8. Severe uncontrolled asthma

8.1 Concept and definition

D **Severe asthma** is characterized by the need to be treated with multiple drugs at high doses (steps 5-6 of GEMA and step 5 of GINA), as mentioned in section 3.2.1. Severe asthma includes both controlled and uncontrolled asthma patients[122].

C Severe asthma is associated with a higher consumption of economic resources than moderate and mild asthma[494,495].

D **Severe uncontrolled asthma (SUA)** is defined as the asthma disease that remains poorly controlled despite treatment with a combination of IGC/LABA, at high doses in the previous year, or with oral glucocorticoids for at least 6 months over the same period (partially based on the ERS/ATS Task Force 2013)[496]. Lack of control will be identified by any of the following characteristics:

D
- ACT < 20 or ACQ > 1.5.
- ≥ 2 severe exacerbations or having received ≥ 2 cycles of oral glucocorticoids (≥ 3 days each) in the preceding year.
- ≥ 1 hospitalization for a severe exacerbation in the previous year.
- Chronic airflow limitation (FEV_1/FVC < 70% or post-bronchodilator FEV_1 < 80%), which is reversed following a course of oral glucocorticoids (30 mg/day for 2 weeks).

SUA has two peculiarities that should be emphasized:

- There is no consensus regarding terminology. Many terms have been proposed over the last two decades, such as difficult asthma, difficult-to-control asthma, refractory asthma, problematic asthma, or difficult-to-treat asthma. The lack of semantic agreement causes considerable conceptual confusion.
- Since evidence is lacking (or rather scarce and of low quality), most recommendations are based on expert opinions, those included in GEMA[4.0] not being an exception.

The term SUA encompasses two subtypes (figure 8.1):

D
- Difficult-to-treat asthma. In this case (despite treatment with various drugs and at high doses), SUA is due to causes unrelated to the disease itself, mainly low adherence to treatment, presence of comorbidities, aggravating factors, and exposure to triggers[496-499].

D
- Refractory asthma. This subtype comprises the remaining cases of SUA in which, after excluding the external causes of difficult-to-control asthma, the disease remains uncontrolled due to partial response to treatment[496].

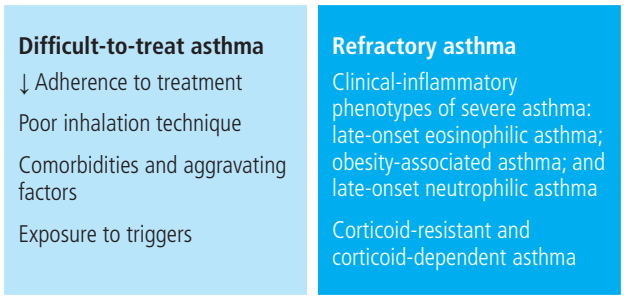

Figure 8.1. Terminology for and classification of severe uncontrolled asthma.

C A study carried out in Spain showed the prevalence of SUA to be 3.9% of the asthmatic population[500].

D Refractory SUA involves some degree of lack of sensitivity to glucocorticoid treatment, with various degrees of corticosteroid-dependence or corticosteroid-resistance[499,501].

However, corticosteroid-resistant asthma is the variety of SUA with FEV_1 values ≤ 75% that does not significantly improve (≤ 15%) following treatment with oral prednisone (40 mg/day for 2 weeks), whereas corticosteroid-dependent SUA requires continuous treatment with systemic glucocorticoids for control to be achieved[502-504].

8.2. Severe asthma phenotypes

B Severe asthma is a heterogeneous syndrome with numerous clinical forms. During the last decade, it has been subject to extensive and increasing research efforts aimed at characterizing certain profiles or phenotypes, amenable to specific treatment[63,505-509].

D Defining asthma phenotypes in patients with SUA (contrary to what occurs in less serious forms of the disease) is currently considered part of the diagnostic or evaluation actions to be carried out in these patients because it may lead to differential treatment modalities[496].

C Studies based on statistical analyses of cases clustered according to natural history, pathobiology, clinical features, pulmonary function tests, and response to treatment have identified different phenotypes. The four phenotypes most consistently observed in studies of severe asthma in adulthood are shown in table 8.1[53,510,511].

Table 8.1. Clinical, biological and therapeutic characteristics of phenotypes in severe adult asthma

	Clinical features/ pulmonary function	Pathogenic biomarkers	Treatment
Allergic asthma	Allergic symptoms	Specific IgE Th2 cytokines Periostin Sputum eosinophils and neutrophils	Glucocorticoids Omalizumab Anti-IL-13
Eosinophilic asthma	Sinusitis Less incidence of allergy Aspirin-exacerbated respiratory disease	Corticosteroid-resistant IL-5 Cysteinyl-leukotrienes Blood and sputum eosinophils	LTRA Mepolizumab Other anti-IL-5 and anti-IL-4
Asthma and obesity	More common in women Many symptoms Less bronchial hyperresponsiveness	Oxidative stress	Weight loss Antioxidants
Neutrophilic asthma	Lower FEV_1 Higher degree of air trapping	Sputum neutrophils Th17 activation IL-8	Azithromycin Anti-IL-17?

8.2.1. Allergic asthma

C

Allergic asthma accounts for 40-50% of severe cases of asthma. It is atopic in origin and is mediated by the activation of type-2 *helper* T lymphocytes (Th2), the production of interleukin (IL) 4, IL-5, and IL-13 and an isotype shift within B lymphocytes towards IgE production[53]. **Allergic bronchopulmonary aspergillosis** is a particularly severe variety of allergic asthma that shows a pure eosinophilic or mixed (eosinophilia and neutrophilia) inflammatory pattern in sputum. Periostin (an IL-13-induced cell matrix protein), which can be measured in blood and bronchial secretions, and the fractional exhaled nitric oxide (FE_{NO}) are good biomarkers of the "increased" Th2 variant[512].

8.2.2. Late-onset eosinophilic asthma

C

It accounts for more than 25% of severe asthma cases and is characterized by the presence of eosinophils in bronchial biopsies and sputum despite treatment with glucocorticoids at high doses. Chronic rhinosinusitis and nasal polyps may also occur. A subset of patients develop intolerance to NSAIDs and, therefore, aspirin-exacerbated respiratory disease (AERD). Late-onset eosinophilic asthma is associated with a lower prevalence of atopy, but IgE and FE_{NO} may be increased. Alterations of the arachidonic acid metabolism and, occasionally, Th2 inflammation are involved in the pathogenesis of this form of asthma. A high production of IL-5 may explain the eosinophilic inflammation in the absence of the traditional allergy-mediated Th2 mechanism[53,513].

8.2.3. Obesity-associated asthma

D

This form of asthma is more commonly observed in women with a high body mass index. Patients present with frequent exacerbations and multiple symptoms but pulmonary function being scarcely affected. Numerous pathogenic mechanisms have been proposed, including immunoinflamatory, hormonal and mechanical factors, vitamin D deficiency and the presence of other comorbidities, such as sleep apnea-hypopnea syndrome (SAHS) or gastroesophageal reflux[53]. Low-grade eosinophilia, reduced FE_{NO} levels and poor response to glucocorticoids are common findings[511].

D

Table 8.2. Diseases mimicking severe uncontrolled asthma by alphabetical order

Acquired tracheobronchomalacia (idiopathic, relapsing polychondritis)
Bronchiectasis
Carcinoid syndrome
Cardiovascular diseases: hear failure, pulmonary thromboembolism
Churg-Strauss syndrome and other pulmonary vasculitis
COPD: chronic bronchitis and emphysema
Drug-induced chronic cough: ACE inhibitors, non-selective β-blockers, etc.
Eosinophilic bronchitis
Eosinophilic lung infiltrates
Gastroesophageal reflux
Hereditary diseases: cystic fibrosis, primary ciliary dyskinesia, α-1 antitrypsin deficiency
Hypersensitivity pneumonitis
Lung infections
Middle airway diseases: intra or extraluminal mechanical airway obstruction (larynx, trachea or main bronchi), vocal cord dysfunction, neoplasias, granulomas, inhaled foreign body, vascular clamp, etc.
Multiple chemical sensitivity syndrome
Psychogenic hyperventilation
Rheumatic diseases: rheumatoid arthritis with or without dry eye syndrome
Upper airway diseases: post-nasal drip

8.2.4. Late-onset neutrophilic asthma

C It is associated with an increased level of the matrix metalloproteinase 9 (MMP-9) in the bronchoalveolar lavage fluid and may be accompanied by a chronic airflow limitation with considerable air trapping[53]. The patient may have a history of smoking and treatment with glucocorticoids is of limited efficicacy[514].

8.3 Diagnosis and evaluation

C When SUA is suspected, a systematic evaluation in specialized asthma centers or units is recommended following a multidisciplinary approach and a diagnostic algorithm based on the following sequential three steps[496,510,515,516]:

8.3.1 Confirmation of asthma diagnosis

C It has been estimated that between 12 and 30% of patients with suspected SUA[516,517] do not have asthma. To confirm the diagnosis of SUA, the more frequently used investigations for an objective diagnosis of asthma, particularly those aimed at demonstrating the variabil ity of expiratory flows (see section 2.2) should be indicated. If diagnosis cannot be confirmed, diseases mimicking asthma should be excluded (table 8.2) by the rational use of work-up studies summarized in table 8.3[496-498,510,518].

D

8.3.2 Identification of external factors

C These are intended to exclude a difficult-to-treat SUA due to circumstances not related to the asthmatic disease. They are grouped into:

- ***Patient-related factors.*** Poor treatment adherence is found in 32-56% of these patients[499,515,516,519]. For this reason, therapeutic adherence and appropriateness of the patient's inhalation technique should be evaluated (excluding involuntary noncompliance) preferably in an objective way by using validated questionnaires and pharmacy drug dispensing data (see section 3.4.4).

C
- ***Comorbidities and aggravating factors.*** When occurring concomitantly with asthma, a number of diseases or pathological processes may contribute to poor disease control. The most frequent conditions are shown in table 8.4[63,520-532].
- ***Exacerbation triggers.*** These include exposure to allergens, particularly molds[533,534], pollens, animal dander, house mites, cockroaches[534-538], as well as occupational agents[539-543], infectious pathogens, such as influenza virus[544-546], contaminants and toxic substances[547-551], drugs, such as acetylsalicylic acid and NSAID[552].

C

Table 8.3. Supplementary tests recommended for the identification of other potential diseases mimicking severe uncontrolled asthma, categorized from lower to higher invasiveness

Blood tests: complete blood count and eosinophil count; immunoglobulins and immunoglobulin subclasses, anti-neutrophil cytoplasmic antibodies (ANCA), total IgE, Aspergillus-specific IgE and IgG, α-1 antitrypsin, thyroid hormones. Anti-Ro, anti-La, rheumatoid factor (RF). D-dimer. Genetic study of cystic fibrosis
Plain chest X-rays
Electrocardiogram
Late skin reaction to Aspergillus
Lung volumes, CO transfer factor and arterial blood gases
Sweat test
Paranasal sinus CT scan
High-resolution thoracic CT scan and expiratory slides
Inflammatory cell count in induced sputum
Psychological evaluation
Bronchial fibroscopy with transbronchial biopsy
24-h esophageal pH monitoring
Laryngoscopy during an exacerbation
Biopsy by thoracotomy

8.3.3. Characterization of the severe asthma phenotype

C On the basis of clinical characteristics (age at onset, allergic symptoms, upper airway involvement, BMI, presence of AERD, *prick-test*), pulmonary function tests (spirometry with bronchodilator and bronchoconstrictor tests) and biomarkers (blood eosinophils, IgE and periostin, eosinophils and neutrophils in induced sputum, FE_{NO}), patients will be classified according phenotypes of severe asthma described in section 8.2 (table 8.1)[146,484,553-562].

D The minimum follow-up period by a specialist or in a specialized unit to accept the diagnosis of SUA will be 6 months[498].

8.4. Treatment

8.4.1 General measures

A
- ***Asthma education.*** Asthma education activities are not different from that normally recommended for the remaining asthma population (see section 3.4). However, approaches such as maximizing avoidance measures,

Table 8.4. Comorbidities and aggravating factors related to poor control of severe asthma

Vocal cord dysfunction	Gastroesophageal reflux
Psychological factors: anxiety, depression	Rhinosinusitis/nasal polyposis
Drugs: NSAIDs, non-selective β-blockers, ACE inhibitors	Hyperventilation syndrome
Fibromyalgia	Sleep apnea-hypopnea syndrome (SAHS)
Hyperthyroidism	Smoking
Menstruation/menopause	Tracheomalacia and other tracheal diseases
Obesity	

smoking cessation and avoidance of NSAIDs in patients with AERD should be especially implemented. Similarly, action plans based on symptoms and measurement of peak expiratory flow (PEF) should be set in place. Furthermore, patients must be trained on the proper use of inhaler devices and PEF meters[272,275].

- ***Background pharmacological treatment.*** According to the inclusion criteria defining SUA, these patients should be receiving maintenance therapy with a combination of IGC/LABA at high doses corresponding to step 5 of asthma treatment. Since disease control is usually insufficient, at least one of the following drugs will be added: an antileukotriene, tiotropium, or theophylline[126,179,202,204,489,563-565] (see section 3.2.1).

Although extrafine IGC has shown to be effective as they act on the peripheral airways, no evidence, however, is yet available of a potentially greater efficacy of this formulation over IGC of respirable size particles in patients with SUA[496,566,567].

- ***Treatment of comorbidities and side effects of glucocorticoids.*** If either an associated comorbid condition or an aggravating factor has been confirmed (see list in table 8.4), the appropriate therapeutic measures should be adopted. In corticosteroid-dependent patients, the following factors will be preventively assessed: bone and calcium metabolism (osteoporosis), blood glucose (diabetes), mental health (anxiety-depression) and vision (cataracts), all of which must be properly managed[568].

8.4.2. Treatment according to severe asthma phenotypes

The preferred therapies for each of the four severe asthma phenotypes described above are as follows (table 8.1):

- ***Allergic asthma.*** Numerous studies have consistently demonstrated the ability of the anti-IgE monoclonal antibody, omalizumab, to reduce the rate of exacerbations, the intensity of symptoms and the use of inhaled glucocorticoids, as well as to improve quality of life. This agent is indicated as an additional treatment for patients of 6 years of age, presenting with allergic SUA, sensitization to perennial allergens, frequent exacerbations and impaired lung function despite receiving a maintenance treatment adjusted to their degree of severity[553,569].

Future anti-Th2 agents, such as the anti-IL-13 antibodies (**lebrikizumab y tralokinumab**), have shown efficacy in preliminary studies of patients with high blood levels of periostin[556,570,571].

Patients with allergic asthma are good responders to oral *glucocorticoids*, which, together with antifungal agents, are the first treatment choice for **allergic bronchopulmonary aspergillosis** (in addition to the above described standard maintenance therapy of SUA)[572].

- ***Late-onset eosinophilic asthma.*** Patients with AERD (intolerance to NSAIDs), a condition in which leukotriene production is increased, could be candidates for treatment with LTRA (**montelukast**) if they have not received them yet. However, the available evidence supporting this recommendation is limited[573].

Although these agents are not yet on the market, favorable results with a significant reduction of exacerbations, have been reported in different of studies assessing the efficacy of anti-IL-5 (such as **mepolizumab**)[145,558,560] and anti-IL-4/IL-13 monoclonal antibodies (**dupilumab**)[484].

- ***Obesity-associated asthma.*** Weight loss (whether surgical or not) has been found to improve symptoms, control of asthma, quality of life and bronchial hyperresponsiveness[532,574].
- ***Late-onset neutrophilic asthma.*** The efficacy of macrolides for asthma maintenance treatment, during prolonged periods of time (3 months) is controversial. However, one study revealed a reduction of exacerbations in a group of patients with non-eosinophilic SUA after prolonged administration of *azithromycin*[211,513].

8.4.3. Other therapies

- ***Systemic glucocorticoids.*** Unfortunately, treatment failure in some of these patients leads to long-term prescription of oral glucocorticoids (corticosteroid-dependent asthma). In these cases, in which control of asthma cannot be achieved, the treatment goal should be to attain the best possible results with minimal side effects (**the degree of control that can be assumed**)[505]. When used in long-term regimens, oral glucocorticoids can be prescribed every other day.
  Some studies with low design robustness and carried out in small samples reported that intramuscular depot *triamcinolone* (a fluorinated GC) in patients with corticosteroid-dependent asthma resulted in a significant reduction of exacerbations, an increased pulmonary function and fewer side effects as compared to oral glucocorticoids[575,576].
- ***Endobronchial thermoplasty.*** It is a bronchoscopic procedure that reduces the bronchial smooth muscle layer by applying radiofrequency heat. Results from studies of patients with moderate-to-severe asthma showed that this therapy results in significantly improved quality of life, increased disease control and fewer exacerbations. These effects persist for several years after the application, with no long- or medium-term side effects[577-583].
  While further evidence is needed to identify the ideal candidate for endobronchial thermoplasty, the procedure is currently advocated for use in patients with SUA, chronic airflow limitation ($FEV_1 > 50\%$ and $< 80\%$) and no bronchial hypersecretion. Furthermore, the procedure should be applied by well-trained endoscopists and in centers with experience in the care of patients with SUA.
- ***Immunomodulators.*** The use of *methotrexate and cyclosporine* is discouraged since they provide little therapeutic benefit and are frequently associated with serious side effects[584].

8.5 Differential features of severe asthma in childhood

8.5.1 Definition

Age has a clear influence on the clinical presentation of severe uncontrolled asthma and the response to treatment,

D which may vary substantially from infants to adolescents585. During the early years of life, children with asthma often experience serious viral-associated exacerbations, often resulting in hospital admission, but with few or no symptoms between episodes. However, in older children, the persistence of clinical symptoms and intolerance to exercise are more frequent, as occurs in adults.

D In children experiencing acute episodes, with or without symptoms between episodes, a diagnosis of SUA is made when the following events are seen despite a correct treatment with IGC at high doses: 1) at least one admission to an intensive care unit; 2) at least two hospitalizations requiring intravenous therapy; or 3) at least two cycles of oral glucocorticoids within the previous year[586].

The definition for older children and adolescents coincides with that for adults[497].

8.5.2 Initial assessment

C Many children initially labelled as having severe asthma would no longer be considered as such after a careful evaluation[586-587] and up to 50% of the referrals to specialized clinics because of persistent symptoms or poor control are due to an inadequate management of the disease[588].

C
- ***Diagnostic confirmation:*** The younger the child, the greater the likelihood of having other diseases mimicking asthma (table 8.5). It has been demonstrated that approximately 50% of preschoolers with poorly controlled asthma have an associated airway malacia[589,590]. Pulmonary function tests, including bronchoprovocation, may support the diagnosis of severe asthma but the diagnosis is not excluded by normal spirometric results[92].

Table 8.5. Diseases mimicking severe asthma in children

Bronchiolitis, bronchiolitis obliterans
Persistent bacterial bronchitis
Recurrent aspiration, gastroesophageal reflux, swallowing disorders
Prematurity and related diseases (bronchopulmonary dysplasia)
Cystic fibrosis
Endobronchial foreign body
Congenital or acquired immunodeficiencies
Primary ciliary dyskinesia
Obstruction/compression of central airway
Congenital malformations, including vascular rings
Tracheobronchomalacia
Carcinoid tumor and other
Mediastinal mass/lymphoid nodule
Congenital heart disease
Interstitial lung disease
Connective tissue diseases
Vocal cord dysfunction

C
- ***Comorbidities.*** Concomitant diseases associated with worse asthma control should be evaluated and adequately treated (table 8.4).

D
- ***Associated factors.*** These situations although avoidable, have a decisive influence on the control and clinical course of the disease. They should be carefully evaluated and prevented: lack of treatment adherence[591], inappropriate inhalation technique[592], exposure to allergens[545], exposure to tobacco smoke[593] and psychosocial factors[594] that can be particularly relevant to the management of adolescents with asthma.
- ***Phenotypes of severe childhood asthma:*** Allergic asthma is the prevailing phenotype in childhood. A neutrophilic inflammation is often found in the bronchoalveolar fluid of preschool children, frequently associated with persistent bacterial bronchitis[590]. The obesity-associated asthma phenotype emerges as early as in adolescence, while eosinophilic asthma phenotype is less well-defined in childhood.

D The evaluation of severe asthma in children, which should be made in a specialized setting, should include measurement of pulmonary function with bronchodilator test, inflammation markers (FE_{NO}, induced sputum, bronchoalveolar lavage), assessment of atopy (*prick test and/or RAST*), fiberoptic bronchoscopy in selected cases and imaging studies (high-resolution computerized tomography), mainly performed to exclude other conditions or comorbidities.

8.5.3 Treatment

D Little good-quality evidence is available on the best therapeutic options for children who suffer from SUA despite receiving an appropriate treatment according to the severity of their disease (IGCs at high doses plus LABAs)[595]. Available regimens include a dose increase of IGC above the recommended doses, oral glucocorticoids, anti-IgE monoclonal antibodies, treatment of distal airway inflammation, theophylline at low doses, intramuscular triamcinolone, and other drugs not indicated for asthma but the use of which could be beneficial, such as macrolides, cyclosporine, methotrexate, or intravenous immunoglobulins. The new biological treatments, although promising, have not yet been sufficiently studied in children[596].

C Although few children benefit from doses of fluticasone higher than 500 µg/day, in refractory cases, a challenge with high doses up to 2.000 µg/day could be tried especially in an attempt to reduce the doses of oral glucocorticoids. The previous standard dose schedule should be reinstated as soon as possible. It should be kept in mind that doses ≥500 µg/day of fluticasone have been associated with important side effects in some children[597].

D No data are available on the effect of oral glucocorticoids in asthma patients treated with IGCs at high doses, plus LABA, plus montelukast, although this is the usually recommended option. A therapeutic trial with prednisone 0.5 mg/kg/day can be used, with further dose reduction as soon as possible. Side effects must be monitored.

A Anti-IgE monoclonal antibodies (omalizumab) are useful for the management of children over 6 years of age with atopic asthma not adequately controlled on standard therapy. Omalizumab reduces the number of exacerbations, the need for rescue medication and improves quality of life in these patients[210,598,599].

C Theophylline given at low doses has some immunomodulating properties, making this drug an attractive alternative for its use in association with an IGC; although extensively used in the past, this option has not been sufficiently studied in children[574]. It is acceptable to try this possibility in patients who remain uncontrolled with other treatments.

D Intramuscular depot triamcinolone may be useful in children with refractory asthma[600] especially in non-adherent patients to oral glucocorticoid treatment.

The immunomodulating effect and the antibacterial activity of macrolides have been the basis for the proposal of these antimicrobials in the treatment of severe neutrophilic asthma. However, in the few studies performed so far, macrolides does not seem to be effective[601]. Probably, the clinical effect observed in preschool children with persistent wheezing is likely to be partially related to antibacterial activity of these drugs.

D In highly selected children with severe asthma failing to respond to oral glucocorticoids, a test treatment with cyclosporine, methotrexate or intravenous immunoglobulins may be considered, but the level of evidence is very low.

D In infants and preschool children the level of evidence of the studies is even lower. When symptoms remain uncontrolled despite IGCs at high doses combined with montelukast, either low doses of theophylline or oral glucocorticoids may be added for a few weeks, although the best therapeutic option has not yet been established. The need to stepped-up treatment should be assessed at each visit, trying to maintain it during the shortest time possible. Also, ensuring a proper inhalation technique is especially relevant at his age.

D Although no sufficient data are available regarding safety and efficacy of LABAs associated with IGC under the age of 4 years, the off-label use of this combination might be considered in selected cases. Other drugs, such as macrolides or omalizumab, have not been investigated in children within this age range. Antibiotics are useful for the treatment of persistent bacterial bronchitis that may confuse or mimic the diagnosis, particularly in preschool children[602,603].

C

RECOMMENDATIONS

8.1.	Severe uncontrolled asthma is defined as asthma that remains poorly controlled despite having been treated with a combination of ICG/LABA at high doses in the previous year, or with oral glucocorticoids for at least 6 months.	R2
8.2.	Severe asthma is a heterogeneous syndrome encompassing multiple clinical variants or phenotypes. Since its identification may need different treatments, it is recommended that phenotype characterization be included in the diagnostic evaluation of severe uncontrolled asthma.	R2
8.3.	Severe uncontrolled asthma in adults includes at least four phenotypes: allergic asthma, late-onset eosinophilic asthma, obesity-associated asthma and late-onset neutrophilic asthma.	R2
8.4.	Diagnostic evaluation of severe uncontrolled asthma should preferably be undertaken in specialized centers or units, and using a stepwise decision algorithm.	R2
8.5.	Protocolized diagnostic evaluation of severe uncontrolled asthma is based on three key actions: 1) to confirm the diagnosis of asthma objectively; 2) to identify those factors that are external to asthmatic disease (treatment adherence, patient's inhalation technique, comorbidities or aggravating factors, exacerbation triggers); and 3) to establish the phenotype of severe asthma.	R2
8.6.	The general treatment of severe uncontrolled asthma includes the prescription of drugs recommended for steps 5 and 6 (combination of IGC/LABA at high doses), plus at least a third drug (anti-leukotriene, tiotropium or theophylline), the implementation of an education program on asthma, the management of comorbidities/ aggravating factors, and the prevention/treatment of side effects of glucocorticoids.	R2
8.7.	The specific management of severe uncontrolled asthma relies on the administration of some drugs or treatments reserved for patients with the following phenotypes of severe asthma:	R1
	• Allergic asthma: omalizumab and glucocorticoids.	
	• Late-onset eosinophilic asthma: LTRA for patients with aspirin-exacerbated respiratory disease (AERD).	R2
	• Obesity-associated asthma associated: weight loss, bariatric surgery.	R2
	• Late-onset neutrophilic asthma: azithromycin may be considered.	R2
8.8.	In patients with corticosteroid-dependent severe uncontrolled asthma a therapeutic trial with intramuscular depot triamcinolone is recommended.	R2
8.9.	In patients with severe uncontrolled asthma and chronic airflow limitation (FEV_1 > 50% and < 80%), endobronchial thermoplasty may be applied by trained endoscopists in centers experienced in the management of patients with severe uncontrolled asthma.	R2
8.10.	Among children with severe uncontrolled asthma, particularly the youngest ones, the first step is to confirm the diagnosis of asthma.	R1
8.11.	Evaluating treatment adherence and inhalation technique is a priority step, as it constitutes the leading cause of loss of control in childhood asthma. At the same time, environmental exposure to allergens and/or environmental pollution should be investigated, along with psychosocial problems.	
8.12.	In children with severe uncontrolled asthma, the presence of concomitant diseases (comorbidities) should be evaluated.	R1
8.13.	In children with severe uncontrolled asthma despite receiving the appropriate medication, a therapeutic trial with IGC at doses higher than those recommended (up to 2000 µg/day of fluticasone) is advisable. Doses should be reduced as soon as possible.	R2
8.14.	The prolonged use of oral glucocorticoids may improve asthma control, although side effects should be carefully assessed.	R2
8.15.	Anti-IgE monoclonal antibodies (omalizumab) may be useful for the treatment of severe atopic asthma in children over 6 years of age.	R1
8.16.	Antibiotic treatment is useful in children with suspected persistent bacterial bronchitis.	R1
8.17.	In highly selected children with severe uncontrolled asthma who are unresponsive or intolerant to oral glucocorticoids, a therapeutic trial with azithromycin, cyclosporine, methotrexate or intravenous immunoglobulins may be considered, although the level of evidence for this strategy is very low.	R2