

7. Severe uncontrolled asthma

7.1 Concepts and definitions

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; see section 2.5). Severe asthma includes both controlled and uncontrolled asthma patients¹.

C Severe asthma is associated with a higher consumption of economic resources than moderate and mild asthma²⁻⁴.

S Severe uncontrolled asthma (SUA) has received multiple and varied terms and there is no consistent agreement for its terminology.

D SUA is defined as the asthma disease that remains poorly controlled despite treatment with a combination of inhaled glucocorticoids/long-acting β_2 -adrenergic agonists (IGC/LABA), at high doses in the previous year, or with oral glucocorticoids for at least 6 months during the same period⁵. Lack of control will be identified by any of the following characteristics (Table 7.1):

- D**
- Asthma Control Test (ACT) < 20 or Asthma Control Questionnaire (ACQ) > 1.5.
 - ≥ 2 severe exacerbations or having being received ≥ 2 courses of oral glucocorticoids (≥ 3 days each) in the previous year.
 - ≥ 1 hospitalization for a severe exacerbation episode in the previous year.

Table 7.1. Severe uncontrolled asthma: definition and control

It is defined as the asthma disease that persists poorly controlled despite treatment with a combination of IGC/LABA at high doses in the previous year, or oral glucocorticoids for at least 6 months during the same period.

The lack of control is shown by:

- ACT < 20 or ACQ > 1.5.
- ≥ 2 severe exacerbations or having being received ≥ 2 courses of oral glucocorticoids (≥ 3 days each) in the previous year.
- ≥ 1 hospitalization for a severe exacerbation episode in the previous year.
- Chronic airflow limitation (FEV_1/FVC ratio < 0.7 or FEV_1 < 80% predicted) after the use of an adequate treatment (as long as the better FEV_1 will be higher than 80%).

- Chronic airflow limitation (forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] ratio < 0.7 or FEV_1 < 80% predicted) after the use of an adequate treatment (as long as the better FEV_1 will be higher than 80%).

It is important to exclude external factors that may contribute to poor asthma control before defining SUA (section 7.2.2)⁵⁻⁹.

Some studies have shown a prevalence of SUA between 3% and 4% among patients with asthma^{10,11}.

SUA can be corticosteroid-dependent or corticosteroid-resistant to a higher or lesser extent¹²⁻¹⁴.

Corticosteroid-dependent SUA is defined in a patient that requires continuous treatment with oral or parenteral corticosteroids for disease control, with glucocorticoid insensitivity, and $FEV_1 \leq 75\%$ that does not improve significantly ($\leq 15\%$) after treatment with oral prednisone, 40 mg/day for 2 weeks^{15,16}.

7.2 Diagnosis and evaluation

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 sequential steps^{5,17-10} (Figure 7.1).

The use of this multidimensional approach has shown good clinical results and to be cost-effective²¹⁻²³.

7.2.1 Diagnostic confirmation of asthma

It has been estimated that between 12% and 30% of patients with suspected SUA do not have asthma^{5,24-26}.

It should be confirmed that the diagnosis of asthma has been made correctly and, in case of doubt, studies aimed to demonstrate objectively the presence of airflow obstruction, variability and/or bronchial hyperresponsiveness (see section 2.2) should be performed. If diagnosis cannot be confirmed, diseases mimicking asthma should be excluded by the rational and progressive use of work-up studies summarized in Table 7.2.

7.2.2 Identification of external factors

It is necessary to identify and evaluate some factors unrelated to the disease, the presence of which can contribute

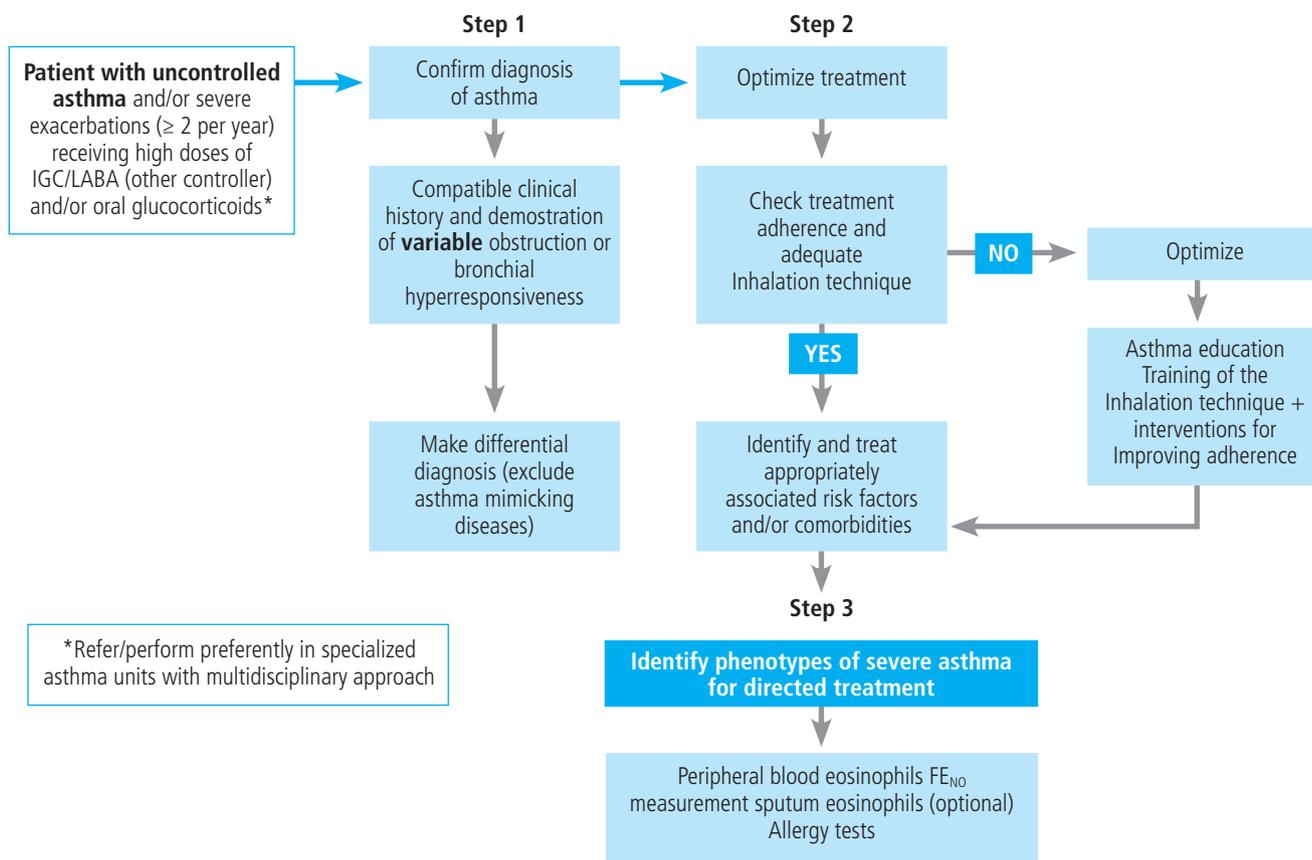


Figure 7.1. Diagnostic algorithm based on sequential step decision for SUA.

Table 7.2. Differential diagnosis: diseases mimicking SUA and their corresponding diagnostic tests

Differential diagnosis	Diagnostic tests
<ul style="list-style-type: none"> – Upper respiratory tract organic disease – Dynamic collapse of airways – Bronchial obstruction 	<ul style="list-style-type: none"> – Spirometry with inspiratory loop – Inspiratory/expiratory computed tomography scans (CT) – Fiberoptic bronchoscopy
<ul style="list-style-type: none"> – Inducible laryngeal obstruction (ILO) 	<ul style="list-style-type: none"> – Laryngoscopy/videostroboscopy during exacerbation or after challenge with methacholine or after ergometry
<ul style="list-style-type: none"> – Chronic obstructive pulmonary disease (emphysema) 	<ul style="list-style-type: none"> – Chest CT – Plethysmography and CO diffusing capacity
<ul style="list-style-type: none"> – Bronchiolitis obliterans 	<ul style="list-style-type: none"> – Inspiratory/expiratory chest CT – Plethysmography/trapped air – Transbronchial/pulmonary biopsy
<ul style="list-style-type: none"> – Functional dyspnea/hyperventilation syndrome 	<ul style="list-style-type: none"> – Hyperventilation perception questionnaire (Nijmegen) – Psychological evaluation
<ul style="list-style-type: none"> – Left heart failure 	<ul style="list-style-type: none"> – Chest CT – Electrocardiogram/echocardiogram
<ul style="list-style-type: none"> – Bronchiectasis – Cystic fibrosis – Allergic bronchopulmonary aspergillosis (ABPA) 	<ul style="list-style-type: none"> – Chest CT – Sweat test/genetic study – Total IgE and Aspergillus specific IgE /precipitins
<ul style="list-style-type: none"> – Eosinophilic granulomatosis with polyangiitis (EGPA) – Pulmonary eosinophilia 	<ul style="list-style-type: none"> – pANCA/biopsy(ies) of organ(s) affected – Fiberoptic bronchoscopy (with bronchoalveolar lavage)

pANCA: perinuclear anti-neutrophil cytoplasmic antibodies.

to a poor control of asthma. These factors can be grouped into the following categories:

– **Factors directly related to the patient: treatment adherence and inhalation technique.** Up to 50% to 80% of cases of SUA are caused by inadequate adherence or by a deficient inhalation technique^{11,24,27}.

Therefore, adherence should always be evaluated (preferably using validated questionnaires or information on dispensing prescriptions in the the community pharmacy) and the inhalation technique (direct observation) (see section 3.4).

– **Factors related to comorbidities and aggravating conditions.** Different diseases or processes when present concomitantly with asthma can contribute to an insufficient control of the disease. It has been shown that 92% of patients with SUA suffer from at least one of these conditions, which in turn are more prevalent than in patients without SUA⁹.

Table 7.3 summarizes the most commonly cited comorbidities and their corresponding tests for evaluation, diagnostic confirmation and treatment approach^{17,19,20,28,29}.

– **Factors related to triggers of exacerbations.** It is necessary to identify whether exposure to triggers of exacerbations are present (see Table 1.3), particularly active and passive smoking, e-cigarettes, cannabis inhalation, allergen exposure (mites, pollens, fungi, dander, cockroaches, etc.), indoor and outdoor air

contamination, occupational agents, molds and harmful chemical products, drugs such as non-cardioselective β_2 blockers, non-steroidal anti-inflammatory drugs (NSAID) or angiotensin-converting enzyme (ACE) inhibitors^{17,19}.

Moreover, lack of response due to SABA abuse (by downregulation of β_2 receptors and increase of bronchial hyperresponsiveness [BHR]) has been reported^{30,31}.

7.2.3. Determination of the phenotype

The classification into phenotypes aims to identify the particular patient who is candidate to receive a specific treatment^{18,32} (see section 7.3). At present, there are no specific biomarkers for each phenotype/endotype³³.

The minimum follow-up period by a specialist or a specialized asthma unit to accept the diagnosis of SUA will be 6 months^{7,17,20}.

7.3 Phenotypes of uncontrolled severe asthma

Severe asthma is a heterogeneous syndrome that encompasses multiple clinical forms. Extensive research during the last two decades resulted in a better knowledge and definition of SUA phenotypes³⁴⁻⁴². Phenotype is defined

Table 7.3. Common comorbidities and aggravating factors of asma with their corresponding diagnostic tests and treatment

Comorbidity	Diagnostic tests	Treatment
Sinonasal disease	Rhinoscopy/nasal endoscopy Sinus imaging studies (CT/MR)	Intranasal glucocorticoids Nasal lavages/antileukotrienes Endonasal surgery
Gastroesophageal reflux	pH-metry/esophageal manometry Treatment test with PPI Upper digestive endoscopy	Hygienic-dietetic counselling Proton pump inhibitors Surgical repair
Obesity	BMI	Weight loss Bariatric surgery
Sleep apnea syndrome (SAS)	Polysomnography	CPAP Weight loss if necessary
Psychopathology (anxiety, depression)	Psychologist/psychiatrist evaluation	Psychotherapy/specific treatment
Fibromyalgia	Rheumatological evaluation	
Functional dyspnea	Specific questionnaires (Nijmegen questionnaire)	Psychotherapy Respiratory re-education
Inducible laryngeal obstruction (ILO)	Laryngoscopy in exacerbation or methacholine/exercise challenge	Logophoniatic rehabilitation Treatment of comorbidities: reflux
Drugs: NSAID, non-selective β -blockers, ACE inhibitors	Clinical history	Substitution
Tobacco and other inhalation toxics	Questionng	Cessation/quit

NSAID: non-steroidal anti-inflammatory; ACE: angiotensin-converting enzyme, CT: computed tomography; MR: magnetic resonance; PPI: proton pump inhibitors; BMI: body mass index; CPAP: continuous positive airway pressure.

B as an observable characteristic of severe asthma that can be associated with an underlying mechanism, named endotype. It is important to differentiate phenotype from comorbidities, since comorbidities coexist with SUA but their treatment is different.

D Establishing the asthma phenotype in patients with SUA constitutes part of the diagnostic or assessment action to be carried out in these patients, as it may entail differential treatment modalities and has prognostic implications^{6,43-45}.

C Studies based on statistical analyses of cases clustered according to natural history, pathobiology, clinical features (age, onset, allergy symptoms, involvement of the upper respiratory tract, body mass index [BMI], aspirin-exacerbated respiratory disease [AERD], pulmonary function, biomarkers (peripheral blood and sputum eosinophils, immunoglobulin E [IgE], fractional exhaled nitric oxide [FE_{NO}], induced sputum neutrophil count) and response to treatment have identified different phenotypes^{18,32,46-49}. Two inflammatory patterns have been recognized: T2 (present in allergic and eosinophilic asthma) and non-T2. In clinical practice, three SUA phenotypes stand out with implications in treatment decision-making:

- C** – Allergic phenotype-T2.
- C** – Eosinophilic phenotype-T2.
- C** – Non-T2 phenotype T2 (Table 7.4).

C However, both T2 phenotypes may show some degree of overlap.

7.3.1 Allergic asthma (T2)

C Allergic asthma accounts for 40-50% of severe cases of asthma, and has an atopic underlying mechanism 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. Allergic bronchopulmonary aspergillosis is a particularly severe variety of allergic asthma that shows a pure eosinophilic or mixed (eosinophilia and neutrophilia) inflammatory pattern

C 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” T2 variant^{50,53}. The diagnosis requires the demonstration of sensitization to an allergen and the triggering of symptoms with exposure to such allergen.

7.3.2 Eosinophilic asthma (T2)

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 develops AERD. Although eosinophilic asthma is associated with a lower prevalence of atopy, IgE and FE_{NO} may be increased. Alterations of the arachidonic acid metabolism 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 T2 mechanism^{54,57}.

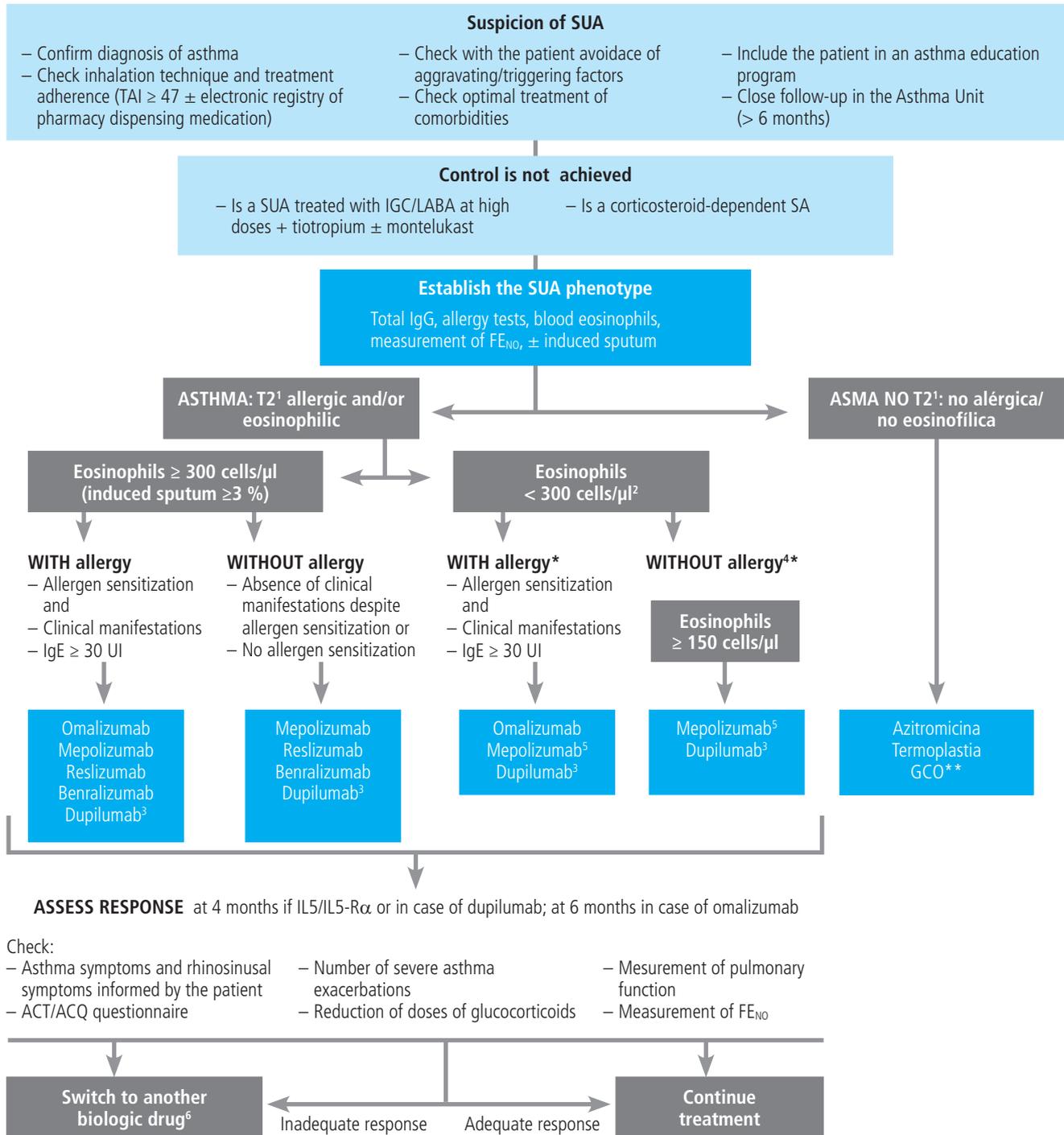
7.3.3 Non-T2 asthma

C This form of asthma occurs without eosinophilia, neither in the peripheral blood, nor in sputum. It frequently shows a paucigranulocytic profile, neutrophilia, scarce local eosinophilia, low FE_{NO} levels, and a poor response to glucocorticoids. It can be accompanied by chronic airflow limitation with important air trapping and, frequently, history of smoking is present^{58,59}. It should be taken into account that inflammatory biomarkers of type T2 phenotype (peripheral blood eosinophils, sputum eosinophils and FE_{NO}) are frequently suppressed by oral glucocorticoids. In our opinion, analysis of peripheral blood eosinophils and FE_{NO} should be repeated up to three times (e.g. when asthma worsens, before administering glucocorticoids), before assuming that asthma does not belong to the T2 phenotype.

Table 7.4. Severe asthma phenotypes

Phenotypes	Clinical characteristics	Biomarkers	Treatment
Allergic (T2)	Allergic symptoms + Allergen sensitization (Prick test and/or specific IgE)	Specific IgE Th2 cytokines Periostin Sputum eosinophils and neutrophils	Glucocorticoides Omalizumab IL-5/IL-5R α (mepolizumab, reslizumab, benralizumab) Dupilumab
Eosinophilic (T2)	Chronic rhinosinusitis/nasal polyposis AERD Corticoid-dependent or refractory to glucocorticoids	Blood and sputum eosinophils IL-5 Cysteinyl-leucotrienes	LTRA IL-5/IL-5R α (mepolizumab, reslizumab, benralizumab) Dupilumab
Non-T2	Lower FEV ₁ Greater trapping Smoking history	Neutrophils or paucigranulocytic in sputum TH17 activation IL-8	Azithromycin

IgE: immunoglobulin E; AERD: aspirin-exacerbated respiratory disease.
FEV₁: forced expiratory volumen in one second.



SUA: severe uncontrolled asthma; SA: severe asthma; OGC: oral glucocorticoids; TAI: Test of Adherence to Inhalers; IGC: inhaled glucocorticoids; LABA: long-acting bronchodilators; ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire.

¹It is usually characterized by elevated levels of eosinophils or FE_{NO} and can be accompanied by atopy (GINA). ²Consider that in patients treated with oral glucocorticoids, the level of eosinophils can be very low. ³Dupilumab has indication if eosinophils > 300/ μ l and/or FE_{NO} ≥ 50 ppb and eosinophils between 150-300 and FE_{NO} > 25 ppb. Consider at least three measurements of FE_{NO}. ⁴Compassionate use of omalizumab can be considered if IgE levels ≥ 30 U/l and eosinophils < 150 cells/ μ l. ⁵Mepolizumab indicated in patients with 150 eosinophils/ μ l if there are historical values of ≥ 300 eosinophils/ μ l. ⁶In T2 asthma, azithromycin is an option in case of no response, intolerance or allergic reactions to monoclonal antibodies; β_2 agonist: prolonged action adrenergic. *In patients with < 300 eosinophils/ μ l, benralizumab can be considered as a possible alternative treatment, particularly if on treatment with OGC. **Last therapeutic option in case of requirement by the clinical condition of the patient and at the minimum possible dose.

Figure 7.2. Treatment of SUA according to inflammatory phenotype.

D In the GINA 2019¹⁹, the possibility of type 2 refractory inflammation is considered, in the presence of any of the following findings in a patient taking IGC at high doses or daily oral glucocorticoids:

- D**
- Peripheral blood eosinophils $\geq 150/\mu\text{l}$, and/or $\text{FE}_{\text{NO}} \geq 20\text{ppb}$, and/or
 - Sputum eosinophils $\geq 2\%$, and/or
 - Asthma is clinically induced by allergens.

7.4 Treatment

7.4.1 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 and smoking cessation should be implemented, with special emphasis to confirm objectively that adherence to treatment and the inhalation technique are both correct. At present, there are different devices for remotely adherence monitoring^{60,61}.

B **Background pharmacological treatment.** According to the inclusion criteria defining SUA, in patients on maintenance therapy with a combination of IGC/LABA at high doses it is advisable to add, at least, a third controller drug, usually *tiotropium*⁶²⁻⁶⁴ (see section 3.2).

D **Treatment of comorbidities.** If either an associated comorbid condition or an aggravating factor has been

confirmed, the appropriate therapeutic measures should be adopted (Table 7.3)^{17,19,28,29}.

7.4.2 Phenotype-directed treatment

Patients with SUA according to the pathophysiological underlying mechanism (T2 or non-T2 asthma) and the presence or absence of different inflammatory markers are classified into the aforementioned phenotypes (see section 7.3).

Inflammation markers of T2 phenotype may be suppressed by treatment with oral glucocorticoids; therefore, they should be preferably measured before starting treatment with oral glucocorticoids or with the lowest possible doses, and at least on three occasions (e.g. during an exacerbation), prior to assume that a patient presents a non-T2 phenotype. In corticosteroid-dependent patients, it is important to check their historical values.

A phenotype-directed treatment algorithm is proposed in the present guideline (Figure 7.2 and Table 7.5); the different monoclonal antibodies available for treating SUA are shown together with their main characteristics.

7.4.2.1 Treatment of T2 asthma

Considering the level of peripheral blood or sputum eosinophils and the presence of relevant allergic clinical manifestations with confirmed sensitization to perennial aeroallergens, one of the available monoclonal antibodies will be selected (Figure 7.2)²⁰.

Table 7.5. Biologics approved for the treatment of SUA and their characteristics

Biologic (SUA)	Approval: TPR Spain	Mechanism of action	Evidences	Adverse events ("frequent" according to technical specifications)	Administration
Omalizumab	> 6 years with severe allergic asthma and sensitization to perennial allergens with IgE between 30-1500 UI/ml and FEV ₁ < 80 %	Binds circulating IgE preventing binding to high and low affinity receptor (FcεR1) for IgE	34% reduction of exacerbations but no improvement of symptoms, HRQoL and pulmonary function in RCT. Efficacy in nasal polyposis	Injection site reactions, headache, upper abdominal pain	75-600 mg s.c. route every 2-4 weeks according to weight and IgE. Possible administration at home
Mepolizumab	≥ 6 years with refractory eosinophilic asthma with Eos ≥ 500 or < 500 with 2 severe exacerbations or 1 hospitalization in the previous year	Blocks IL-5 from binding to the IL-5 receptor	53% reduction of severe exacerbations and improvement of HRQoL, control of symptoms and pulmonary function in RCT. Reduces doses of maintenance OGC. Efficacy in nasal polyposis	Injection site reactions, headache, pharyngitis, pyrexia, upper abdominal pain, eczema, back pain, Hypersensitivity reactions	6-11 years: 40 mg every 4 weeks ≥ 12 years: 100 mg every 4 weeks Possible administration at home
Reslizumab	> 18 years with severe eosinophilic asthma on treatment with IGC at high doses plus another controller with Eos ≥ 500 or between 400-500 and 2 severe exacerbations or 1 hospitalization in the previous year	Binds to the same domain that IL-5 receptor blocking binding of IL-5 to its receptor	54% reduction of exacerbations in patients with ≥ 400 Eos and ≥ 1 exacerbation in the past year	Increased blood CPK	3 mg/kg i.v. route every 4 weeks Day hospital
Benralizumab	> 18 years with severe eosinophilic asthma on treatment with IGC at high doses plus LABA with Eos ≥ 500 or < 500 with 2 severe exacerbations or 1 hospitalization in the previous year	Binds Fcα of IL-5 receptor inhibiting its activation. Induces direct elimination (by Ac-mediated cytotoxicity) of eosinophils and basophils involving NK cells	57% reducción of exacerbations in patients with ≥ 300 Eos and ≥ 3 exacerbations in the past year, and improvements of pulmonary function and reduction of OGC doses	Injection site reactions, pharyngitis, headache, hypersensitivity reactions	30 mg s.c. route every 8 weeks (first 3 doses at one month intervals) Possible administration at home
Dupilumab	(TPR pending in Spain) > 12 years with severe asthma with T2 markers (Eos ≥ 300 o FE _{NO} ≥ 25 ppb) or corticosteroid-dependent	Blocks subunit α of IL-4 receptor (anti-IL-4 and IL-13 effect)	50% reduction of severe exacerbations and improvement of HRQoL, control of symptoms and pulmonary function in RCT. Reduces maintenance doses of OGC Efficacy in nasal polyposis	Injection site reactions, transient blood eosinophilia (4-13%)	Initial dose 400 mg followed by: 200 mg s.c. route every 2 weeks (severe eosinophilic asthma/T2) 300 mg in corticosteroid-dependent or with associated atopic dermatitis) Possible administration at home

TPR: therapeutic positioning report; s.c.: subcutaneous; i.v.: intravenous; HRQoL: health-related quality of life; RCT: randomized controlled trial; Eos: eosinophils; FEV₁: forced expiratory volumen in one second; IGC: inhaled glucocorticoids; LABA: long-acting β₂-adrenergic agonist; IgE: immunoglobulin E; OGC: oral glucocorticoids; CPK: creatine phosphokinase; Ac: antibody.

Notes

Definitions

SUA: asthma requiring treatment with 5-6 therapeutic steps according to GEMA and presents ≥ 1 of the following criteria:

- ACT < 20 or ACQ ≥ 1.5 .
- ≥ 2 courses of oral corticoids (OGC) during ≥ 3 days in the previous year.
- ≥ 1 hospital admission due to asthma exacerbation in the previous year.
- FEV₁ ≤ 80 % predicted.

Type 2 refractory inflammation: ≥ 1 of the following criteria in a patient using inhaled glucocorticoids (IGC) at high doses or daily OGC:

- ≥ 150 eosinophils per microliter in blood.
- FE_{NO} ≥ 25 ppb/ul (American Thoracic Society Committee).
- ≥ 2 % eosinophils in sputum.
- Asthma is clinically induced by allergens.

Patients requiring maintenance treatment with oral glucocorticoids can also have an underlying type 2 inflammation. However, OGC often suppress type 2 inflammation biomarkers (blood and sputum eosinophils and FE_{NO}). Therefore, if is possible, these tests should be performed before starting a short course or maintenance treatment with OGC, or when the patient receives the lowest possible dose of OGC.

Thresholds of peripheral blood eosinophila: At least one analytical result of more than 300 Eos/ μ l in the last year. Low values of eosinophils may appear in patients recently treated or on chronic treatment with systemic glucocorticoids. In this case, it can be useful to review the patient's historical values.

Thresholds of FE_{NO}. The cutoff value is established at 25 ppb. However, it should be considered that results of FE_{NO} measurement can altered by the recent use of systemic glucocorticoids and total dose of inhaled glucocorticoids, age and current smoking (lower values in smokers). In the presence of high FE_{NO} levels, it is necessary to confirm that self-administration inhaled medication is correct (treatment adherence and inhalation technique).

Response to a biologic drug. It is defined by:

- ACT score equal or higher than 20 or a significant change as compared with baseline score (≥ 3 points).
- Absence of hospital admissions or visits to the emergency room.

- Reduction of exacerbations by more than 50%.
- Suppression of the use of oral corticosteroids or significant decrease of doses (≥ 50 %).

Choice among monoclonal antibodies

The order in which biologics appear in the scheme when they coincide for the same indication only takes into account the time since each drug has been commercialized.

In the choice of biologics should be considered: blood eosinophil count, pulmonary function, use of maintenance treatment with oral glucocorticoides, presence of comorbidities: nasal polyposis/AERD, chronic urticaria, atopic dermatitis and asthma-associated diseases (eosinophilic granulomatosis with polyangiitis, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, eosinophilic esophagitis).

- Benralizumab (higher efficacy ≥ 300 eosinophils/ μ l): patients with poor pulmonary function, polyposis, maintenance with oral glucocorticoids and difficult access to asthma unit due to far away [long distances]).
- Reslizumab efficacy ≥ 400 eosinophils/ μ l): improves pulmonary function. Not effective for reducing OGC doses. Intravenous administration.
- Mepolizumab (indication from 150 eosinophils/ μ l, but higher efficacy ≥ 500 eosinophils/ μ l): indication in patients with ≥ 150 eosinophils/ μ l if there are historical values of ≥ 300 eosinophils/ μ l. It has been shown that allows reduction or withdrawal of OGC.
- Dupilumab (higher efficacy ≥ 300 eosinophils/ μ l and FE_{NO} ≥ 50 ppb): improves pulmonary function, nasal polyposis and severe dermatitis. It has been shown that allows reduction or withdrawal of OGC and increases eosinophils values. Administration every two weeks.

To choose between drugs with potential efficacy in a given patient, criteria of posology, patient's preference and costs should be also considered.

Thermoplasty is indicated in patients neither with emphysema/bronchiectasis/atelectasis nor with important comorbidities, without treatment with anticoagulants or immunosuppressants, and who do not present recurrent infections. FEV₁ should be greater than 40% and any contraindication for fiberoptic bronchoscopy with sedation should be absent.

Anti-IgE treatment: omalizumab

Monoclonal antibody blocking IgE, with more than 15 years in clinical practice, that has shown its efficacy in randomized controlled trials (RCT) reducing severe exacerbations, intensity of symptoms, use of inhaled IGC and improvement of quality of life^{65,69}.

Omalizumab is indicated in allergic SUA with sensitization to perennial allergens in patients aged ≥ 6 years with serum total IgG values between 30-1500 IU. The dose varies according IgE levels and body weight. The administration route is subcutaneous (s.c.) every 2 or 4 weeks.

Subsequent studies carried out in daily practice conditions have shown a decrease of exacerbations, improvement of quality of life and reduction of OGC⁷⁰, independently of the baseline value of biomarkers⁷¹ or the eosinophil count⁷⁰.

In some cases, after a prolonged period of treatment (5 years), withdrawal of omalizumab is possible. Treatment discontinuation should be performed gradually, on an individual basis, in agreement with the patient and with close monitorization of the control of asthma⁷²⁻⁷⁴.

Good results with the use of omalizumab in allergic bronchopulmonary asperillosis have been reported^{75,76}, but up to the present time RCTs have not been carried out.

**Anti-IL-5/IL-5Ra treatment
Mepolizumab**

Monoclonal antibody that blocks circulating IL-5. In RCTs, the use of mepolizumab has shown to reduce exacerbations in patients with ≥ 300 eosinophils/ μl in peripheral blood during the previous year, or with $\geq 150/\mu\text{l}$ at the time of treatment but with high historical values^{77,78}. A post hoc analysis showed a greater reduction of exacerbations (70%) in the group of patients with > 500 eosinophils/ μl ⁷⁹. Also, this drug has shown to be effective in reducing the doses of OGC in patients on maintenance treatment with systemic glucocorticoids⁸⁰⁻⁸². It is indicated in patients with eosinophilic asthma of ≥ 6 years of age, at doses of 100 mg s.c. in patients aged 12 years or older, and 40 mg s.c. every 4 weeks between 6-11 years of age.

Studies at 4 years show a favorable safety profile, and stable and long-lasting effect^{83,84}.

Recent studies have shown the effectiveness of this drug in patients with partial response to omalizumab⁸⁵.

Its positive effect on symptoms, endoscopic and radiological findings in aggravating comorbidities such as chronic rhinosinusitis with nasal polyposis (CRS_{NP}) (dose of 750 mg i.v. every 4 weeks) may favor its indication in SUA with this comorbidity (see section 6.5)⁸⁶.

The Food and Drug Administration (FDA) has approved the use of the dose of 300 mg s.c. every 4 weeks in granulomatosis with polyangiitis (former Churg-Strauss vasculitis), based on a reduction of relapses and maintenance treatment with OGC⁸⁷.

Reslizumab

Monoclonal antibody against IL-5 that has shown a significant reduction of exacerbations and improvement of current control-related variables in severe asthma with ≥ 400 eosinophils/ μl ⁸⁸⁻⁹⁰. The efficacy is independent of allergic sensitization⁹¹. However, there are no studies showing a reduction of the dose of OGC. It is indicated in patients with

eosinophilic asthma > 18 years of age, at doses of 3 mg/kg i.v. every 4 weeks.

Some studies in small series of patients in which treatment with other monoclonal antibodies (*omalizumab* and *mepolizumab*) have been unsuccessful, showed improvement after the use of reslizumab^{92,93}. Studies at 2 years demonstrate a favorable safety profile⁹⁴.

Benralizumab

Monoclonal antibody binding subunit α of the IL-5 receptor preventing its activation and inducing direct elimination (by antibody-dependent cell-mediated cytotoxicity) of eosinophils and basophils involving NK cells; so that, it is known as anti-eosinophilic effect. In RCTs carried out in eosinophilic SUA, benralizumab has shown to reduce severe exacerbations, to improve pulmonary function (FEV₁) and to decrease asthma symptoms^{95,96}, particularly in patients with peripheral blood eosinophils $\geq 300 \mu\text{l}$ or $\geq 150 \mu\text{l}$ on maintenance treatment with OGC. It is indicated in patients with eosinophilic asthma aged ≥ 18 years, at doses of 30 mg s.c. every 4 weeks for the first 3 doses, and every 8 weeks thereafter.

It has also demonstrated a significant reduction of the dose of OGC⁹⁷.

In phase III trials, a number of baseline clinical factors were associated with a greater response, including the use of OGC, history of nasal polyposis, reduced pulmonary function based on FVC $< 65\%$ and frequent exacerbations^{42,98,99}.

Follow-up studies at 2 years have confirmed efficacy and safety results¹⁰⁰.

Anti-IL4/IL-13 treatment**Dupilumab**

Monoclonal antibody binding receptor α of IL-4, blocking both IL-4 and IL-13. RCTs with this drug have shown reduction of exacerbations, improvements in quality of life, control of symptoms and pulmonary function (FEV₁) in patients with moderate to severe uncontrolled asthma. These improvements were also observed in patients with peripheral blood eosinophils between 150 and 300/ μl with FE_{NO} ≥ 50 ppb¹⁰¹⁻¹⁰³. It is indicated in patients of ≥ 12 years of age with SUA with high eosinophil count and/or FE_{NO}.

Reduction of OGC has also been demonstrated in corticosteroid-dependent patients¹⁰⁴, and a better response in cases of higher values of eosinophils and FE_{NO}¹⁰⁵.

7.4.2.2 Treatment of non-T2 asthma

In patients in whom there is no evidence of the presence of T2 inflammation biomarkers, other therapeutic options should be selected.

Azithromycin

Because of their immunomodulatory effect, macrolides have been used in asthma with inconsistent results^{54,106}. In the AMAZES study¹⁰⁷, it was found that azithromycin administered at doses of 500 mg orally, 3 times a week during 48 weeks, reduced exacerbations and improved quality of life, independently of the inflammatory phenotype.

An individualized indication is recommended in SUA patients with triple therapy with non-T2 phenotype especially if they suffer from frequent exacerbation episodes^{19,29}.

Bronchial thermoplasty

This bronchoscopic procedure reduces the bronchial smooth muscle layer by heating the tissue through the deliver of radiofrequency energy¹⁰⁸.

Results of studies of bronchial thermoplasty in patients with moderate and severe asthma showed a significant improvement of the quality of life, control of symptoms and reduction of exacerbations¹⁰⁹⁻¹¹³. Efficacy regarding reduction of exacerbations is still present after 5 years of the procedure^{108,114}.

This is a therapeutic option to be considered in patient with SUA with phenotypes unsuitable for the use of monoclonal antibodies or in which monoclonal antibodies have been unsuccessful, provided that there are no contraindications to the technique and it is applied in experienced centers.

Systemic glucocorticoids

In some patients with SUA suffering from an exacerbation episode, treatment with OGC is necessary. Patients requiring OGC courses can present adverse effects, and the risk of adverse effects increases with the use of ≥ 4 courses of OGC in a year or > 30 days a year^{115,116}.

The use of OGC at the minimum necessary dose and for the shortest time possible, should be reserved as one of the last alternatives for patients in which control is not achieved with other therapeutic options¹¹⁷. In these circumstances, preventive or treatment measures for possible adverse effects will be considered.

Some studies with not very robust designs, carried out in small samples of patients showed that intramuscular triamcinolone depot (glucocorticoid with the addition of a fluorine group), in patients with corticosteroid-dependent asthma, compared to the usual OGCs, provided a significant reduction of exacerbations, an increase in pulmonary function and fewer side effects^{118,119}. However, they are free of adverse effects and the pharmacokinetic profile is unknown.

7.4.2.3 New treatments for SUA under investigation

Tezepelumab

It is a human monoclonal antibody that binds to thymic stromal lymphopoietin (TSLP), an epithelial-cell derived cytokine of the alarmins group. In a phase 2 RCT, tezepelumab administered subcutaneously at 3 different doses every 4 or 2 weeks showed a reduction in the rate of exacerbations greater than 60% as compared with placebo, independently of the baseline blood eosinophil count¹²⁰. Tezepelumab is currently being evaluated in ongoing phase 3 trials.

Fevipirant

Orally administered antagonist of the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2 or PGD2 receptor) that binds to prostaglandin D2 expressed in Th2 cells and various cell types including eosinophils, basophils, epithelial cells and ILC2. Some studies showed a reduction of eosinophils in sputum and bronchial biopsies, as well as an improvement in pulmonary function and clinical parameters¹²¹. However, the development of the drug has been discontinued as per the pharmaceutical company's decision.

Other new molecules such as antagonists of IL-33 and its receptor, DNA-binding of the GATA3 protein, etc. are currently at early stages of development¹²².

7.5 Severe uncontrolled asthma in children

7.5.1 Epidemiology. Definition

Severe asthma in childhood is more common from school age^{123,124} with a prevalence of 2-5%^{125,126}. It is associated with a high morbidity¹²⁷, costs¹²⁸ and future risk of chronic obstructive pulmonary disease (COPD)^{129,130}.

The clinical presentation and response to treatment vary from infants to adolescents^{131,132}.

In children with severe recurrent exacerbations, and in younger than 5 years of age, with or without symptoms between episodes, a diagnosis of SUA may be considered when the following events are seen despite a correct treatment with IGC at high doses:

- > 1 admission to an intensive care unit.
- > 2 hospital admissions requiring intravenous therapy, or
- > 2 courses of OGC in the previous year¹³³.

The definition for children older than 5 years of age coincides with that for adults⁵.

7.5.2 Evaluation

A cost-effective multidimensional, multidisciplinary and stepwise evaluation is necessary¹³³⁻¹³⁵ (Figure 7.3).

Up to 50% of patients present potentially avoidable factors and/or associated comorbidities responsible for difficult asthma control^{5,136}.

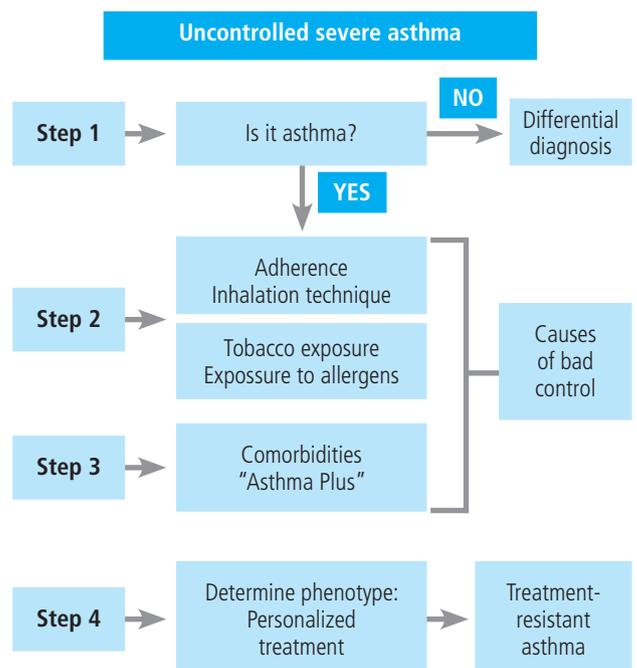


Figure 7.3. Uncontrolled severe asthma in children: stepwise assessment.

Table 7.6. Diseases mimicking severe asthma in children

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

Diagnostic confirmation

Also, up to 12-30% of patients with SUA may be diagnosed with other diseases mimicking symptoms of asthma⁵.

A detailed medical history, physical examination, and pre- and post-bronchodilation spirometry are necessary. Many children with SUA have normal lung function¹³⁷, requiring a bronchoprovocation test. In addition, other complementary tests oriented by the clinical suspicion or atypical presentation will be necessary. Also, in children with SUA under 5 years of age and in non-atopic children, the possibility of other diagnoses is high (Table 7.6).

Identify causes of poor control

To this purpose, the presence of comorbidities (Table 7.3) and/or avoidable associated factors that affect asthma control should be investigated¹³⁶. The following should be carefully evaluated: lack of adherence to treatment¹³⁸, inadequate inhalation technique¹³⁹, exposure to allergens¹⁴⁰, tobacco smoke and other inhaled toxic substances¹⁴¹ as well as the presence of psychosocial factors¹⁴².

Resistance to glucocorticoids

Assessing the response to steroids after the administration of a course of OGC or a dose of triamcinolone, can help to make therapeutic decisions, such as adding tiotropium or monoclonal antibodies instead of increasing treatment with OGC¹⁴³.

Severe asthma phenotypes in children

Assessment of phenotypes is necessary for an adequate personalized treatment. The allergic phenotype is the most common, being frequent the presence of polysensitization, association with other atopic comorbidities (allergic rhinitis, atopic dermatitis, food allergy) and a high T2 inflammatory profile (elevated IgE, peripheral blood eosinophilia and increase of FE_{NO})^{123,127}.

Non-allergic eosinophilic severe asthma is less common, and neutrophilic severe asthma is rare.

7.5.3 Treatment

Children with SUA, despite adequate management of associated factors and comorbidities, are candidates for increasing the therapeutic step.

Inhaled glucocorticoids. A few children benefit from doses of *fluticasone propionate* or equivalent higher than 500 µg/day, which in turn are related with adverse effects¹⁴⁴.

Oral glucocorticoids. No data are available on the efficacy of OGC in the maintenance treatment of children with asthma treated with IGC at high doses plus LABA and/or *montelukast*. After the availability of tiotropium and monoclonal antibodies, they have been relegated to a second step due to their adverse effects. If necessary, they should be used at the lowest dose, for the shortest period of time and monitoring their adverse effects.

Triamcinolone. Triamcinolone could be useful in children with SUA, particularly in non-adherent patients to OGC or to determine the sensitivity or response to steroids¹⁴⁵. However, the use of triamcinolone should be very limited because of side effects and unknown pharmacokinetics.

Theophylline. The evidence for its recommendation is scarce and its use in children is not recommended¹⁴⁶. It may play a role in improving sensitivity to glucocorticoids¹⁴⁷.

Tiotropium. Associated with IGC/LABA in children aged 6 years or more is an option for trying to achieve asthma control^{148,149} prior to the use of monoclonal antibodies.

Omalizumab. Is an anti-IgE monoclonal antibody that has shown efficacy for treating children aged 6 years or more with allergic SUA. It reduces exacerbations, symptoms, the use of rescue medication and improves quality of life^{69,150}.

Mepolizumab. It is an anti-IL5 monoclonal antibody, effective in severe eosinophilic asthma¹⁵¹. Currently there is indication for its use after 6 years of age, with limited data available for children aged between 6 and 11 years. The recommended dose is 40 mg between 6-11 years and 100 mg from 12 years, administered subcutaneously, once every 4 weeks.

Macrolides. They have an immunomodulator and antibacterial effect. However, in the few studies performed so far, macrolides did not seem to be effective¹⁵². The use of macrolides may be considered in SUA on treatment with OGC, non-eosinophilic inflammation and/or recurrent respiratory infections.

In **infants and preschool children** the level of evidence of the studies is even lower, although emerging studies are trying to define therapeutic position alternatives.

When symptoms remain uncontrolled despite IGC at high doses combined with *montelukast*, either LABA (off-label indication)¹⁵³, tiotropium¹⁵⁴, macrolides or even OGC may be added, although the best therapeutic option has not yet been established. The need to stepped-up treatment should be re-evaluated at each visit, trying to maintain it during the shortest possible period of time.

RECOMMENDATIONS

- | | |
|--|-----------|
| 7.1. It is suggested to define severe uncontrolled asthma (SUA) as asthma that remains poorly controlled despite having being treated with a combination of IGC/LABA at high doses in the previous year, or oral glucocorticoids for at least 6 months during the same period. | R2 |
| 7.2. The lack of control will be objectively determined by any of the following characteristics: ACT < 20 or ACQ > 1.5; ≥ 2 severe exacerbation or having being treated with ≥ 2 courses of oral glucocorticoids (≥ 3 days each) in the previous year; ≥ 1 hospital admission due to severe asthma in the previous year (FEV ₁ /FVC ratio < 0.7 or FEV ₁ < 80% predicted) after use of adequate treatment (as long as the best FEV ₁ is higher than 80%). | R2 |
| 7.3. It is recommended that diagnostic evaluation of SUA should preferably undertaken in centers or specialized asthma units, and using a stepwise decision algorithm. | R2 |
| 7.4. It is suggested to perform a protocolized diagnostic evaluation of SUA (in adults and children) based on three key actions: 1) to confirm the diagnosis of asthma objectively; 2) to identify those factors that are external to the asthmatic disease (treatment adherence, patient's inhalation technique, comorbidities or aggravating factors, triggers of exacerbations); and 3) to establish the phenotype of severe asthma. | R2 |
| 7.5. In the absence of diagnostic confirmation, the presence of other possible disease mimicking asthma should be excluded. | R2 |
| 7.6. It is recommended to establish asthma phenotype in patients with SUA as part of the diagnostic assessment. This identification can involve a differential treatment approach and have prognostic implications. | R2 |
| 7.7. In daily clinical practice, it is suggested the use of three severe asthma phenotypes for treatment decision-making, which are the following: allergic asthma (T2), eosinophilic asthma (T2) and non-T2 asthma | R2 |
| 7.8. General treatment of SUA includes: the prescription of drugs recommended in steps 5 and 6 (IGC/LABA combination at high doses and a third controller drug preferably tiotropium), adherence to an asthma education program, treatment of comorbidities/aggravating factors, and prevention/treatment of side effects of glucocorticoids. | R2 |
| 7.9. Given that inflammation markers of phenotype T2 may be suppressed by treatment with OGC, it is recommended assessing these markers before starting treatment of OGC, or with the lowest possible dose, and at least on three occasions (e.g. during an exacerbation) prior to assuming that the patient presents a non-T2 asthma. | R2 |
| 7.10. In the treatment of SUA T2, on the basis of the level eosinophils in the peripheral blood and sputum, and the presence of relevant allergic clinical manifestations with confirmed sensitization to perennial aeroallergens, one or other of the available monoclonal antibodies will be chosen: omalizumab, mepolizumab, reslizumab or benralizumab. | R1 |
| 7.11. In case of non-T2 asthma, treatment with azithromycina or bronchial thermoplasty or systemic glucocorticoids is recommended. | R2 |
| 7.12. Omalizumab is indicated in allergic SUA in children older than 6 years of age. | R1 |
| 7.13. Mepolizumab is indicated in eosinophilic SUA in children older than 6 years of age. | R1 |

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