

# 4. Assessment and treatment of asthma exacerbations

## 4.1 Introduction and life-threatening risk factors

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- **Concept:** an asthma exacerbation is defined by an episode of deterioration of the baseline clinical status of a patient that implies the need of administering specific treatment.
- **Synonyms:** in addition to exacerbations, it can receive other names such as crisis, agudization, or asthma attack.
- **Identification:** it can be clinically identified by an increase of symptoms, need of reliever medication, or worsening of pulmonary function in comparison of usual daily variation in a given patient<sup>1</sup>.
- **Onset:** depending on how fast exacerbations occur, two types are identified: rapid-onset with progression in less than 3 hours, and slow-onset (usually developing in days or weeks). The identification of the type of exacerbation is important because of differences in causative factors, pathogenesis and prognosis<sup>2,3</sup>.

*Rapid-onset* exacerbations develop by a mechanism of bronchoconstriction, are associated with a higher initial severity and vital risk than slow-onset exacerbations, although therapeutic response is usually more rapid and favorable. Triggering factors include inhaled allergens, drugs (NSAID or  $\beta$ -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.

*Slow-onset* exacerbations account for more than 80 % of patients with asthma attacks attended in the emergency setting, and are mainly caused by an inflammatory mechanism, so that treatment response is slower. Slow-onset exacerbations are commonly caused by upper respiratory tract infections or a poor disease control.

- **Severity:** 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.
- **Vital risk:** a series of factors that increase the probability of suffering from life-threatening exacerbations have been reported. These factors are related to the characteristics of the current and past exacerbation episodes, adequate control of the disease, and presence of a specific comorbidity (Table 4.1)<sup>4,6</sup>.

Table 4.1. Risk factors for life-threatening asthma exacerbation

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- Related to the asthma exacerbation:
    - Current exacerbation of rapid-onset.
    - Previous episodes requiring medical consultation or hospital admission:
      - a. Multiple visits to the emergency department in the previous year.
      - b. Frequent hospitalizations in the previous year.
      - c. Previous episodes of ICU admission, intubation or mechanical ventilation.
  - Related to chronic asthma disease and its adequate control:
    - Absence of periodic control.
    - Abuse of a short-acting  $\beta_2$ -adrenergic agonist.
  - Cardiovascular comorbidity.
  - Psychological, psychiatric and social conditions that difficult treatment adherence: alexithymia, denial attitudes, anxiety, depression, psychosis.
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ICU: intensiv care unit.

## 4.2 Assessment of severity

Assessment of the severity of the exacerbation episode determines its treatment (Figure 4.1)<sup>7</sup>, and is carried out in two steps:

- *Initial or static (pre-treatment)* evaluation: aimed at identifying signs and symptoms and objectively measuring the degree of airflow obstruction by determining FEV<sub>1</sub> or PEF and their impact on gas exchange. in order to establish the level of severity of the exacerbation episode (Table 4.2).
- *Dynamic (post-treatment)* evaluation: aimed to measure changes in the degree of airflow obstruction versus initial values, and to assess the need of other diagnostic studies.

Assessmen should be aimed at determining the parameters described in Table 4.2. The presence of signs of a life-threatening asthma attack makes it necessary to consider the possibility of admission to the ICU.

Signs and symptoms that are not indicative of life-threatening asthma have a low clinical usefulness due to a poor correlation with the degree of obstruction and the large variability in their interpretation<sup>8,9</sup>.

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Table 4.2. Assessment of severity of asthma exacerbation

	Mild attack	Moderate attack	Severe attack	Life-threatening attack
Dyspnea	Mild	Moderate	Intense	Agonal breathing, respiratory arrest
Speech	Paragraphs	Sentences	Words	Absent
Respiratory rate (x')	Increased	> 20	> 25	Bradypnea, apnea
Heart rate (x')	< 100	> 100	> 120	Bradycardia, cardiac arrest
Blood pressure	Normal	Normal	Normal	Hypotension
Use of accessory muscles	Absent	Present	Very evident	Paradoxical thoracoabdominal movement, or absent
Wheezing	Present	Present	Present	Silence on auscultation
Level of consciousness	Normal	Normal	Normal	Decreased or coma
FEV <sub>1</sub> or PEF (reference values)	>70%	<70%	<50%	Not applicable
SaO <sub>2</sub>	>95%	<95%	<90%	<90%
PaO <sub>2</sub> mm Hg	Normal	< 80 (hypoxemia)	< 60 (partial respiratory failure)	< 60
PaCO <sub>2</sub>	Normal	< 40	< 40	> 45 (hypercapnic respiratory failure)

FEV<sub>1</sub>: forced expiratory volumen in one second; PEF: peak expiratory flow; x': per minute; SaO<sub>2</sub>: oxyhemoglobin saturation; PaO<sub>2</sub>: arterial oxygen partial pressure; PaCO<sub>2</sub>: arterial partial pressure of carbon dioxide.

**C** The objective assessment of the degree of airflow obstruction by spirometry (FEV<sub>1</sub>) or using a peak expiratory flow (PEF) meter is crucial to ascertain the initial severity and evaluate treatment response. It is preferable to use the percentage value of the previous best value of the patient in the last two years, but if this datum is unknown, the percentage value in relation to the predicted value can be used. According to the values obtained, exacerbations are classified as mild, if FEV<sub>1</sub> or PEF are equal to or greater than 70%; moderate, if FEV<sub>1</sub> or PEF values range between 70 and 50%; and severe, if these values are lower than 50%. Life-threatening asthma attack is usually associated with values lower than 33%. The initial therapeutic response of airflow obstruction is the main prognostic factor in the assessment of the exacerbation episode<sup>9-12</sup>.

**D** Measurement of oxygen saturation by pulse oximetry is easy to obtain in all patients and has a complementary role. Values lower than 90-92%, with or without supplemental oxygen therapy, can be associated with hypercapnia respiratory arrest; therefore in these cases, arterial blood gases analysis is indicated<sup>13</sup>.

**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 or suspicion of infection (pneumonia), pain or intense breathlessness that may suggest the presence of pneumothorax or pneumomediastinum, or when therapeutic response, as shown by objective parameters, is not appropriate and in the presence of a life-threatening asthma attack<sup>14-16</sup>.

## 4.3. 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 Table 4.3. Treatment according to severity is shown in Figure 4.1.

### 4.3.1. Mild exacerbation

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<sup>1</sup>.

Milder attacks can be managed at home by the patient him/herself or in primary care centers, provided a correct clinical and respiratory function assessment has been carried out and treatment response can safely be achieved within the first 2 hours.

Asthma patients who have been provided with written action plans, including home PEF monitoring and how to act in case of loss of control, have an excellent and readily usable tool for managing mild exacerbations<sup>17</sup>. 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,

Table 4.3. Drugs and doses commonly used for treating asthma exacerbations

Therapeutic groups	Drugs	Doses
<b>First-choice</b>		
$\beta_2$ -adrenergic agonists	Salbutamol	<b>pMDI + spacer:</b> 200-800 $\mu\text{g}$ (2-8 puffs of 100 $\mu\text{g}/\text{puff}$ ) every 10-15 min during the first hour <b>NEB intermittent:</b> 2.5-5 mg every 20 min during the first hour <b>NEB continuous:</b> 10-15 mg/hour
Anticholinergics	Ipratropium bromide	<b>pMDI + spacer:</b> 80-160 $\mu\text{g}$ (4-8 puffs of 20 $\mu\text{g}/\text{puff}$ ) every 10-15 min <b>NEB intermittent:</b> 0.5 mg every 20 min
Systemic glucocorticoids	Prednisone	<b>Oral route on discharge:</b> 50 mg every/24 hours (5-7 days) <b>Oral route on admission:</b> 20-40 mg every/12 hours
	Hydrocortisone	<b>i.v.:</b> 100-200 mg every/6 hours
Inhaled glucocorticoids	Fluticasone propionate	<b>pMDI + spacer:</b> 500 $\mu\text{g}$ (2 puffs of 250 $\mu\text{g}/\text{puff}$ ) every 10-15 min
	Budesonide	<b>pMDI + spacer:</b> 800 $\mu\text{g}$ (4 puffs of 200 $\mu\text{g}/\text{puff}$ ) every 10-15 min <b>NEB:</b> 0.5 mg every 20 min during the first hour
Magnesium sulfate i.v.		<b>i.v.:</b> 2 g infused over 20 min (one time only)
<b>Alternative in case of previous failure</b>		
$\beta_2$ -adrenergic agonists i.v.	Salbutamol	<b>i.v.:</b> 200 $\mu\text{g}$ in 30 min followed by 0.1-0.2 $\mu\text{g}/\text{kg}/\text{min}$
Magnesium sulfate inhaled		<b>NEB:</b> 145-384 mg in isotonic solution

pMDI: pressurized inhaler; NEB: nebulized; i.v.; intravenous route.

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  $\beta_2$ -agonists (SABA), such as *salbutamol* or *terbutaline*, and inhaled glucocorticoids (IGC) or oral glucocorticoids. The addition of *ipratropium bromide* is not needed for mild attacks, and antibiotics should not be routinely prescribed.

**Inhaled SABA** are the most effective and rapidly acting bronchodilators for treating asthma exacerbations. Salbutamol at doses of 200 to 400  $\mu\text{g}$  (2 to 4 puffs) with spacer is used<sup>18,19</sup>.

Treatment with *salbutamol* at doses of 2 puffs every 3-4 hours can be continued until remission of the exacerbation.

If a favorable outcome is observed 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 are necessary.

The lack of response requires referral of the patient to the hospital emergency department.

The use of **systemic glucocorticoids** accelerates resolution of exacerbations and prevents relapses<sup>20</sup>. Except for very mild attacks, systemic glucocorticoids should always be administered as early as possible<sup>21,22</sup>, particularly if:

- Pulmonary obstruction cannot be reversed with inhaled SABA.

- The patient is already on oral glucocorticoids.
- The patient has treated him/herself a previous loss of asthma control with other therapeutic options.
- There is a history of previous exacerbations requiring oral glucocorticoids.

The daily dose of prednisone is 0.5-1 mg/kg of the ideal body weight (or equivalent doses of other steroids), up to 50 mg; this dose should be maintained for 5 to 7 days, and may be discontinued without down-titration in order to achieve a quick improvement and prevent early relapses<sup>22,23</sup>.

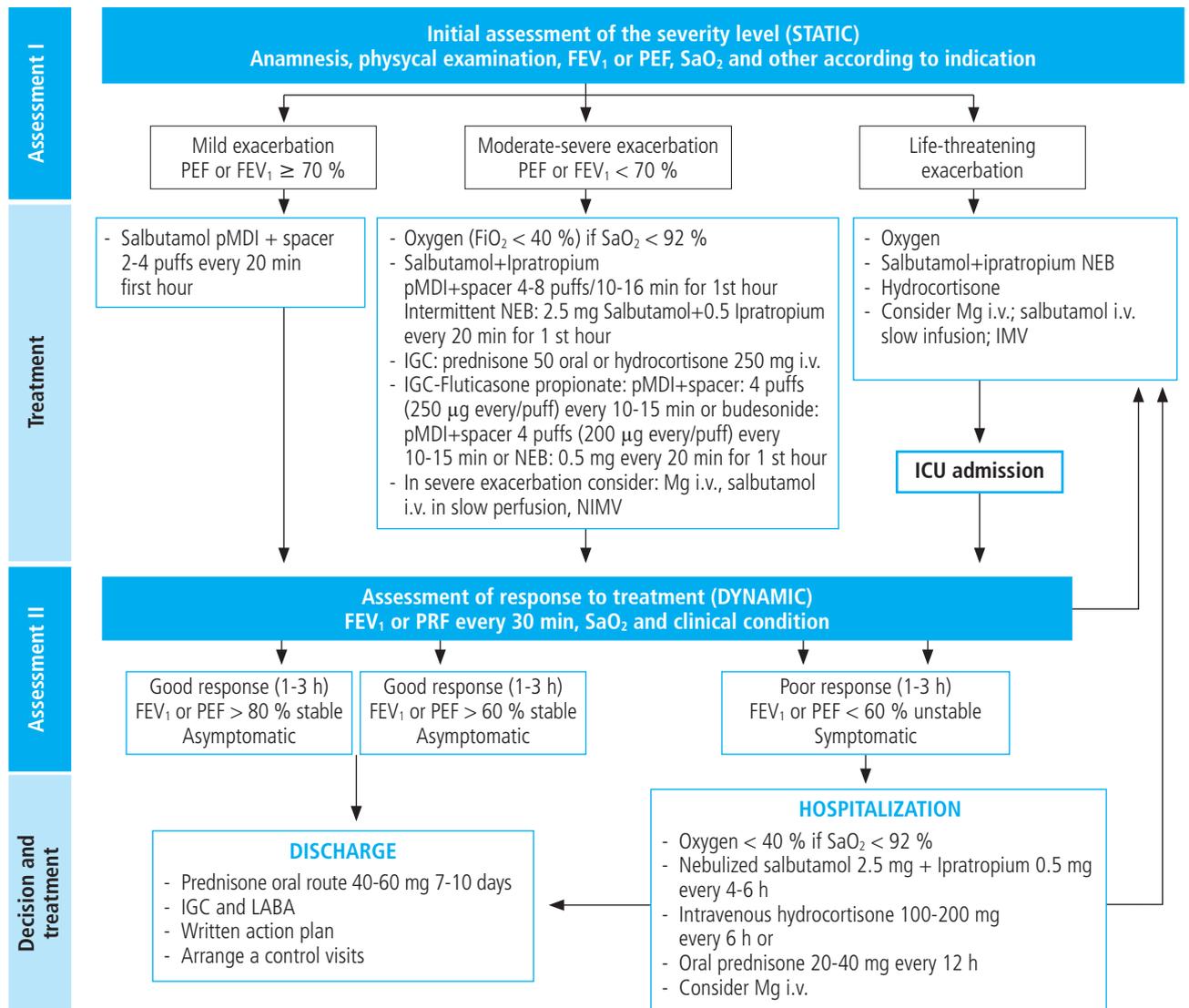
The administration of glucocorticoids by the oral, intramuscular or intravenous route provides similar biological results, but the oral route is less invasive and cheaper<sup>22,24-26</sup>.

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 adequate adherence to the treatment prescribed, their maintenance treatment plan should be reviewed, and a minimal asthma education intervention should be provided<sup>27,28</sup>.

#### 4.3.2 Moderate and severe exacerbations

The first measure consists of immediate oxygen administration, with a flow providing a saturation over 90% (95% in pregnant women or in patients with concomitant heart disease)<sup>29</sup>.

In severe exacerbations with greater obstruction and risk of hypercapnia, the use of oxygen with controlled  $\text{FiO}_2$  to



FEV<sub>1</sub>: forced expiratory volume in one second; PEF: peak expiratory flow; SaO<sub>2</sub>: oxyhemoglobin saturation; pMDI: pressurized metered-dose inhaler; NEB: nebulized; i.v.: intravenous route; IGC: inhaled glucocorticoid; NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation; min: minute; Mg: magnesium; h: hour; µg: micrograms; 1st: first.

Figure 4.1. Therapeutic management of asthma exacerbation in adults.

**B** obtain saturations around 93-95% is preferable than the use of high-flow oxygen therapy with which saturations around 100% can be achieved<sup>29,30</sup>.

**D** In patients with severe exacerbations, the use of capnography to assess the trend to hypercapnia can be considered<sup>31</sup>.

**A** **Inhaled short-acting β<sub>2</sub>-agonists (SABA)** are the first-choice bronchodilator treatment. Both the dose and the dosing intervals should be individualized according to the choice of the administration system and the therapeutic response.

**A** There is evidence that the use of a pressurized inhaler with spacer is the most cost-effective system<sup>32</sup>; however, it is lower in patients with very severe exacerbations.

It has been shown that the administration of SABA using a nebulizer or a pMDI inhaler with spacer have a similar clinical efficacy in terms of pulmonary function, length of stay in the emergency department and risk of hospitalization. However, the dose used by pMDI is lower<sup>32-36</sup>.

There is some debate as to whether nebulized treatment should be administered continuous or intermittently<sup>37,38</sup>. A practical approach could consist in applying an initial continuous nebulization therapy to stabilize the patient and then switching to an intermittent therapy.

There is no evidence to support the use of a route other than inhalation for the administration of bronchodilator medication<sup>39</sup>. The intravenous route, with a very slow

**A** continuous infusion, should be used when there is no response to inhalation therapy in patients under mechanical ventilation and monitored in an ICU.

**B** Similarly, no beneficial effects have been obtained when adding intravenous medication to inhaled therapy<sup>39</sup>.

**B** Parenteral adrenaline (subcutaneous or intravenous) is not indicated for treating exacerbations, except when these occur in a patient with anaphylaxis. In this case, the intramuscular route is the route of choice because higher and more quickly plasma concentrations are obtained as compared with the subcutaneous route, as well as there is a greater safety margin<sup>40,42</sup>.

**B** When administered in aerosol form, doses higher than 2 mg, equivalent to 5 mg *salbutamol* are required as lower doses are ineffective<sup>43</sup>.

**D** Intravenous adrenaline would only be indicated in the case of cardiac arrest or in hypotensive patients who do not respond to intravenous volume replacement and multiple doses of intramuscular adrenaline<sup>44,45</sup>.

**A** The use of *ipratropium bromide* during the initial phase of moderate or severe exacerbations concomitantly with a SABA is associated with a greater increase in pulmonary function (estimated by FEV<sub>1</sub> or PEF) and a decrease in hospitalizations as compared to the use of a SABA alone<sup>46,47</sup>.

**A** **Systemic glucocorticoids** accelerate the resolution of asthma attacks and prevent relapses<sup>22,46,48</sup>. 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 exacerbation episodes requiring these drugs had occurred.

The preferred administration route of glucocorticoids is the oral route, as it is very effective<sup>49</sup>, less invasive and cheaper than the intravenous route<sup>24,25</sup>. The latter is reserved for cases in which patients are unable to swallow because of breathlessness, vomiting or are under mechanical ventilation.

**B** Daily dose is 50 mg of prednisone, as a single morning dose<sup>21</sup> for 5-7 days, with no down-titration being necessary<sup>50,51</sup>.

**A** Early use of **IGC** within the first hour of treatment reduces the need for hospital admission as in the case with systemic administration of glucocorticoids<sup>48</sup>.

**B** The use of IGC together with systemic glucocorticoids provides even a higher reduction in the number of hospital admissions<sup>48</sup>.

Theophyllines should not be used in exacerbation episodes because of their lower efficacy and safety as compared with *salbutamol*<sup>52</sup>.

**A** Routine administration of **magnesium sulfate** is not indicated, although in selected patients experiencing severe obstruction (FEV<sub>1</sub> 25-30% predicted) or persistent hypoxemia, a single dose of 2 g administered by infusion reduces the need for hospitalization<sup>53-55</sup>.

**A** A systematic review of patients with severe exacerbations treated with intravenous **magnesium sulfate** only showed a mild improvement of pulmonary function<sup>56</sup>.

**B** However, a more recent systematic review showed beneficial effects of inhaled magnesium sulfate added to

SABA or SABA plus *ipratropium bromide*, reducing hospital admissions, in addition to a mild improvement of pulmonary function<sup>57</sup>.

**B** **Heliox**, a mixture of helium and oxygen, in 80/20 70/30 proportion, has no place in the routine management of exacerbations due to the lack of consistent data regarding the efficacy of this compound. However, it may be considered in patients who do not respond to the usual treatment<sup>58,59</sup>, particularly to nebulizing SABA<sup>60</sup>.

Regarding leukotriene antagonists, no data supporting their use either orally or intravenously are available. There is no evidence supporting the use of antibiotics, except in the presence of a clearly symptomatic respiratory infection.

#### 4.3.3 Treatment failure

The use of non-invasive mechanical ventilation may be an option in severe exacerbations resistant to treatment. It allows improvement of the respiratory rate, dyspnea, and, in particular, airflow obstruction due to a direct effect of positive pressure, or indirectly contributing to a better distribution of aerosols<sup>61</sup>.

Close monitoring is necessary so as not to delay the use of invasive mechanical ventilation in patients with imminent life-threatening situation.

## 4.4 Criteria for hospitalization

The rate of hospital admission in asthma patients attended in the emergency setting is around 20%<sup>62</sup>, although there is a large variability among different countries<sup>63,64</sup>. It is well known that adherence to guidelines is associated with a lower risk of hospitalization<sup>63</sup>. In a systematic review, the degree of pulmonary function impairment was the most important risk factor for in-patient care<sup>62</sup>.

The decision to hospitalize a patient should be made within the first three hours after the start of treatment of the exacerbation episode, given that decision-making is rarely modified by longer periods of monitorization<sup>65</sup>.

However, 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<sup>66,67</sup>.

Criteria for admission to the hospital or to the ICU are summarized in Table 4.4.

## 4.5 Criteria for hospital discharge

There are no functional parameters that allow a patient to be discharged with complete safety, so the decision is usually the result of the doctor's clinical observation of the patient's condition and results of arterial oxygen saturation<sup>71</sup>.

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<sup>70</sup>.

However, it is highly recommended to have an objective pulmonary function test, such as spirometry, or a PEF

**D** determination. FEV<sub>1</sub> or PEF values > 70% and with minimal symptoms can be criteria for discharge<sup>72</sup>. If the FEV<sub>1</sub> or PEF values are between 50% and 70%, possible risk factors should be considered (Table 4.4).

**D** Before hospital discharge a minimal education plan including checking of the inhalation technique must be

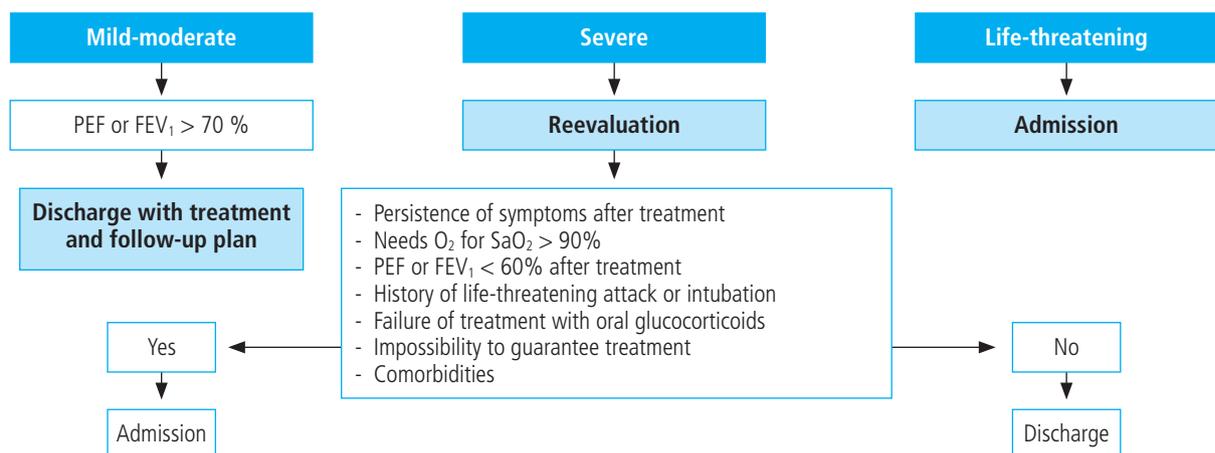
implemented and a written action plan will be provided (section 3.4.3). Also, an appointment with the patient's attending physician will be scheduled within the next five days<sup>28</sup>.

Figure 4.2 shows an algorithm for hospital admission or discharge.

Table 4.4. Criteria for hospital admission and ICU admission (modified from Piñera-Salmerón et al., 2020)<sup>68</sup>

Criteria for hospital admission	Criteria for ICU admission
Remain symptomatic after treatment	Respiratory arrest
Need O <sub>2</sub> for maintaining SaO <sub>2</sub> > 92% <ul style="list-style-type: none"> <li>– PEF or FEV<sub>1</sub> &lt; 50-60 % after treatment<sup>69</sup></li> <li>– PEF or FEV<sub>1</sub> = 50-70 % on arrival. A minimum observation period of 12 hour is advisable.</li> <li>– There is no functional parameter that defines when a patient should be discharged, although PEF &lt; 75 % and variability higher than 25% are associated with a high rate of re-admissions<sup>70</sup></li> </ul>	Decrease in the level of consciousness Progressive functional deterioration despite treatment
Previous life-threatening exacerbation with history of intubation and ventilation, hospital admission or visit to the emergency department due to recent asthma	SaO <sub>2</sub> < 90 % despite supplemental O <sub>2</sub> PaCO <sub>2</sub> > 45 mm Hg = alarm sign of muscle exhaustion
Failure of treatment with oral glucocorticoids in the outpatient setting	Hypercapnia, need of ventilatory support or pneumothorax
Impossibility to ensure necessary care measures at home	
Respiratory (pneumonia, pneumothorax, pneumomediastinum) or non-respiratory comorbidities	

ICU: intensive care unit; SaO<sub>2</sub>, arterial oxygen saturation; PEF, peak expiratory flow; FEV<sub>1</sub>, forced expiratory volume in one second; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide.



FEV<sub>1</sub>: forced expiratory volume in one second; PEF: peak expiratory flow.

Figure 4.2. Algorithm for the site of care based on severity of the exacerbation episode.

## 4.6 Referral and control after discharge

**D** The care of patients who have suffered an asthma attack does not finish at the time of hospital discharge, and all patients should be assessed after the episode.

**D** All patients should be evaluated by his/her family physician within five days after discharge, as well as those who had suffered from a severe exacerbation by the pneumologist or allergologist within one month<sup>71</sup>. Table 4.5 shows criteria for referral to the next healthcare level.

Table 4.5. Criteria indicating specialized assessment of patients within one after an asthma exacerbation episode<sup>71</sup>

- Severe or life-threatening exacerbation.
- Repeated exacerbations requiring care in the emergency department<sup>13,16</sup>.
- Exacerbations that require in-patient care<sup>16,73</sup>, uncontrolled severe asthma, particularly in corticosteroid-dependent asthma, allergic bronchopulmonary aspergillosis, vasculitis.
- Pregnancy<sup>74</sup>.
- Exacerbations triggered by NSAID, aeroallergens, food allergens or presenting with anaphylaxis.
- Known associated comorbidities.
- Clinical suspicion of vocal cord dysfunction, nasal, rhinosinusitis, gastroesophageal reflux, sleep apnea-hypopnea syndrome, asthma-COPD overlap syndrome.

NSAID: non-steroidal anti-inflammatory drug; COPD: chronic obstructive pulmonary disease.

### RECOMMENDATIONS

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|---|-----------|
| 4.1. The initial assessment of the patient with an exacerbation episode should include the analysis of the life-threatening risk, severity level and degree of airflow obstruction.   | <b>R2</b> |
| 4.2. Depending on the signs and degree of airflow obstruction, the patients with an asthma exacerbation episode should be classified into four levels of severity: mild, moderate, severe and life-threatening.                             | <b>R2</b> |
| 4.3. The degree of airflow obstruction will be objectively established by means of spirometry (FEV <sub>1</sub> ) or peak expiratory flow (PEF) measurement.  | <b>R2</b> |
| 4.4. In patients with asthma exacerbation, it is recommended to consider the initial therapeutic response of airflow obstruction and signs of severity, in order to establish the approach that should be followed.                         | <b>R2</b> |
| 4.5. Treatment with SABA is recommended in mild exacerbation episodes.  | <b>R1</b> |
| 4.6. For moderate or severe exacerbations, early administration of systemic glucocorticoids and oxygen at the lowest concentration enabling SaO <sub>2</sub> > 90% is recommended.  | <b>R1</b> |
| 4.7. The decision of hospital admission should be made within the first three hours after starting treatment of the exacerbation episode, because the level of bronchodilation achieved does not increase significantly beyond this period. | <b>R2</b> |
| 4.8. Patients with FEV <sub>1</sub> or PEF > 70% (predicted or best personal value) and with minimal symptoms can be discharged.  | <b>R2</b> |
| 4.9. 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.  | <b>R2</b> |
| 4.10. After an exacerbation, it is recommended that the patient should be evaluated by his/her family physician within five days and, if necessary, by a specialist within one month.   | <b>R2</b> |

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