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2021 Brazilian Thoracic Association recommendations for the management of severe asthma

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ABSTRACT

Advances in the understanding that severe asthma is a complex and heterogeneous disease and in the knowledge of the pathophysiology of asthma, with the identification of different phenotypes and endotypes, have allowed new approaches for the diagnosis and characterization of the disease and have resulted in relevant changes in pharmacological management. In this context, the definition of severe asthma has been established, being differentiated from difficult-to-control asthma. These recommendations address this topic and review advances in phenotyping, use of biomarkers, and new treatments for severe asthma. Emphasis is given to topics regarding personalized management of the patient and selection of biologicals, as well as the importance of evaluating the response to treatment. These recommendations apply to adults and children with severe asthma and are targeted at physicians involved in asthma treatment. A panel of 17 Brazilian pulmonologists was invited to review recent evidence on the diagnosis and management of severe asthma, adapting it to the Brazilian reality. Each of the experts was responsible for reviewing a topic or question relevant to the topic. In a second phase, four experts discussed and structured the texts produced, and, in the last phase, all experts reviewed and approved the present manuscript and its recommendations.

Keywords: Asthma/therapy; Asthma/drug therapy; Asthma/prevention & control; Antibodies, monoclonal, humanized.

INTRODUCTION

Advances in the understanding of the pathophysiology and heterogeneity of severe asthma have led to new approaches to diagnosis and characterization of severe asthma, as well as to new effective drugs for asthma control. These are promising times for the management of severe asthma, which, despite being an uncommon presentation of asthma, has a major impact on the health care system and on patients' quality of life.

Increasing knowledge of cellular, molecular, and genetic mechanisms involved in the pathophysiology of asthma has led to advances in the characterization of phenotypes and endotypes, as well as in the personalized management of asthma.[1]

Given the heterogeneity and complexity of severe asthma, case identification requires specialist follow-up, preferably at a referral center. Systematized approach and follow-up are needed in order to confirm the diagnosis; gather evidence of treatment adherence; ensure correct inhaler use; investigate and control comorbidities; and optimize pharmacological and nonpharmacological interventions.[2-4]

Previous estimates of disease prevalence and cost have been based on older definitions that are no longer current used,[5] resulting in overestimated prevalence. More recently, a study conducted in the Netherlands and using the American Thoracic Society/European Respiratory Society (ATS/ERS) definition of severe asthma,[3] 3.7% of asthma patients were estimated to have severe asthma.[6] In a database

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analysis conducted in the United Kingdom in 2018, < 1% of asthma patients were estimated to have uncontrolled severe eosinophilic asthma.[7]

Patients with severe asthma have increased morbidity and mortality,[8] a greater number (and increasingly severe) of comorbidities,[9] and more frequent health care utilization for asthma.[10] Severe asthma has been shown to result in very high costs to families and to the Brazilian Unified Health Care System.[11] An intervention implemented at an asthma referral center in Brazil and involving the provision of free medication was found to be effective in improving disease control and reducing associated costs.[12] In a study analyzing a database from the Brazilian private health care system between 2010 and 2015, the mean cost per hospitalization for asthma was shown to be $8,655.00 (in U.S. dollars).[13] Therefore, the cost of not providing access to experienced specialists at referral centers or personalized treatment alternatives for specific asthma phenotypes can be very high.

The present recommendations provide physicians with guidance on the management of severe asthma in adults, adolescents, and children ≥ 6 years of age. A total of 17 pulmonologists from referral centers for severe asthma in Brazil were invited to review the current knowledge of severe asthma and develop these recommendations adapted for Brazil. An expert panel examined major advances in topics such as the definition of severe asthma, phenotyping, biomarkers, and new treatments for severe asthma. On the basis of current evidence and international guidelines, each panel member was assigned a topic for review. Harmonization was performed in two phases. In the first phase, 4 panel members discussed and structured all texts. In the second phase, all panel members reviewed, discussed, and revised the recommendations until a consensus was reached.

DEFINITION OF SEVERE ASTHMA

Severe asthma is a subset of difficult-to-control asthma (DCA). DCA is asthma that remains uncontrolled despite step IV or V treatment[2,14] or that requires step IV or V treatment because of the concomitant presence of one or more factors affecting disease control. Potentially modifiable or controllable factors are responsible for the difficulty in achieving and maintaining disease control.

This document defines as having severe asthma the patient with asthma confirmed by an objective method, with good adherence to treatment, and who, despite the elimination or minimization of factors associated with lack of disease control, requires high doses of inhaled corticosteroids (IC; (budesonide ≥ 1600 µg or equivalent) associated with a second controller drug (long-acting beta2 bronchodilator - LABAs and/or long-acting antimuscarinic - LAMAs and/or antileukotrienes) or oral corticosteroids (OC) ≥ 50% of the days of previous year, to maintain control of the disease or that it still remains uncontrolled, due to the intrinsic severity of the asthma.[3]

DIAGNOSTIC INVESTIGATION OF DCA AND SEVERE ASTHMA IN ADULTS

Confirmation of asthma diagnosis

The diagnostic investigation of DCA and severe asthma begins with an objective confirmation of the diagnosis because, given the complexity of diagnosing asthma, misdiagnosis is common and results in inappropriate management.[15] Asthma is characterized by respiratory symptoms, variable airflow limitation, and airway hyperresponsiveness.[14] An FEV_1/FVC ratio below the lower limit of normal constitutes evidence of obstructive lung disease on spirometry. Airflow obstruction reversibility is evidenced by an acute (10-15 min) FEV_1 response to a short-acting inhaled bronchodilator (albuterol, 200-400 µg). A significant bronchodilator response is defined as a ≥ 12% and ≥ 200 mL increase in FEV_1 from baseline[16] or a ≥ 7% and ≥ 200 mL increase in FEV_1 over the reference values.[17] Airflow obstruction reversibility is also demonstrated by comparing baseline lung function and lung function parameters after 4 weeks of treatment with corticosteroids or by comparing lung function parameters between visits during periods of clinical stability.[18,19] Daily PEF variability > 20% can also be helpful in confirming the diagnosis of asthma.[4]

Changes in bronchodilator response are also evidenced by an increase in FVC, a ≥ 350 mL increase being considered significant.[17] This most commonly occurs in the presence of severe obstruction as a consequence of hyperinflation, air trapping, or both.[20]

The absence of bronchodilator response on spirometry does not exclude a diagnosis of asthma, particularly in severe asthma, which can present with airway remodeling, increased airflow obstruction, and reduced FEV_1.[21] In such cases, when spirometry fails to characterize asthma, other diagnostic methods can be used. Spirometry can be repeated after appropriate washout from bronchodilators[22] during the onset of symptoms, or after a course of systemic corticosteroids showing a > 10% change in FEV_1.[23]

Another diagnostic option is methacholine challenge testing.[24] Corticosteroid treatment reduces bronchial hyperresponsiveness (BHR); therefore, negative challenge testing in patients treated with corticosteroids does not exclude a diagnosis of asthma.[24,25] In addition, corticosteroid treatment can be gradually tapered in clinically stable patients with negative challenge testing, a 2- to 4-week follow-up period being followed by another functional assessment.

In patients with severe asthma, lung function can be assessed with plethysmography by measuring lung volumes,[3,4] adding parameters that express airflow obstruction such as lung hyperinflation and air trapping. Plethysmography can also be used in order to demonstrate airflow obstruction reversibility

by showing significant reductions in RV and specific airway resistance after bronchodilator administration.[26]

Although small airway changes can be present in patients with asthma regardless of asthma severity, they are more common in those with disease that is more severe.[27] Tests such as impulse oscillometry, nitrogen washout, plethysmography, spirometry, or any combination of the four can contribute to the identification of small airway dysfunction. $FEF_{25-75\%}$ and CVF reduction have been found to be the physiological parameters that best reflect small and medium airflow obstruction.[27] Small airway dysfunction must be carefully evaluated in patients with severe asthma because it can increase the difficulty in achieving disease control.

In the diagnostic investigation of severe asthma, HRCT is recommended[4] for making a differential diagnosis and investigating respiratory comorbidities. In addition, HRCT can help characterize small airway involvement, air trapping, airway narrowing, bronchial wall thickening, and mucus plugging, all of which are associated with increased asthma severity.[28] Dynamic HRCT (including neck imaging) can be used in order to evaluate vocal cord dysfunction and excessive central airway collapse (tracheobronchomalacia, dynamic airway collapse, or both).[29]

Assessment of treatment adherence and inhaler technique

Treatment adherence is associated with patient level of education, beliefs, and access to medication and health care.[30] There is no relationship between poor adherence to asthma controller medications and the severity of asthma.[31] In patients with DCA, adherence to inhaled controller medications is approximately 50%,[32,33] even in specialized severe asthma centers.[34] Assessing treatment adherence in clinical practice is challenging because the instruments that are currently available still need improvement.[35]

Adherence to treatment with the ICS+LABA combination is > 80% in less than half of severe asthma patients before and after initiation of treatment with biologicals.[36-39] In addition, adherence to maintenance treatment should be constantly evaluated[36,40] because patients with good adherence to ICS respond better to treatment with biologicals.[40,41]

Inhaler technique is as important as treatment adherence, being one of the major causes of poorly controlled asthma.[34] A systematic evaluation of all inhaler technique steps is essential because of the association between some of the steps and poorly controlled asthma.[42]

Correct inhaler use requires ongoing training. Despite educational interventions, inhaler technique errors are common even in patients with severe asthma.[43] In a study in which treatment adherence and inhaler technique were simultaneously and objectively evaluated in patients with moderate-to-severe asthma, 27% achieved asthma control after improving their inhaler technique.[43]

Investigation of exposures that can worsen asthma control

Achieving and maintaining asthma control can be difficult because of exposures such as allergens, irritants, environmental pollution, smoking, occupational agents, and/or drugs. Because these exposures lead to poor asthma control, they should be addressed in all asthma patients, especially those with DCA.[4]

Household exposure

Mites, cats, dogs, cockroaches, rodents, and fungi are the urban and domestic allergens that are most commonly associated with difficulty in controlling asthma.[44,45] Although only a few population-based studies have examined the prevalence of atopy in Brazil, evidence suggests that sensitization to aeroallergens varies across regions and types of study.[46,47]

Studies examining the efficacy of measures to prevent exposure to house dust in controlling asthma[48,49] have yielded controversial results. There is no consensus among guidelines regarding the usefulness of such measures in accordance with a study carried out in 2020.[49]

Environmental exposure

There is an association between air pollution and asthma exacerbation.[50,51] Air pollutants associated with worsening asthma control include fine particulate matter ($PM_{2.5}$), ozone, nitrogen dioxide, and carbon monoxide. In 2015, ozone and $PM_{2.5}$ accounted for 8-20% and 4-9%, respectively, of asthma ER visits worldwide.[52] Special attention should be given to exposure to $PM_{2.5}$ from biomass burning, because it is associated with increased ER visits and hospitalizations for asthma.[53] In a study conducted in Brazil, there was a 50% increase in hospital admissions for asthma during the sugarcane burning season.[54]

Exposure to smoking

Active and passive smoking are associated with increased exacerbations, hospitalizations, and lung function impairment, but smoking cessation or reduction is an independent, modifiable factor for asthma control.[55] Therefore, it is important to evaluate patient smoking status at each visit in order to achieve smoking cessation.

Asthma patients who use illicit drugs are more likely to require intensive care or experience severe exacerbations, especially when illicit drug use is associated with poor adherence to asthma controller medications.[56]

Work-related exposure

Workplace exposures have major clinical implications for severe asthma. Work-related asthma (WRA) includes occupational asthma (OA) and work-exacerbated asthma (WEA), which is also known as work-aggravated asthma.

OA is defined by the presence of asthma symptoms and reversible airflow obstruction, BHR, or a combination of the two as a result of workplace exposures rather than exposures outside the workplace. It can be caused by sensitizers or irritants.[57,58] WEA is defined as preexisting asthma worsened by workplace conditions.[59]

OA and WEA are primarily triggered by inhaled fumes, gases, dust, and smoke.[60] Workers such as bakers, agricultural workers, metalworkers, carpenters, and workers exposed to latex are at an increased occupational risk, and these workplace exposures should be carefully investigated and excluded as a cause of poorly controlled asthma.[61]

The estimated incidence and prevalence of OA and WEA vary depending on the study population and workplace exposure. In an analysis of 9 studies, the estimated incidence of OA was 16%.[60] However, there is little information on the impact of occupational exposure on severe asthma.[62]

In a European cohort of patients with OA (N = 997), the prevalence of severe asthma was 16.2%. Asthma severity was correlated with persistent exposure to the causative agent, asthma duration, education level, early-onset asthma, and sputum production.[62]

In severe asthma patients suspected of having poorly controlled asthma because of workplace exposures, a diagnostic flow chart[63] should be used for diagnostic confirmation. Once the diagnosis is confirmed, patients should be removed from exposure.[63]

Identification and management of comorbidities

Identification and management of comorbidities potentially affecting asthma control is part of the multidisciplinary approach to DCA and severe asthma because comorbidities are associated with worse outcomes.[64,65] Comorbidities are, for the most part, treatable, and appropriate comorbidity management can reduce the dose and required number of asthma controller medications, contributing to improving asthma control and patient quality of life, as well as reducing asthma exacerbations.

The prevalence of comorbidities in patients with severe asthma is high (ranging from 51% to 95%).[66,67] In a study conducted in Brazil, all of the patients with severe asthma reported having at least one comorbidity, and approximately 70% reported having at least three. The most common comorbidities were rhinitis, gastroesophageal reflux disease (GERD), and hypertension.[68]

Upper airway comorbidities

Allergic rhinitis and chronic rhinosinusitis with or without nasal polyps

The prevalence of allergic rhinitis is 80% in patients with asthma.[69] In Brazil, the prevalence of allergic rhinitis in patients with severe asthma ranges from 72% to 96.5%.[68,70] A diagnosis of allergic rhinitis is made on the basis of patient clinical history and a nasal symptom questionnaire, as well as a positive aeroallergen-specific IgE screen, a positive skin prick test for aeroallergens, or both. Nearly half of patients with severe asthma have chronic rhinosinusitis with or without nasal polyps.[71,72] A diagnosis of chronic rhinosinusitis is made on the basis of patient clinical history, a nasal symptom questionnaire, sinus CT, and nasofibroscopy.

Studies have shown that appropriate management of allergic rhinitis and rhinosinusitis with or without nasal polyps has a positive impact on asthma control.[73-75]

Obstructive sleep apnea

In adults, obstructive sleep apnea (OSA) is most prevalent in patients with severe asthma and is an independent risk factor for poor asthma control,[76] being associated with more severe exacerbations[77] and accelerated decline in lung function.[78]

A diagnosis of OSA is made on the basis of nighttime and daytime symptoms, as well as abnormal polysomnographic findings. Asthma control, quality of life, and lung function were found to improve after initiation of CPAP therapy in asthma patients with moderate-to-severe OSA.[79]

Vocal cord dysfunction

Vocal cord dysfunction (VCD) is defined as abnormal adduction of the vocal cords resulting in airflow obstruction. The prevalence of VCD in patients with DCA is as high as 32%.[80] The most common symptoms are inspiratory dyspnea, wheezing and/or stridor in the neck, dysphonia, and hoarseness.[81] Common triggering factors include emotional stress, airway irritants, sudden changes in temperature, infections, and physical exercise.

Laryngoscopy is the gold standard for confirming a diagnosis of VCD[82,83] and must be performed during an attack, demonstrating abnormal adduction of the vocal cords during inspiration. Flattening of the inspiratory loop on the flow-volume curve on spirometry is suggestive of VCD.[84] Dynamic CT of the neck,[29] questionnaires,[85,86] and laryngoscopy during exercise can help to identify cases of VCD.[87]

There is no specific treatment for VCD. Treatment options include speech therapy (respiratory training and voice therapy), psychotherapy, and elimination of triggering factors.[72]

Other comorbidities

Dysfunctional breathing

The pathophysiology of dysfunctional breathing is poorly understood,[72] and dysfunctional breathing symptoms can be confused with asthma symptoms. Dysfunctional breathing coexists with DCA and is underdiagnosed.[88] On the basis of the Nijmegen Questionnaire,[89] the prevalence of dysfunctional

breathing in patients with DCA ranges from 30% to 64%.[80,90]

Dysfunctional breathing involves abnormal breathing patterns[91] described and classified elsewhere,[92,93] a disordered breathing pattern being a major component of dysfunctional breathing. The most well-known forms of dysfunctional breathing are hyperventilation syndrome and idiopathic hyperventilation.[94]

In asthma patients, dysfunctional breathing is associated with an increase in ER visits and unscheduled visits, as well as with activity limitations and impaired physical and mental health.[95,96] Dysfunctional breathing can coexist with other comorbidities, is common in patients with anxiety disorders such as panic disorder[97] and in those with VCD,[83,98] and is independently associated with worsening of quality of life and asthma control.[80]

Few studies have examined the treatment of dysfunctional breathing.[94] In patients with DCA, breathing exercises have been found to improve the Nijmegen Questionnaire score and asthma control, as well as reducing the frequency of exacerbations.[99]

Anxiety and depression

Patients with severe asthma are more likely to experience symptoms of anxiety and depression than are those with asthma that is less severe.[100] Although the prevalence of anxiety and depression symptoms in patients with severe asthma has been reported to be 38% and 25%, respectively,[101] anxiety and depression have been overlooked in the evaluation of DCA and severe asthma.[64] Anxiety and depression symptoms are associated with difficulty in controlling asthma,[102] increased use of health services,[103] near-fatal asthma attacks, and increased mortality.[104] These unfavorable outcomes might be related to poor adherence to the prescribed medication regimen, irregular medical follow-up care, and inappropriate asthma management practices.[105]

In a real-life study,[106] asthma control and quality of life questionnaires were found to correlate well with anxiety and depression scales. Therefore, patients with uncontrolled asthma and low quality of life should be screened for symptoms of anxiety and depression[106] and referred for follow-up in specialized centers.

GERD

GERD is a common comorbidity in patients with severe asthma.[68,107-109] A diagnosis of GERD is made on the basis of clinical symptoms, upper gastrointestinal endoscopy, and 24-h esophageal pH monitoring, with or without esophageal manometry and pH-impedance testing. Patients with DCA and symptoms of GERD should undergo treatment, which consists of lifestyle changes, pharmacological interventions, and, in some cases, surgery.[110]

Obesity

Evidence from cross-sectional studies suggests that obese individuals are at an increased risk for asthma.[111,112] Obese asthma patients have disease that is more severe, poorly controlled asthma, reduced quality of life, and increased ER visits and hospitalizations.[113-115] This might be due to several factors, including the type of inflammation, obesity-related comorbidities (OSA and GERD), and factors related to respiratory mechanics.

There is evidence that obesity increases the production of proinflammatory mediators in asthma, which are associated with visceral fat and can lead to increased BHR and bronchospasm.[116,117] Cross-sectional studies have suggested that obese asthma patients have predominantly neutrophilic airway inflammation.[117,118] This inflammatory pattern is predominantly seen in obese women with asthma, constituting the "asthma-obesity" phenotype.[71]

Weight loss should be included in the treatment plan for obese patients with severe asthma.[119,120] Weight loss can improve asthma control and lung function (FVC), as well as reducing the need for medications, without affecting inflammatory markers or markers of bronchial responsiveness.[120,121] Obese asthma patients who were enrolled in a weight loss and physical activity program and who lost 5-10% of their body weight were found to have improved asthma control and quality of life.[122] Bariatric surgery also results in improved asthma control, quality of life, and lung function.[4,123-125]

Figure 1 shows a flow chart for the management of DCA in adults.

BIOMARKERS

Biomarkers can help to identify different phenotypes and endotypes, as well as predicting the response to severe asthma treatment.[126] The most widely used biomarkers of type 2 (T2)-high inflammation are IgE, eosinophils in induced sputum (EosIS), eosinophils in peripheral blood (EosPB), and fractional exhaled nitric oxide (FeNO).[127]

IgE

IgE plays an important role in the pathogenesis of allergic asthma. Exposure to exogenous allergens triggers an inflammatory cascade with interleukins (IL-4, IL-5, and IL-13), as well as activation of different cells. IL-4 and IL-13 stimulate B lymphocytes to produce IgE.[128]

The allergic asthma phenotype is confirmed by clinical history and an immediate hypersensitivity response (a positive skin prick test), a positive specific serum IgE response to at least one aeroallergen, or a combination of the two. Age can affect IgE levels, and nonatopic patients can present with elevated IgE levels.[129] Diagnosis of the allergic asthma phenotype does not depend on total serum IgE; serum IgE, although, total serum IgE is used in order to calculate the dose of anti-IgE for the treatment of patients with severe asthma.

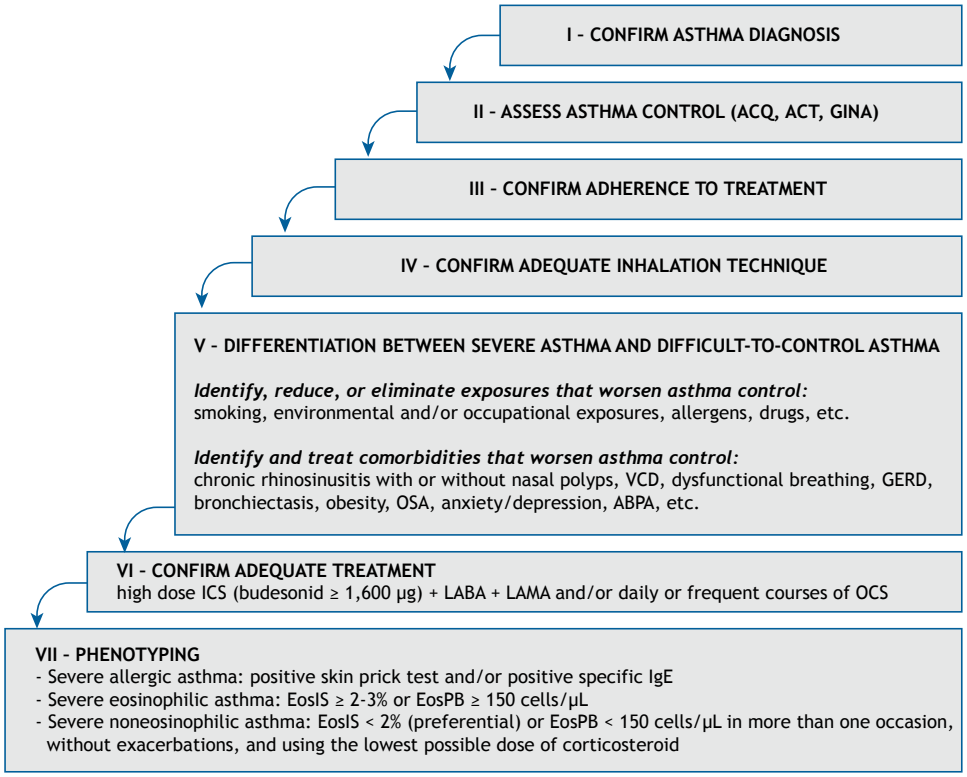

Figure 1. Flow chart of severe asthma diagnosis and phenotyping. ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; VCD: vocal cord dysfunction; GERD: gastroesophageal reflux disease; OSA: obstructive sleep apnea; ABPA: allergic bronchopulmonary aspergillosis; ICS: inhaled corticosteroid; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; EosIS: eosinophils in induced sputum; EosPB: eosinophils in peripheral blood; FeNO: fractional exhaled nitric oxide.

EosIS and EosPB

Induced sputum (IS) is a noninvasive method that allows quantification of airway inflammatory cells[130,131] and, consequently, identification of different phenotypes, although the cutoff point to characterize T2-high eosinophilic inflammation in asthma varies across studies (≥ 2% or ≥ 3%).[4,132]

In a study analyzing a database from the Belgian Severe Asthma Registry,[132] 55% and 21% of the patients, respectively, were found to have eosinophilic and nonesosinophilic asthma. In Brazil, the prevalence of inflammatory phenotypes in patients with severe asthma varies across cohorts, the eosinophilic phenotype having predominated in one study[70] and the noneosinophilic phenotype having predominated in another one.[133]

An increased percentage of EosIS (≥ 2% or ≥ 3%) is a predictor of response to ICS and OCS,[134] as well as of uncontrolled asthma and an increased risk of exacerbations.[135] The use of a therapeutic approach to maintain the percentage of EosIS below 3% has been reported to reduce the risk of exacerbations in comparison with standard management.[136-138]

Difficulties in implementing IS in clinical practice have led to a search for surrogate markers,[131] EosPB therefore being proposed as a simpler, cheaper, and more widely available option. Although EosPB counts partially correlate with EosIS counts,[139] eosinophilia in blood is also associated with increased severity and an increased risk of asthma exacerbation.[140] There is also evidence that an elevated EosPB count is associated with a better response to ICS.[141]

Caution is needed when interpreting EosPB counts because eosinophilia in blood can be caused by different diseases,[142] can vary over time,[143] and can decrease with the use of a corticosteroid, especially OCS.[144] In Brazil, a controlled study of individuals without asthma showed that major factors associated with increased EosPB were atopy, allergic rhinitis, and smoking.[145] Therefore, EosPB counts must be interpreted in the context of medical conditions and factors that can potentially influence EosPB levels.

For patients with severe asthma, the GINA suggests an EosPB count of ≥ 150 cells/µL as a cutoff point for detection of T2-high inflammation. Given the variability of EosPB counts, they should be performed at least three times and with the lowest possible dose of OCS.[4]

FeNO

FeNO is a noninvasive measurement of airway inflammation. An elevated FeNO is a marker of eosinophilic inflammation.[14] Although elevated FeNO and EosPB commonly occur concomitantly, these

biomarkers represent different aspects of T2-high inflammation.[146] An elevated FeNO correlates with increased lung function impairment[147] and more severe exacerbations.[148,149]

FeNO cutoff points vary across studies. Some guidelines state that, in adults, FeNO < 25 ppb is normal, FeNO > 50 ppb is high, and FeNO values of 25-50 ppb should be interpreted in association with clinical factors at the time of evaluation.[147,150,151] However, according to the GINA, FeNO ≥ 20 ppb characterizes T2-high inflammation.[14]

In addition to the wide variability of FeNO cutoff points, FeNO can increase or decrease as a result of factors such as use of ICS, OCS, or a combination of the two, as well as nonadherence to treatment.[152]

PHENOTYPING

Severe asthma is a complex heterogeneous disease with several different pathophysiological mechanisms and phenotypes, the identification of which can lead to successful targeted therapy.[1] A phenotype is defined as the observable characteristics of an organism that result from the interaction of its genotype with the environment.

Phenotyping based on the cellularity of the inflammatory response has resulted in the recognition of two major asthma phenotypes, namely, eosinophilic asthma and noneosinophilic asthma. Noneosinophilic asthma is associated with neutrophilic or paucigranulocytic inflammation.[153] Eosinophilic asthma is the more common phenotype, being found in most (70%) of the patients without previous treatment for asthma (i.e., treatment-naïve patients)[153-155] and in half of those undergoing treatment with corticosteroids.[132,156]

Severe asthma can also be classified by molecular phenotype (endotype), which is related to identification of a specific pathophysiological pathway for a given phenotype. The characteristics of a clinically useful endotype are as follows: a plausible molecular mechanism; longitudinal stability; correlation with relevant clinical outcomes; association with a biomarker that characterizes this pathophysiological pathway and that can be measured in practice; and response to targeted therapy.[1]

T2-high asthma is the best characterized endotype, resulting from the interaction between innate and adaptive immunity.[157] The T2-high endotype was initially designated Th2-high in recognition of the central role that Th2 lymphocytes play in the adaptive inflammatory response, with production of IL-4, IL-5, and IL-13 (Figure 2). However, the Th2-high asthma endotype was later designated T2-high asthma after evidence that innate immunity also plays an important role in this inflammatory pathway, with group 2 innate lymphoid cells (ILC2) producing large quantities of IL-5 and IL-13.[158,159]

The T2-high inflammatory response is mediated by Th2 lymphocytes and ILC2, as well as by IgE-producing B lymphocytes, eosinophils, mast cells, and basophils.[128,158] Whether the innate or adaptive immune response will predominate in the inflammatory response of asthma depends on the phenotype (i.e., allergic or nonallergic asthma).[160]

IL-4 is essential for the maturation of naïve lymphocytes into Th2 lymphocytes and for the switch of B lymphocytes to IgE-producing B lymphocytes. IgE binds to high-affinity receptors on basophils and mast cells, promoting their degranulation and thus releasing several proinflammatory mediators.[161] IL-5 is responsible for the recruitment, maturation, activation, and survival of eosinophils, which secrete several proinflammatory cytokines and chemokines.[128] IL-13 promotes fibrosis and smooth muscle remodeling and, together with IL-4, regulates IgE production and induces goblet cell hyperplasia, with increased mucus production. Mast cells produce prostaglandin D2, which binds to its receptor on Th2 lymphocytes, leading to the release of IL-5 and IL-9, which increase mucus production.[128,160,162] IL-4 and IL-13 also induce the expression of adhesion molecules in vascular endothelial cells, thus promoting the transmigration of eosinophils from the bloodstream to the airway tissue, which results in accumulation of eosinophils in the bronchial mucosa.[163]

Damage to the airway epithelium—the interface between the external and internal environments—leads to increased expression and release of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), all of which stimulate ILC2 to produce IL-4 and IL-13 (Figure 2). Epithelial cell-derived cytokines, also known as alarmins, play an important mediating role in the inflammatory response to a variety of external stimuli, including allergens, viruses, bacteria, smoke, and pollutants.[128,158,160,164,165] At the same time, inadequate epithelial repair occurs, resulting in airway remodeling. In turn, airway remodeling leads to an increase in proinflammatory mediators, resulting in more inflammation and epithelial damage (Figure 2).[157]

The T2-high endotype is characterized by increased expression of IL-4, IL-5, and IL-13; airway and blood eosinophilia; airway epithelial dysfunction; and IgE production in the allergic phenotype.[1,158] This results in BHR, airflow obstruction, and exacerbations. The T2-high endotype is characterized by elevated biomarkers such as EosIS, EosPB, and FeNO.[157] It accounts for 50-75% of severe asthma cases.[166,167]

Although the T2-low endotype has yet to be completely defined, it is characterized by the absence of a T2-high inflammatory response. The pathophysiology of T2-low asthma has yet to be fully understood and is possibly associated with the activation of innate and acquired immune responses. The T2-low endotype includes neutrophilic asthma

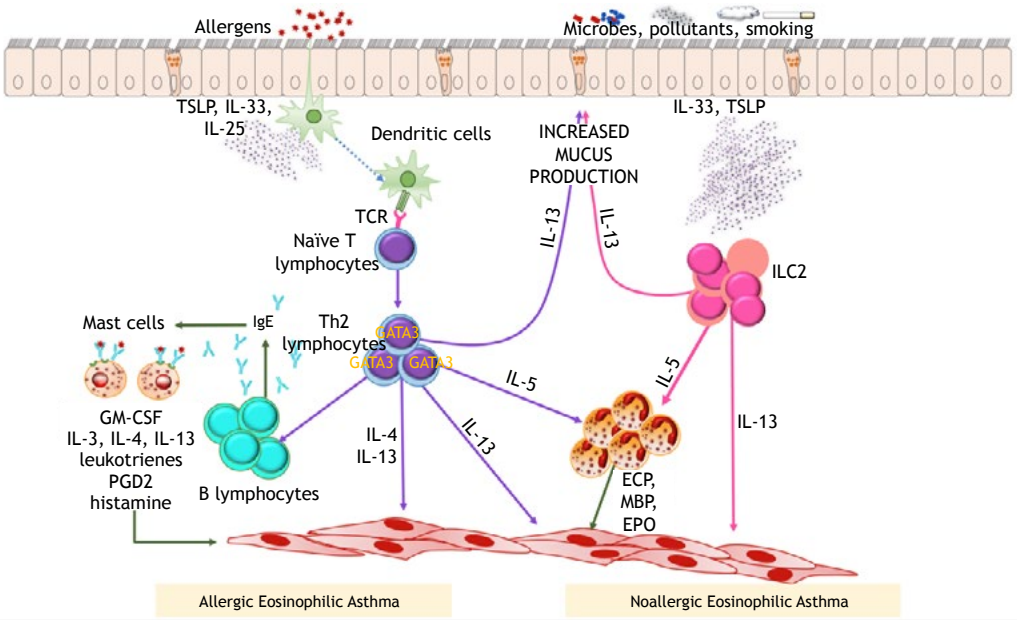

Figure 2. Inflammatory mechanisms of T2-high asthma phenotype. The figure schematically represents the main cells and cytokines involved in the adaptive and innate inflammatory response of the T2-high phenotype in severe asthma. In genetically susceptible individuals, inhalation of allergens (adaptive immunity), smoke, bacteria, and viruses (innate immunity) initiates and perpetuates the T2-high inflammatory cascade. TSLP: thymic stromal lymphopoietin; TCR: T-cell receptor; MHC2: major histocompatibility complex class 2; GATA3: transcription factor encoded by the *GATA3* gene; ILC2: group 2 innate lymphoid cells; PGD2: prostaglandin D2; ECP: eosinophil cationic protein; MBP: major basic protein; EPO: eosinophil peroxidase.

and paucigranulocytic asthma.[168] In patients with T2-low asthma, the gene-external trigger interaction can result in the production of alarmins (IL-33 and TSLP), which stimulate Th17 lymphocytes to produce IL-6, IL-8, and IL-17, all of which playing an important role in the attraction and stimulation of neutrophils. In addition, activation of Th1 lymphocytes can occur, stimulating neutrophilic inflammation via the production of TNF-α and INF-γ.[153]

Severe allergic eosinophilic asthma

Patients with allergic eosinophilic asthma have atopy, variable airflow obstruction, and bronchodilator response. They also have good response to ICS and present with eosinophilic inflammation associated with elevated total serum IgE levels and/or FeNO (≥ 20 ppb).[1,153] Patients with severe allergic eosinophilic asthma present with frequent exacerbations and do not always respond well to high-dose ICS alone or in combination with OCS, incomplete airflow reversibility occurring in some cases.

A confirmed diagnosis of severe allergic eosinophilic asthma requires an objective measure of atopy (skin prick testing and/or allergen-specific IgE in peripheral blood) and an increase in EosIS (≥ 2-3%) and/or EosPB (≥ 150 cells/μL).[4]

From a pathophysiological standpoint, airway inflammation in T2-high allergic asthma begins with repeated exposure of epithelial cells to inhaled allergens; in genetically susceptible individuals, this triggers an inflammatory response that is predominantly mediated by Th2 lymphocytes, IgE-producing B lymphocytes, eosinophils, mast cells, and basophils.[128] In this inflammatory pathway, dendritic cells present inhaled antigens to naïve T lymphocytes, which, in turn, switch to Th2 lymphocytes and starts producing IgE IL-4, IL-5, and IL-13. IL-4 stimulates the switch of B lymphocytes (Figure 2), which begin to produce IgE. IgE binds to high-affinity receptors on mast cells and basophils, which release inflammatory mediators (leukotrienes, prostaglandin, and histamine).[169]

Severe nonallergic eosinophilic asthma

Patients with nonallergic eosinophilic asthma usually have late-onset asthma associated with eosinophilic inflammation but not with atopy. This phenotype predominates in females and in asthma patients with chronic rhinosinusitis, with or without nasal polyposis, and/or obesity. In addition, these patients tend to have more severe airflow limitation, frequent exacerbations, and poorer response to corticosteroids.[1,153,158] The severe nonallergic eosinophilic asthma phenotype is confirmed by an increase in the percentage of EosIS (≥ 2-3%) and/or EosPB (≥ 150 cells/μL) in the absence of parameters for atopy.

In severe nonallergic eosinophilic asthma, ILC2 plays an important role (Figure 2). Nonallergic triggers, such as environmental or occupational pollutants, irritants, or microbes, stimulate airway epithelial cells to produce alarmins (TSLP, IL-33, and IL-25) which,

by activating ILC2, stimulate the production of IL-5 and IL-13 that induce eosinophilic inflammation.[153,169]

Severe noneosinophilic asthma

The T2-low endotype includes a heterogeneous group of asthma patients. In general, these patients present with highly symptomatic, late-onset disease, no atopy, and poor response to corticosteroids. This endotype is often associated with obesity.

The prevalence of severe noneosinophilic asthma phenotypes (neutrophilic or paucigranulocytic) varies between 30% and 50%.[167,170] The absence of T2 inflammatory characteristics may be due to several factors unrelated to the asthma endotype. Therefore, it is recommended that the diagnosis of severe noneosinophilic asthma be made only after excluding situations that may interfere with eosinophilia, such as the effect of corticosteroid treatment,[137,138,171] recent infections,[172,173] and exposure to occupational irritants or pollutants.[174,175]

Neutrophilic asthma

Neutrophilic asthma, whose pathophysiology is poorly understood, also involves innate and adaptive immunities. The diagnosis of neutrophilic asthma is confirmed by IS cell count confirming the absence of eosinophilia and the presence of neutrophilia (≥ 40-70%) more than once.[153,176] Neutrophilic IS is commonly associated with frequent respiratory infections, smoking, exposure to environmental or occupational pollutants, and, in some cases, chronic treatment with corticosteroids.[153] In individuals with neutrophilic asthma, the gene-external trigger interaction results in the production of alarmins (IL-33 and TSLP), stimulating Th17 lymphocytes to produce IL-6, IL-8, and IL-17, which play an important role in neutrophil attraction and stimulation. In addition, Th1 lymphocyte activation may occur, which also promotes neutrophilic inflammation via TNF-α and INF-γ production.[153]

The differential diagnosis of neutrophilic asthma includes persistent bacterial airway infections, nontuberculous mycobacteriosis, cystic fibrosis, primary ciliary dyskinesia, bronchiectasis, primary immunodeficiency, smoking, and COPD.[168]

Paucigranulocytic asthma

Paucigranulocytic asthma is uncommon. Diagnosis is made by the absence of eosinophilia and neutrophilia in IS. This pattern does not exclude airway inflammation, since this phenotype is accompanied by smooth muscle hypertrophy, remodeling, goblet cell hyperplasia, and BHR.[153]

PHARMACOLOGICAL TREATMENT OF SEVERE ASTHMA IN ADULTS

In recent years, important changes have taken place in the management of severe asthma in parallel with a better understanding of the pathophysiology and phenotyping of the disease. Current recommendations[2,14,151] for the treatment of severe asthma include high doses of ICS+LABA as the preferred treatment. In patients with uncontrolled asthma, LAMA and/or biologicals can be associated.

LAMA

LAMAs are long-acting bronchodilators that inhibit muscarinic acetylcholine receptors located in the airways. Consequently, they cause relaxation, decreased bronchial muscle tone, and decreased mucus secretion.[177] Several LAMAs (tiotropium, aclidinium, glycopyrronium, and umeclidinium bromides) are available or under study for the treatment of asthma.

Tiotropium bromide

At present, tiotropium bromide is the only LAMA approved for use in Brazil for the treatment of asthma. Evidence for tiotropium prescription as an additional treatment for uncontrolled, moderate-to-severe asthma (steps IV and V) are based on randomized controlled trials (RCTs) in adults and adolescents,[178-180] as well as in children.[181] In adults with severe uncontrolled asthma, the addition of tiotropium significantly increased lung function and decreased exacerbations.[182] This effect was similarly reported in two other studies in adolescents[178] and children[179] with severe asthma. In adults, these results were independent of baseline characteristics,[183] eosinophil counts, and serum IgE levels.[184]

Tiotropium is approved for the treatment of asthma of patients older than 6 years of age at a dose of 5 μg/day. This medication is recommended as an additional medication for patients with uncontrolled asthma who are already receiving moderate or high doses of ICS+LABA (steps IV or V).[2,4] Tiotropium has been shown to be a safe drug when added to other medications in asthma treatment.[178]

Other LAMAs

Evidence from RCTs suggests that other combinations of ICS+LABA or ultra LABA (indacaterol and vilanterol)+LAMA (umeclidinium and glycopyrronium) may be treatment options for severe asthma.[185-187]

Biologicals

In Brazil, four biologicals are approved for use in the treatment of severe asthma (omalizumab, mepolizumab, benralizumab, and dupilumab). Given the heterogeneity and complexity of severe asthma and assuming that the selected agent should target a particular phenotype/endotype (Chart 1), this approach requires experience. In addition, treatment with biologicals depends on differences in the local health care system, reimbursement policies, and accessibility; therefore, specialists should be responsible for this management.

Omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody that acts as an inhibitor of free IgE binding to

its high-affinity receptor on the membrane of mast cells and basophils. By means of this mechanism of action, IgE cannot act on effector cells, blocking degranulation and the consequent release of inflammatory mediators. It also promotes downregulation[188] of these membrane receptors, making them less numerous. Omalizumab does not alter IgE production, but it blocks free circulating IgE, forming immune complexes that will be eliminated by the reticuloendothelial system.[189] It is indicated for the treatment of severe allergic asthma (step V).[2,14,151]

Efficacy and effectiveness

Pivotal studies on omalizumab were carried out when the understanding of severe asthma differed from the current one. The most important study that comes close to the concepts used today is that by Humbert et al.[190] In this scenario, adding omalizumab to the combination of high-dose ICS+LABA reduced exacerbations by 26% and improved quality of life. However, a real-life study[191] showed that the inclusion of omalizumab for the treatment of severe asthma caused a 50-60% reduction in the exacerbation rate and a 50% reduction in the OCS dose.

A systematic review[192] that included 25 RCTs involving patients with moderate-to-severe allergic asthma showed that omalizumab, when compared with placebo, reduced exacerbations and hospitalizations and allowed a small reduction in the ICS dose. Another review[193] that included 42 real-life studies in adults and children with asthma showed that the addition of omalizumab in the treatment improved asthma control, reduced ER visits and hospitalizations, as well as the dose of ICS (mean reduction of 32% in the ICS dose). On average, 83% of patients were able to reduce or eliminate the use of OCS.

Predictors of response

Response to treatment with omalizumab has no predictor or single outcome, although patients with high EosPB and FeNO levels tend to have a better response.[194] The GINA suggests that EosPB ≥ 260 cells/μL and/or FeNO ≥ 20 ppb can be used as predictors of good response.[14] This document, in line with those by the ATS/ERS,[3] the British Thoracic Society,[195] and The National Institute for Health and Care Excellence,[196] questions the use of these biomarkers to assess the response to omalizumab, because the abovementioned cutoff points were derived from a retrospective analysis[194] and are in disagreement with the results of a real-life study,[191] which found no differences in the effect of omalizumab in patients with severe eosinophilic or noneosinophilic asthma. Therefore, the use of these cutoff values could limit the use of omalizumab to a group of patients who would eventually benefit from this treatment.

Indication

Omalizumab is recommended for patients with severe allergic asthma ≥ 6 years of age. The dose varies depending on patient weight (20-150 kg) and total serum IgE (30-1,500 IU/mL) and is administered subcutaneously every 2 or 4 weeks (Chart 2). However, the baseline IgE level does not characterize atopy and does not predict the response to treatment.[197] In addition, after starting treatment, that level should not be used as an indicator of response.[198] It is recommended that the efficacy of omalizumab be evaluated based on clinical outcomes at least 16 weeks after treatment onset.[199]

Safety

The most common adverse effects are local reactions. Anaphylaxis can occur in up to 0.2% of patients within the first 2 h of its administration, both in the first and in subsequent applications.[200] For this reason, it is recommended that the patient be monitored in an environment equipped for the treatment of this complication. The possibility of cardiac and cerebrovascular events should also be monitored.[201]

Mepolizumab

Mepolizumab is a fully humanized IgG1/k monoclonal antibody with high affinity for the IL-5 ligand, which inhibits IL-5 from binding with its alpha receptor epitope, blocking its activity and, consequently, the eosinophilic inflammatory response.[202]

Efficacy and effectiveness

RCTs have demonstrated that adding mepolizumab to the treatment of patients with severe eosinophilic asthma and frequent exacerbations reduced EosPB and exacerbations.[203-206] In patients with severe asthma and OCS-dependent, the median OCS dose reduction, in comparison with placebo, was 50%.[206] These benefits persisted for up to 4.5 years.[207]

The effectiveness and safety of mepolizumab have also been proven in real-life studies.[207-209] A British study including 99 patients with EosPB ≥ 300 cells/μL has demonstrated a 54% reduction in exacerbations. The use of mepolizumab reduced OCS doses in corticosteroid-dependent asthma patients, and the

Chart 1. Endotypes, phenotypes, and biomarkers.

Endotype	Phenotype		Biomarker
T2-high	Eosinophilic	Allergic	Positive specific IgE and/or positive skin prick test
		Nonallergic	EosPB or EosIS + negative specific IgE and/or negative skin prick test
T2-low	Noneosinophilic	Neutrophilic	Neutrophilia in IS + absence of T2 biomarkers
		Paucigranulocytic	Absence of eosinophilia and neutrophilia in IS + absence of T2 biomarkers

EosPB: eosinophils in peripheral blood, EosIS: eosinophils in induced sputum.

use of OCS could be discontinued in 57% of patients. Approximately 73% of patients were classified as responders and 28% as super-responders. Patients with nasal polyposis, better asthma control—determined by the Asthma Control Questionnaire with six questions (ACQ-6)—low BMI, and using OCS have shown to have the best treatment response.[208]

In a study,[209] the inclusion of mepolizumab in the treatment of patients with severe eosinophilic asthma (N = 309) showed that 86% were responders (reduction in symptoms and in exacerbations, as well as improvement in quality of life and lung function). After 12 months of treatment, 24% of the patients were considered super-responders (ACQ-5 < 1.0, no exacerbations, and OCS free).

Predictors of response

The main predictors of response to mepolizumab are EosPB ≥ 150 cells/μL,[210,211] presence of exacerbations in the previous year,[203] adult-onset asthma,[209] and presence of nasal polyposis.[212]

Indication

Mepolizumab is recommended for patients with severe eosinophilic asthma (≥ 150 cells/μL) ≥ 6 years of age. In 6-to 11-year-old patients, the dose is 40 mg, and in those > 12 years of age or who weighs > 40 kg, the dose is 100 mg, subcutaneously, every 4 weeks (Chart 2). It is recommended that its efficacy be evaluated based on clinical outcomes at least 12 weeks after treatment onset.[14,151]

Safety

The major adverse events are bronchial infections, irritation at the site of application, and headache. Anaphylaxis is rare.[14,151,213]

Benralizumab

Benralizumab is a monoclonal antibody that binds to the alpha chain of the IL-5 receptor, which blocks the effect of IL-5 on eosinophils, causing their apoptosis through cell-mediated cytotoxicity.[214] Benralizumab also significantly reduces eosinophils in the airways, bone marrow, blood, and IS.[215]

Efficacy and effectiveness

The efficacy of benralizumab has been proven in several RCTs[216-219] and in two systematic reviews.[220,221] Although phase III studies included patients with moderate-to-severe asthma,[216,217] a reanalysis of these studies evaluating only patients with severe asthma (according to the ATS/ERS criteria)[3] showed that the inclusion of benralizumab in the treatment of patients with EosPB ≥ 300 cells/μL reduced exacerbations and increased FEV1.[222] In OCS-dependent patients with severe asthma, the median dose reduction was 50% when compared with placebo.[223]

Real-life studies have confirmed the effectiveness of benralizumab in the management of severe asthma.[224,225] A British study including 130 patients with severe asthma and EosPB ≥ 400 cells/μL has demonstrated a 72.8% reduction in exacerbations. In 51% of corticosteroid-dependent patients the use of OCS could be discontinued. Patients were classified as responders (86%) and super-responders (39%), these responses being associated with higher EosPB and less severe disease (better FEV1, better asthma control, better quality of life, and lower dose of OCS).[225]

Predictors of response

The best predictors of response to treatment with benralizumab are chronic use of OCS, nasal polyposis, pre-bronchodilator FEV1 < 65% of the predicted value, and late-onset asthma.[222]

Indication

Benralizumab is recommended for patients with severe eosinophilic asthma ≥ 18 years of age.[2,14,151] It is administered subcutaneously at a dose of 30 mg. The first three applications are made every 4 weeks and, from the fourth application on, every 8 weeks (Chart 2). The first assessment of the response to treatment should be made at least after 12 weeks.[14,151]

Safety

The most common adverse events are nasopharyngitis, bronchial infections, reactions at the site of application, and headache. Anaphylaxis is rare.[219,226]

Dupilumab

Dupilumab is a human monoclonal antibody of the IgG4 class that binds to the alpha subunit of the IL-4 receptor, blocking common signaling for IL-4 and IL-13,[227] which are important mediators in T2 inflammation.

Efficacy and effectiveness

Initial studies with dupilumab in patients with uncontrolled, moderate-to-severe asthma showed a reduction in exacerbations, improvement in lung function, and asthma control.[228,229] The efficacy of dupilumab has been proven in a phase III RCT[230] with a 52-week follow-up that included asthma patients ≥ 12 years of age and uncontrolled, moderate-to-severe disease. When compared with placebo, dupilumab reduced exacerbations by up to 48%, increased FEV1 (140 mL difference in comparison with placebo), and improved symptoms and quality of life. When patients were stratified by EosPB, those with a level of ≥ 300 cells/μL had a more significant reduction in exacerbations (67%) and a greater increase in FEV1 (difference in relation to placebo of 240 mL). Dupilumab also reduced inflammatory markers (FeNO, IgE, and periostin).

Another RCT[231] including corticosteroid-dependent patients with severe asthma has demonstrated that dupilumab was effective in reducing the OCS dose (−70% vs. −42% when compared with placebo). In addition, the treatment reduced severe exacerbations

Chart 2. Biologicals for T2-high severe asthma endotype.

Parameter	Omalizumab	Mepolizumab	Benralizumab	Dupilumab
Age, years	≥ 6	≥ 6	≥ 18	≥ 12
Route of administration/dose	s.c. dose-dependent relationship with total serum IgE and body weight	s.c. 40 mg (6-11 years) and 100 mg (≥ 12 years or > 40 kg)	s.c. 30 mg	s.c. initial dose of 400 or 600 mg followed by 200 or 300 mg
Frequency of administration	every 2 or 4 weeks	every 4 weeks	First 3 doses every 4 weeks, followed by doses every 8 weeks	every 2 weeks
Eosinophils, cells/μL[a]	N/A	≥ 150	≥ 300	EosPB ≥ 150 (and/or FeNO ≥ 25 ppb)
Serum IgE, IU/mL	30-1,500	N/A	N/A	N/A

EosPB: eosinophils in peripheral blood, FeNO: fractional exhaled nitric oxide. [a]Based on pivotal studies.

by 59%, increased FEV1 by 220 mL, improved asthma control, and reduced FeNO. In that study,[231] the favorable effects were independent of the baseline levels of EosPB and FeNO. The beneficial effects of dupilumab have also been confirmed in a real-life study.[232]

Predictors of response

The major predictors of response to treatment with dupilumab are high EosPB levels and FeNO ≥ 25 ppb.[4]

Indication

In Brazil, dupilumab is recommended for patients ≥ 12 years of age and uncontrolled, severe eosinophilic asthma (elevated EosPB and/or FeNO). It is also recommended for patients on continuous use of OCS, regardless of baseline levels of EosPB and FeNO. The recommended initial dose is 400 mg subcutaneously, followed by 200 mg every 2 weeks. In corticosteroid-dependent patients and/or with comorbidities (atopic dermatitis, nasal polyposis, or eosinophilic esophagitis), an initial dose of 600 mg is recommended, followed by doses of 300 mg every 2 weeks (Chart 2).

Safety

In clinical studies, dupilumab was well tolerated and safe, and some patients may have a transient increase in EosPB.[230-232] Given that patients with baseline levels of EosPB > 1,500 cells/μL were not included in phase III clinical trials, there are no safety data for the use of dupilumab in this population, and, therefore, its use in these patients is not recommended to date.[233]

Azithromycin

The intermittent (250-500 mg three times/week) and prolonged (12 months) use of azithromycin as an additional therapy in uncontrolled severe asthma has been considered an option by various guidelines.[4,151,234] Azithromycin reduces exacerbations in other chronic neutrophilic respiratory diseases, including bronchiectasis and COPD.[168] However, its place in the prevention of exacerbations in severe asthma is still limited by the lack of robust scientific evidence regarding potential side effects. The use of azithromycin is off-label in asthma.[2,3,14]

Azithromycin is a macrolide antibiotic with antibacterial, antiviral, and immunomodulatory properties, the latter of which include inhibition of cytokines and chemokines, decreased expression of adhesion molecules, and increased neutrophil apoptosis.[235] However, the exact mechanism by which azithromycin is effective in preventing asthma exacerbations remains unclear.[168]

Although initial studies were directed toward noneosinophilic asthma and presented controversial results, RCTs produced evidence of the benefit of including azithromycin in the treatment of uncontrolled asthma.[236,237] In the largest of these studies,[237] 420 adults with uncontrolled, moderate-to-severe asthma were included. Add-on therapy with azithromicin reduced exacerbations by 40% and improved quality of life, showing similar efficacy on eosinophilic and noneosinophilic phenotypes.

Side effects of prolonged use of azithromycin include diarrhea, QT interval prolongation, hearing loss, and increased *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and nontuberculous mycobacteria (NTM) antimicrobial resistance. Performing an electrocardiogram prior to treatment onset is recommended to rule out active NTM infection. Sputum culture for NTM screening should be performed every 6 months in cases of prolonged treatment.[238]

HOW TO ASSESS RESPONSE TO TREATMENT WITH BIOLOGICALS IN SEVERE ASTHMA

Pivotal and real-life studies have shown that most patients with severe asthma with a T2-high profile, when properly investigated, phenotyped, and considered eligible for use of biologicals, respond well to treatment.[204,209,218,225,231] Patients are likely to respond to treatment in different ways, and direct comparative studies between different biologicals are unavailable. Therefore, the selection of a specific biological should be individualized according to the

possible predictors of response and accessibility to the medication.

Severe asthma patients should be evaluated more frequently, especially if they are using biologicals.[2] It is important to identify the objectives of treatment clearly and establish the parameters that will be systematically evaluated at each visit.

Although studies on how to assess the response to biologicals are scarce, this topic is extremely relevant in clinical practice. In order to propose a systematic approach for evaluating the response to treatment with biologicals, the present document was based on RCTs[202-205,215-218,228-230,238-241] and real-life studies.[193,208,209,225,243-246] RCTs have evaluated the effect of biologicals on one or more of the following outcomes: decrease in exacerbations, OCS-sparing effect, improvement of asthma control, increase in FEV1, and improvement in quality of life.[203,206,216-219,229-231,239-242] Real-life studies with a 24-48 week follow-up using inclusion criteria similar to those of RCTs identified responders, super-responders, and nonresponders to treatment.[208,209,225]

Responders

Responders[208,209,225,247] are patients with improved asthma control (a 0.5 point decrease in ACQ) and/or a reduction in exacerbations ≥ 50% and/or in the dose of OCS ≥ 50%.

Super-responders

Super-responders[208,209,225] are considered to be the patients with well-controlled asthma (ACQ < 1.5), free of exacerbations, and with a reduction in the dose of OCS ≥ 80% in corticosteroid-dependent patients.

Nonresponders

Nonresponders[209,247] are patients who fail to meet at least two of the following criteria: improvement in asthma control (0.5 point decrease in ACQ), reduction in exacerbations ≥ 50%, or reduction in the dose of OCS ≥ 25% in corticosteroid-dependent patients.

Figure 3 presents a suggestion of assessment of response to management of biological treatment between 6 and 12 months.

A few patients previously considered responders may, over time, have a poorer response, identified by a ≥ 25% reduction in baseline FEV1, the need to increase the dose of maintenance corticosteroids, or an increase of ≥ 0.5 point in the ACQ-5.[247] Clinical worsening can result from poor compliance, incorrect inhalation technique, occupational/environmental exposures, and infections. In such cases, chest CT and bronchoscopy may be necessary to investigate alternative or concomitant diagnoses. The production of antibodies against the biological can also be the cause of loss of response to treatment.[225,247,248]

In the absence or loss of response, treatment must be interrupted and the patient reassessed for the possible introduction of another biological. In cases of intermediate response, treatment can be continued for 12 months. When the response is adequate, treatment should be continued; if the response is inadequate, the use of another biological should be considered.[249]

Duration of treatment is yet to be established. However, it is known that interruption of treatment in responders is followed by eosinophilia[250,251] and exacerbations.[250]

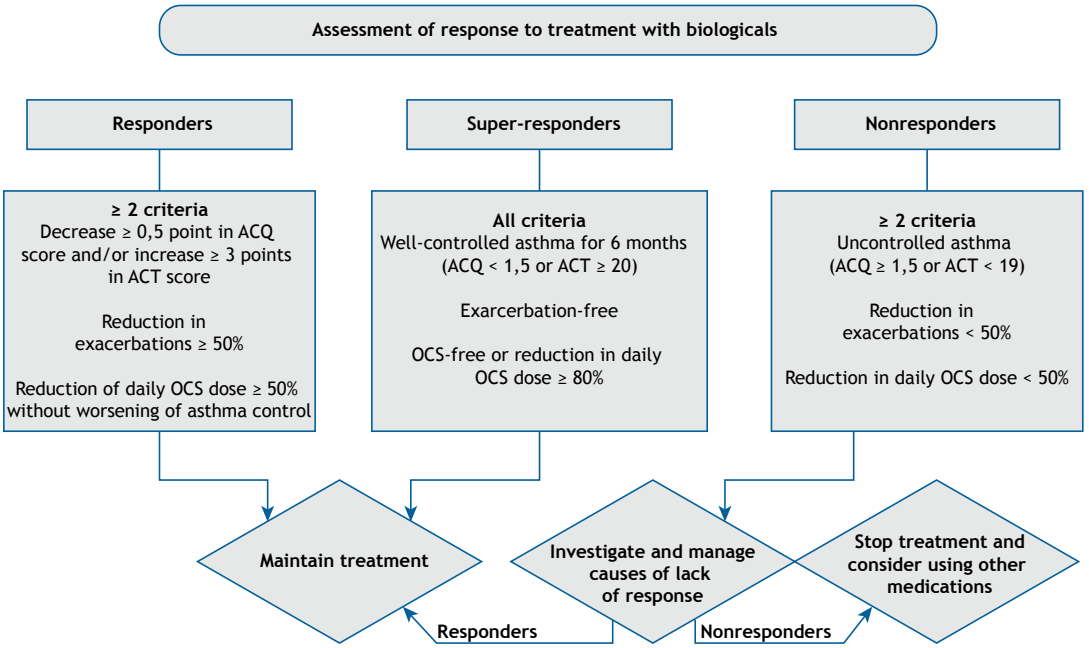

Figure 3. Assessment of response to treatment with biologicals. ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; OCS: oral corticosteroid.

Low-dose OCS

The use of OCS is an alternative option in step V with the lowest possible dose,[2,4] because the regular use or repeated courses of OCS is associated with serious adverse effects, although it is effective in achieving and maintaining asthma control.[252] Major adverse effects are bone mass loss and increased risk of bone fracture, body weight gain, metabolic syndrome, diabetes mellitus, systemic arterial hypertension, adrenal insufficiency, and immunosuppression.[3,9,14,151,253-255] These undesirable effects are dose-dependent.[256]

Gradual reduction and cessation of maintenance OCS

Due to the adverse effects of OCS, an attempt should be made to reduce its dose in all patients. No evidence-based guidelines on the best way to reduce OCS dose is available. However, expert recommendations[254] suggest that this should gradually be carried out up to a minimum effective dose or complete weaning of the medication has been reached. The pace and speed of dose reduction should be patient tailored, based on the history of severe exacerbations, prior treatment duration, and risk and type of adverse effects. Assessment of possible adrenal insufficiency during and after the OCS reduction process is recommended.[257]

NONPHARMACOLOGICAL TREATMENT

Bronchial thermoplasty

Bronchial thermoplasty is an approved nonpharmacological procedure for the treatment of uncontrolled, severe asthma patients being regularly treated.[258] By means of bronchoscopy, a catheter is inserted into the airways, generating radiofrequency energy and heating the bronchial walls in a controlled manner. The mechanism of action involves reduction of smooth muscle and airway nerve endings, as well as mechanical and physiological actions resulting from these reductions. The procedure must be performed in trained centers and consists of three sessions with intervals of 21 days.[259] Three RCTs[258,260,261] have investigated the safety and efficacy of bronchial thermoplasty, demonstrating improvement in quality of life and asthma control, as well as a decrease in exacerbations, emergency visits, hospitalizations, and OCS dose. These effects have been maintained for at least 10 years, with an acceptable safety profile.[262] Bronchial thermoplasty can be considered a treatment option for those patients with severe asthma who do not qualify for or adequately respond to treatment with biologicals.

Physical activity

The paradigm of exercise practice by patients with asthma began to change at the turn of the century with data from a systematic review[263] that compared studies that evaluated asthma patients participating in a physical training program with a group that did not perform physical activities. The group of asthma patients who performed exercises showed a significant improvement in aerobic capacity, but not in pulmonary function parameters assessed at rest.

In the following years, experimental studies have shown a reduction in IL-4 and IL-13 (pro-inflammatory cytokines) levels, suggesting an effect of physical training on reducing airway inflammation[264] and a significant increase in IL-10 (anti-inflammatory cytokine) expression.[265] The reduction in the levels of EosIS and FeNO were demonstrated in a clinical trial[266] that compared asthma patients who performed aerobic training with a control group, indicating that training reduced airway inflammation. However, this finding was not observed in a later study.[267]

A study that evaluated physical training programs for asthma patients has shown improvement in quality of life, as well as a decrease in anxiety/depression and asthma symptoms.[268] Another study showed that physical training improved asthma control and promoted weight loss and reduction of systemic and airway inflammation.[122]

A systematic review[269] including studies with adult asthma patients who underwent aerobic physical training demonstrated improvements in asthma control and pulmonary function. In obese asthma patients, physical exercise also helps with weight loss.[270]

Interventions aimed at promoting behavioral changes to improve physical activity in physically inactive adult patients with asthma have resulted in improvements in asthma control and a decrease in exacerbations, use of rescue medication and OCS bursts, as well as an increase in the practice of physical activities.[271] However, other studies have found no clinically significant improvements in asthma control with increased physical activity after interventions for behavioral change. This might indicate that clinical benefits are dependent on the magnitude of the increase in regular physical activity in asthma patients.[272,273]

Although supervised physical exercise based on structured programs might potentially improve asthma,[269] personal preferences of patients and barriers encountered in the practice of physical activity should be taken into account.[274] These findings point to the important role of physical activity in asthma management, indicating that the implementation of nonpharmacological measures, such as the practice of physical activity, needs to be considered together with pharmacological treatment in patients with severe asthma or DCA as well. The GINA recommends that adults with asthma engage in regular physical activity.[4]

DIAGNOSIS AND MANAGEMENT OF SEVERE ASTHMA IN CHILDREN AND ADOLESCENTS

Diagnostic aspects

The diagnostic criteria for asthma in children are the same as those established for adults. We emphasize, however, that in the 6- to 11-year age group, there are differences in lung function parameters: FEV1/FVC ratio < 0.9; reversibility to bronchodilator use > 12% of baseline values; mean variability of PEF > 13%; and > 12% reduction in FEV1 after exercise challenge

testing.[4] In addition, children with severe asthma do not commonly present with significant changes in or loss of pulmonary function.[275] Methacholine challenge testing should be restricted to cases with normal spirometry results and symptoms suggestive of asthma. A negative test result makes the diagnosis of asthma unlikely.[276]

The definition of severe asthma in patients between 6 and 11 years of age does not differ from that in adolescents and adults. However, it is important to highlight that ICS doses differ in this age group, being considered as a high dose > 400 µg/day of beclomethasone dipropionate (fine particle—hydrofluoroalkane) or equivalent.[4] Children suspected of having severe asthma should always be evaluated and managed by a specialist.[2,4]

The differential diagnosis of severe asthma in this age group includes cystic fibrosis, post-infectious bronchiolitis obliterans, foreign body aspiration, primary ciliary dyskinesia, congenital immunodeficiencies, congenital heart disease, among others.[4]

The investigation of severe asthma in this age group includes some aspects that are worth mentioning. There is no evidence to recommend routine chest CT. In severe asthma, CT should only be performed to exclude other diseases.[277] Investigation of gastroesophageal reflux should only be performed in selected cases. Treatment of asymptomatic gastroesophageal reflux rarely results in clinical improvement of asthma.[277] The risk of exacerbations is reduced by measuring FeNO levels to guide the pharmacological treatment in children.[278] Collection of IS is not recommended for pharmacological management in children.[279]

Severe asthma in children between 6 and 11 years of age should be phenotyped for a T2-high inflammatory profile using allergen sensitization testing, EosPB or EosIS (when available), and FeNO.[4] T2-high allergic eosinophilic asthma is the predominant phenotype in children with severe asthma.[280]

Treatment in children between 6 and 11 years of age

High doses of ICS+LABA are recommended for the treatment of severe asthma (step V) in children between 6 and 11 years of age. Prior to phenotyping, it is recommended to associate tiotropium with ICS+LABA in order to achieve and maintain asthma control.[2,281] Phenotyping is recommended in patients who do not achieve control.

In Brazil, two biologicals—omalizumab (anti-IgE) and mepolizumab (anti-IL-5)—have been approved for the treatment of asthma patients with the T2-high phenotype in this age group. The choice of the biological should be defined individually, considering biomarkers and access to treatment.

Efficacy and safety of omalizumab in children with severe asthma has been proven in an RCT[282] and in a real-life study.[283] A study in children and adolescents in Brazil showed that the inclusion of omalizumab in the treatment regimen improved asthma control and reduced hospitalizations and OCS dose.[284] Some children present with total IgE levels higher than the limits recommended in the manufacturer directions for omalizumab, contraindicating its use.[285]

Efficacy and safety of mepolizumab for children between 6 and 11 years of age was demonstrated in one study.[286] The doses of biologicals in this age group are described in Chart 2.

The response to treatment with biologicals should periodically be evaluated by means of objective measures of asthma control and reductions in exacerbations/hospitalizations and in the dose of OCS. Treatment duration in patients with good clinical response and recommendations on replacing biologicals in cases of treatment failure are yet to be established.

SUMMARY OF RECOMMENDATIONS FOR THE MANAGEMENT OF SEVERE ASTHMA

- Patients diagnosed with or suspected of having severe asthma should be referred to a specialist
- Adherence to treatment and proper inhalation technique must be verified at all medical visits
- Comorbidities and environmental/occupational exposures that may worsen asthma control should be investigated and, if present, eliminated or minimized
- Patients who need treatment with high-dose ICS (budesonide ≥ 1,600 µg or equivalent) associated with LABA and/or LAMA and/or antileukotrienes and/or OCS to maintain control or those whose asthma still remains uncontrolled should be considered as patients with severe asthma, due to the intrinsic severity of the disease
- The inclusion of tiotropium bromide in the treatment of severe asthma is recommended, preferably prior to the use of biologicals
- Patients with a confirmed diagnosis of severe asthma and a recommendation for treatment with biologicals should be phenotyped
- When available, IS analysis should be performed to phenotype severe asthma
- Measuring EosPB levels should be carried out for severe asthma phenotyping when EosIS analysis is unavailable
- Specific IgE and/or skin prick testing should be carried out for phenotyping all patients with severe asthma
- The total serum IgE level should be used to calculate the dose of omalizumab but not for phenotyping or treatment follow-up
- Routine use of FeNO for phenotyping or as a management strategy for severe asthma is not recommended
- The choice of the biological should be based on the phenotype and access to the medication
- The evaluation of response to treatment should be objective, using as parameters asthma control and reduction in exacerbations and of the dose of corticosteroids

- The treatment of responders should be continued indefinitely

AUTHOR CONTRIBUTIONS

RMCP, JEDC, MMMP, and JF: project conceptualization, methodology and administration; supervision; validation; and guarantors of the article. ASR, CAN, ÁAC, ALGF, AMSA, DCB, GCJ, LSBC, MFR, MBM, MAO, MAL, and PMP: drafting, reviewing, and editing the manuscript. All authors approved the final version of the manuscript.

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