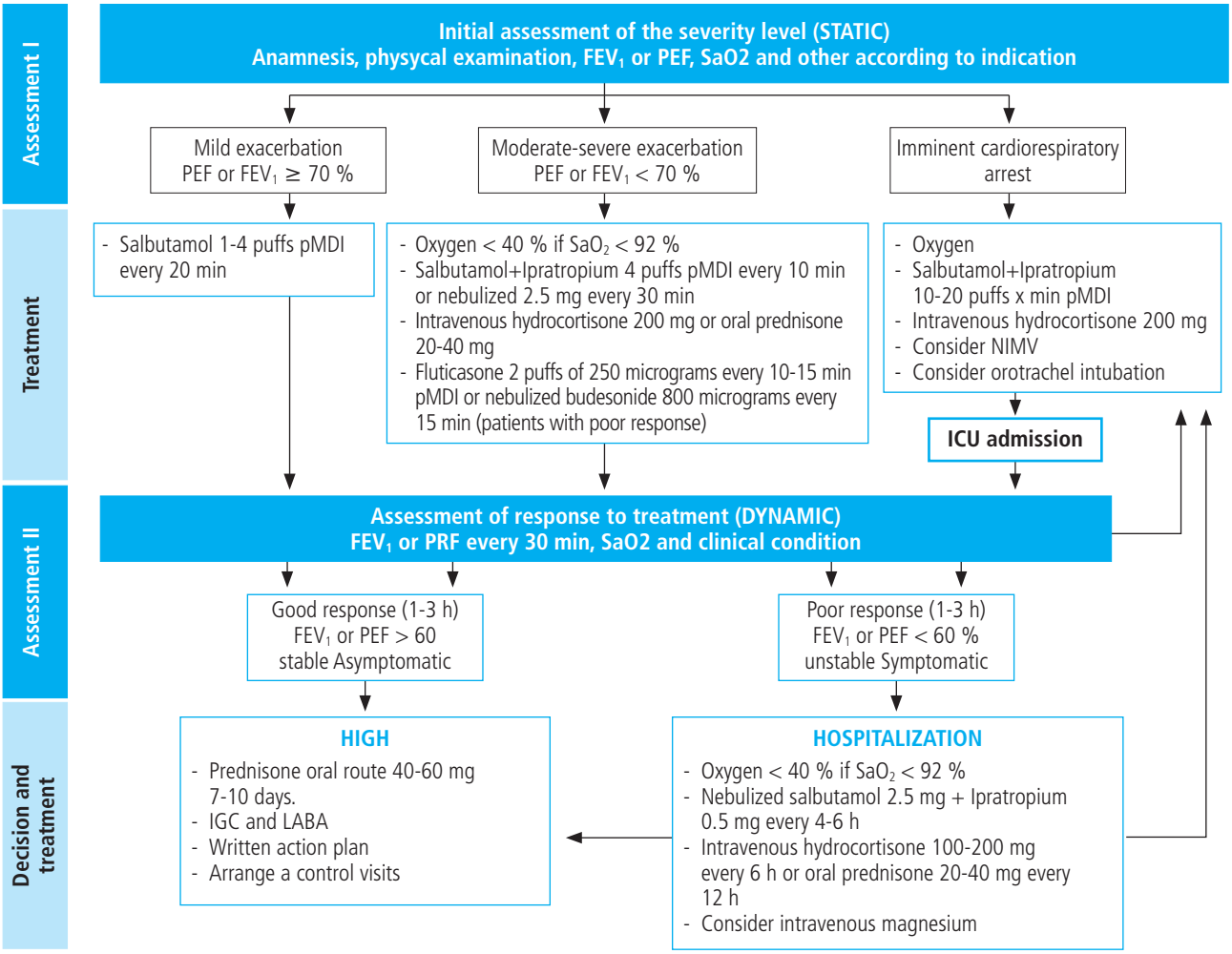
C Milder attacks can be managed not only at hospital emergency departments but also in the patient's home or in primary care centers, provided a correct clinical and respiratory function assessment is carried out and treatment response can safely be achieved within the first 2 hours.

Asthma patients who have been provided with written action plan, including home PEF monitoring, in which how to act in case of loss of control have an excellent and readily usable tool for managing mild exacerbations[313]. In order to quickly implement the adequate measures, patients should be trained in identifying the early markers of exacerbations and be ready to act immediately according to their assigned action plan, which must include the measures to be adopted depending on treatment response.

The treatment schedule to be followed does not depend on the setting where the patient is being cared for. The therapeutic regimen must include the administration of short-acting β_2-agonists (SABA) (salbutamol or terbutaline), oral glucocorticoids and oxygen, if required. The addition of ipratropium bromide is not needed for mild attacks, and antibiotics should not be routinely prescribed.

A ***Inhaled short-acting β_2-agonists (SABA)*** are the most effective and rapidly acting bronchodilators for treating asthma exacerbations. **Salbutamol** (o **terbutaline**, interchangeably) at doses of 200 to 400 µg with a spacer (2 to 4 puffs) every 20 minutes during the first hour is recommended[314,315]. If the exacerbation is being managed on an outpatient basis, lack of response should prompt urgent referral to a hospital emergency department. In case of good response, **salbutamol** will be continued at a dosage of 2 puffs every 3-4 hours until remission of the asthma attack is achieved.

If a favorable outcome is reached within the first 2 hours of treatment (symptom resolution, PEF over 80% predicted or personal best value) and if this clinical response is maintained for 3-4 hours, no more treatments will be necessary.



FEV_1: forced expiratory volume in one second; h: hour; IGC: inhaled glucocorticoids; LABA: long-acting β_2-agonist; mg: milligram; min: minute; NIMV: non-invasive mechanical ventilation; PEF: peak expiratory flow; pMDI: pressurized metered-dose inhaler; SaO_2: arterial oxygen saturation

Figure 4.1. Diagnostic and therapeutic management of asthma exacerbation in adults[308]

Table 4.3. Drugs and dosages commonly used for the treatment of asthma exacerbations

Therapeutic groups	Drugs	Doses
β2-adrenergic agonists	Salbutamol or Terbutaline	- 4-8 puffs (100 µg/puff) every 10-15 min (pMDI + spacer) - 2.5-5.0 mg every 20 min (intermittent NEB) - 10-15 mg/hour (continuous NEB)
Systemic β2-adrenergic agonists	Salbutamol	- 200 µg i.v. in 20 min followed by 0.1-0,2 µg/kg/min.
Anticholinergics	Ipratropium bromide	- 4-8 puffs (18 µg/puff) every 10-15 min (pMDI + spacer) - 0.5 mg every 20 min (intermittent NEB)
Systemic glucocorticoids	Prednisone Hydrocortisone	- 20-40 mg every 12 h (oral) - 100-200 mg every 6 h (i.v.)
Inhaled glucocorticoids	Fluticasone Budesonide	- 2 puffs (250 µg/ puff) every 10-15 min (pMDI + spacer) - 800 µg every20 min (NEB)
Systemic magnesium sulfate		- 2 g to be infused in 20 min (i.v.)
Inhaled magnesium sulfate		- 145-384 mg in isotonic solution (NEB)Aminophylline - 6 mg/kg to be administered in 30 min followed by 0.5-0,9 mg/kg/h

IGC: inhaled glucocorticoids; i.v.: intravenous route; h: hour; kg: kilogram; min: minute; mg: miligram; µg: microgram; NEB: nebulized; pMDI: pressurized metered- dose inhaler.

A The use of **systemic glucocorticoids** accelerate resolution of exacerbations and prevents relapses[316]. Except for very mild attacks, systemic glucocorticoids should always be administered as early as possible[317,318], particularly if:

a. Pulmonary obstruction cannot be reversed with inhaled SABAs.
b. The patient is already on oral glucocorticoids.
c. The patient has already treated a previous loss of control with other therapeutic options without success.
d. There is a history of previous exacerbations requiring oral glucocorticoids.

A The daily dose of *prednisone* is 0.5-1 mg/kg (or equivalent doses of other steroids) of ideal body weight, up to 50 mg; this dose should be maintained for 5 to 10 days, and may be discontinued without down-titration in order to attain a quick improvement and prevent early relapses[318,319].

A If response to inhaled bronchodilator treatment within the first hours is satisfactory, no hospital referral is required. Patients should be instructed on the need for an adequate subsequent treatment, a revision of their maintenance treatment plan and the provision or to review the asthma education program[320,321].

4.2.2 Moderate-severe exacerbation

A The first measure consists of immediate oxygen administration by a nasal cannula or a Venturi mask, with a flow providing a saturation over 90 % (95 % in pregnant women or concomitant heart disease)[322].

B For patients with a higher degree of obstruction, caution must be exercised when high-flow oxygen is given. Oxygen saturation levels around 93-95%, rather than 100%, are preferable[322].

A ***Inhaled short-acting β_2-agonists (SABA)*** are the first-choice bronchodilator treatment. Both the dose and the dosing intervals should be individualized according to the selected administration system and the therapeutic response. Evidence shows that the most cost-effective system is the pressurized inhaler with a spacer chamber[323]; but evidence is weaker for patients with very severe exacerbations.

D There is some debate as to whether continuous may be superior to intermittent nebulization therapy. In a systematic review, no significant differences were found between the two delivery methods in relation to changes in pulmonary function tests and hospital admission[324], but these results were not supported by other studies[325]. A practical approach could consist in applying an initial continuous nebulization therapy to stabilize the patient and then switching to an intermittent therapy.

A No available evidence supports the use of an administration route different from inhalation to deliver bronchodilator medication[326], with intravenous route being reserved for patients under mechanical ventilation or those failing to respond to inhalation therapy.

B Similarly, no beneficial effects have been obtained when adding intravenous medication to inhaled therapy[326].

Parenteral adrenaline (subcutaneous or intravenous) is not indicated for treating exacerbations, except when these occur in a patient with anaphylaxis. When administered in aerosol form, doses higher than 2 mg, equivalent to 5 mg salbutamol are required as lower doses are ineffective[327].

A The use of **ipratropium bromide** during the initial phase of moderate-to-severe exacerbations concomitantly with a SABA is associated with a greater increase in pulmonary function (estimated by FEV_1 or PEF) and a decrease in hospitalizations, as compared to the use of a SABA alone[317,328].

A ***Systemic glucocorticoids*** accelerate the resolution of asthma attacks and prevent relapses[318,329,330]. They should be prescribed early, within the first hour of treatment in the emergency room, since their effect starts 4-6 hours after administration. They are especially indicated if no improvement is seen after the first dose of a SABA, if the patient was already receiving them or if previous attacks requiring these drugs have occurred.

A The preferred administration route of glucocorticoids is oral, as it is very effective[331], fast, less invasive and cheaper than intravenous route[332,333]. The latter is reserved for situations in which patients are unable to swallow because of breathlessness, vomiting or are under mechanical ventilation (either invasive or not).

B Daily dose is 50 mg of prednisolone, as a single morning dose, or 400 mg of hydrocortisone (100 mg every 6 hours)[317] for 5-7 days, with no down-titration being necessary[334,335], particularly if treatment with inhaled glucocorticoids has been initiated.

A Early use of **inhaled glucocorticoids** at high doses, within the first hour of treatment, reduces the need for hospital admission as in the case with systemic administration[330].

B The use of inhaled glucocorticoids does not exclude that of systemic glucocorticoids, although when added to the latter, an even greater reduction is seen in the number of hospital admissions[330]. There is insufficient evidence to recommend inhaled glucocorticoids instead of systemic glucocorticoid therapy.

Theophyllines should not be used in acute asthma episodes because of their lower efficacy and safety as compared with salbutamol[336].

A Routine administration of ***magnesium sulfate*** is not indicated, although in selected patients experiencing severe obstruction (FEV_1 25-30 % predicted) or persistent hypoxemia, a single dose of 2 g administered by infusion reduces the need for hospitalization[337-339].

B An extensive review on the effect of nebulized magnesium sulfate[340] showed only pulmonary function improvement in severe asthma exacerbations in adults when added to an inhaled SABA.

B Heliox (helium and oxygen mixtures) has no place in the routine management of exacerbations, although it may be considered for patients failing usual treatment[341,342], particularly when used to nebulize SABA[343].

Concerning leukotriene antagonists no data supporting their use either orally or intravenously are available. No evidence exists supporting the use of antibiotics, except in case of clearly symptomatic respiratory infections.

4.2.3 Treatment failure

C If refractory respiratory insufficiency or signs and symptoms of severe exacerbation persist despite treatment, it is possible to use non-invasive mechanical ventilation (NIMV) or to refer the patient to the ICU for orotracheal intubation and mechanical ventilation. Increasing evidence exists about the

C utility of NIMV in asthma exacerbations, since this procedure improves obstruction (as a consequence of the direct effect of positive pressure or a better dispersal of aerosolized medication), respiratory rate and dyspnea[344].

4.3 Criteria for hospitalization

C The decision to hospitalize a patient should be be made within the first three hours since the start of treatment because beyond that period, the bronchodilation degree already obtained does not usually increases significantly[310].

B However, the assessment of the patient's clinical condition and pulmonary function within the first hour after admission to the emergency room already enables to predict the need for in-patient care[345,346].

D Patients who had been treated correctly according to the severity of their asthma attack and remain symptomatic or require oxygen to maintain a saturation level over 92% or show a decrease in pulmonary function (FEV_1 o PEF lower than 40% predicted) should be admitted to the hospital[347].

B Patients not meeting these criteria may be discharged after a period of clinical observation, not shorter than 60 minutes, in order to ensure that they remain stable[347,348].

4.4 Criteria for hospital discharge

B The decision to discharge a patient cannot be made on the basis of a particular functional parameter, although a PEF value below 75% and variability over 25% are associated with a higher rate of readmission[349].

B Patients may be discharged from hospital if they are capable of following their prescribed treatment at home, are paucisymptomatic or there is a reduced need for reliever medication[349].

D Before hospital discharge a minimal education plan including the inhalation technique must be implemented and a written action plan will be provided (chapter 3.4.3). A visit to the patient's physician will be scheduled for within the next seven days[321].

RECOMMENDATIONS

4.1.	The evaluation of any asthma exacerbation should include the identification of clinical signs and the history of life-threatening attacks, as well as the use of objective measures (PEF or spirometry) in order to quantify the degree of airflow obstruction/limitation (static evaluation).	R2
4.2.	In patients with an asthma exacerbation, the initial therapeutic response of airflow obstruction should be considered in order to decide on the next steps to be taken (dynamic evaluation).	R2
4.3.	For the management of asthma attacks the use of β_2-adrenergic agonists of rapid onset and short duration of action (SABA) is recommended.	R1
4.4.	For moderate-severe exacerbations early administration of systemic glucocorticoids and oxygen at the lowest concentration enabling a $SaO_2 > 90$ % is recommended.	R1
4.5.	Before hospital discharge a minimal education plan, including an assessment of the patient's inhalation technique and the provision of a written action plan, should be undertaken.	R1