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GEMA^{5.0}

SPANISH GUIDELINE ON THE MANAGEMENT OF ASTHMA



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Foreword

Five years have elapsed since the publication of the previous edition of the Spanish Guideline for Asthma Management (*Guía Española para el Manejo del Asma, GEMA*). Every 5 years, GEMA is completely renewed, with an in-depth review of concepts and statements. Therefore, the present fifth edition of the guideline, GEMA^{5.0}, had to be prepared. In this new edition, and given its great acceptance, the format used in the previous editions (concise and clear writing, straightforward classification of evidence, proposal of robust/weak recommendations, and profusion of algorithms and tables) has been maintained¹. Thus, this new GEMA is an update of the state of knowledge about asthma based on the scientific evidence published in prestigious journals.

Sections and chapters have been slightly reordered, and among other novelties (re-design and new contents of www.gemasma.com web site; program for the diffusion in mass media; use of new communication technologies, etc.), the logos' initiative and colors (now red and black) have been remodeled. Also, on this occasion, the quality of writing and the appropriate use of scientific plain-Spanish have been particularly considered, given the large international diffusion especially in Latin America where the asthma guideline is currently in use.

This new edition follows to the same "philosophy" of its predecessors, i.e. drawing up a clinical practice guideline on asthma that is addressed to clinical healthcare professionals, practically oriented, independent and agreed-on by the highest possible number of experts pertaining to various Spanish scientific societies involved in the management of asthma. Given this guideline's scope and the high relevance of the participating professionals, as well as its design and content, this new GEMA^{5.0} is born under the best auspices. Experts of different scientific societies have participated in the present edition, including the following: Spanish Association of Primary Care Pediatrics, Latin American Chest Association, Spanish Society of Allergology and Clinical Immunology, Spanish Society of Family and Community Pharmacy, Spanish Society of Clinical Pharmacology, Spanish Society of Hospital Pharmacy, Spanish Society of Clinical Immunology, Allergology and Pediatric Asthma, Spanish

Society of Family and Community Medicine, Spanish Society of Primary Care Physicians, Spanish Society of Urgent and Emergency Medicine, Society of Pneumology in Primary Care, Spanish Society of General and Family Physicians, Spanish Society of Pediatric Pneumology, Spanish Society of Otorhinolaryngology, Spanish Society of Pneumology and Thoracic Surgery, Spanish Society of Outpatient and Primary Care Pediatrics, and Portuguese Society of Pneumology. In addition to having the collaboration of the Institute for Clinical and Healthcare Excellence, the Spanish Society of Healthcare Managers, Humans Foundation, and the National Federation of Associations of Respiratory Diseases on behalf of the patients.

Overall, **108** experts in asthma, and accredited representatives from **21** societies, scientific groups and associations have participated in the drafting and revision of the document. Because of the number of participants and societies contributing to consensus, this new *GEMA* guideline is the largest ever performed and, most likely, the greatest multidisciplinary consensus ever reached in our geographic environment.

Finally, on behalf of all of the participants of GEMA^{5.0}, we wish to thank the Spanish Pharmaceutical Industry for its invaluable support and patronage that has enabled the drawing-up, edition and diffusion of this guideline. We also would like to acknowledge the highly professional contribution of the staff from Luzán 5 (editing professionals, computer specialists, designers, journalists) throughout the entire editorial process. We expect this new edition of GEMA to obtain at least the same recognition as the previous ones, as well as a widespread diffusion and impact among healthcare professionals involved in asthma care. We also expect it to enhance their education on asthma which in turn will be associated with a better quality in the care of their patients with asthma, and consequently better control and quality of life, which is the reason to be of *GEMA*.

Dr. Vicente Plaza Moral

on behalf of the coordinators, editors,
and reviewers of GEMA^{5.0}

Objective

The main objective of the present guideline is to improve the control and quality of life of persons with asthma by increasing technical training of healthcare professionals in charge of the patients, particularly in aspects related to prevention and diagnostic-therapeutic assessment of the disease.

GEMA, however, is a platform that brings together a series of complementary actions, all designed to reach the aforementioned objective, among which this document acquires a special relevance: an evidence-based clinical practice guideline.

Other documents (*GEMA* pocket, *GEMA* for patients, *GEMA* for educators, etc.) will complete the GEMA “family” in the future.

Specifically, the current document (clinical practice guideline) as well as the whole strategy conforming the GEMA^{5.0} platform, is addressed to healthcare professionals in the settings of Family and Community Medicine, Primary Care Pediatrics, Pneumology, Allergology, Pediatric Allergology and Pneumology, Otorhinolaryngology, Pharmacology, Hospital and Primary Care Pharmacy, General and Specialized Nursing in Respiratory Diseases, as well as to educators, teachers, patients and their families, and caregivers.

Method

Searching for evidence. Based on the previous (complete) edition of GEMA² published in 2015, and following the recommendations for Updating Clinical Practice Guidelines of the National Health System³, members of the Executive Committee performed a systematic search of the literature, with assessment and selection of publications on asthma published from 2015 to 2020 (Pro-GEMA Project). After reviewing high impact journals of Pneumology, Allergology, Pediatrics, Primary Care, Internal Medicine and Otorhinolaryngology, which were also classified into the two first quartiles of their specialty field, a total of **120** documents were selected (abstracts available at <http://www.progema-gemasthma.com/foco.html>) that were considered of interest for updating this guideline. All these documents were provided to the editors for evaluation. Also, they were encouraged to perform bibliographic searches of specific topics by their own. To this purpose, the procedure usually established to develop clinical practice guidelines was followed⁴. Also, the reference lists of the main international practice guidelines^{5,6} were reviewed in order to identify the most relevant systematic reviews and clinical trials. These guidelines were searched in specialized databases (*National Guideline Clearinghouse*, *National Library of Guidelines*) and the TRIP medical literature meta-search engine database. Databases from the *Centre for Reviews and Dissemination* (DARE and HTA database) and *The Cochrane Library* were searched to identify additional systematic reviews and technological evaluations. The search was completed with an update of the systematic reviews since the date of the original search and of relevant studies included in the main electronic databases of original studies (*MEDLINE*, *CENTRAL* and *EMBASE*).

Classification of the evidence. To assess the quality of evidence, an alphabetic classification was used (Table 0.1) that classifies the information into four categories (A, B, C, D) and represents a gradient of confidence in the results obtained in the available studies. Category A would correspond to a high quality evidence and D to a very low quality. For category A, confidence in the results is high and the potential modification of available findings by further studies is unlikely. By contrast, for lower categories, C or D, confidence will be low or very low, and there is a high probability that further studies will modify the results, or even the direction of the effect. However, it should be remember that this system is very useful to categorize the evidence regarding therapeutic

efficacy of drugs or other therapeutic actions, but the effect of other interventions may be underestimated. This can explain why evidence from studies aimed at determining the appropriateness of some diagnostic procedures had often been assigned a level of evidence C.

Taking into account the recent emergence of new approaches used to classify the quality of evidence based on aspects other than the study design^{7,8}, some of the characteristics of the GRADE⁹ framework were used, although the GRADE system was not applied in full.

Classification of recommendations. To classify the relevance and consistency of clinical recommendations, the same method used in the previous editions of GEMA was followed, in which recommendations are categorized into two levels: robust recommendations (R1), that is, those considered by the guidelines making group to be associated with more benefits than risks; and weak recommendations (R2), that is, those in which some uncertainty exists as to whether its application might entail more benefits than risks. To perform this distribution in R1 or R2, the quality of information was weighed (based on the aforementioned classification), the balance between risks and benefits of interventions, the costs (according to the available specialized literature), and the patients' values and preferences (through the participation of FENAER members).

Table 0.1. Classification of the quality of evidence

Category of the evidence	
A	SR of RCTs with or without MA; and RCTs with low risk of bias. Evidence based on a substantial number of well-designed studies with consistent results.
B	SR of RCTs with or without MA; and RCTs with moderate risk of bias. Evidence obtained from a limited number of studies and/or inconsistent results.
C	Evidence based on non-randomized, observational or non-controlled studies.
D	Clinical experience or scientific literatura that cannot be included in category C.

Abbreviations: SR: systematic reviews; RCT: randomised controlled trials; MA: meta-analysis.

The categorization of the recommendation level was established by consensus, firstly by the editors (see below for the working method used) and finally by agreement with the reviewers (through the Delphi method), whose opinions were binding for the final version of all recommendations.

Drafting and consensus of the text and recommendations.

The development of the writing task was based on a pyramidal consensus system, from an initial consensus among the authors of each chapter to a large final consensus among all editors and reviewers. Based on the document of the previous edition and the new bibliographic references on asthma published between 2015 and 2020, a group of editors and coordinators made up by experts from the participating scientific societies drew up the new chapter sections they were assigned (including the classification of evidence and recommendations). The editors submitted their texts to each chapter coordinators who were members of the GEMA Executive Committee. After unifying

and reviewing the texts, the chapter coordinator submitted the draft to the editors of each chapter in order to reach the first partial consensus. After implementation of changes, all chapters were brought together in one single document which, in turn, was sent to all editors and coordinators for telematic discussion (and for face-to-face discussion, when necessary) and approval. The resulting document was submitted to experts in the methodology of clinical practice guidelines from the INPECS (*Instituto para la Excelencia Clínica y Sanitaria* [Institute for Clinical and Healthcare Excellence]), who made a critical review of the methodology and writing of both the text and the recommendations. Finally, after these modifications and improvements, recommendations were reviewed and agreed on (through the Delphi method) by a group of experts in asthma from the participating societies. Recommendations not achieving a certain consensus level were removed from the final document.

Editorial independence

The GEMA^{5.0} project was funded by the pharmaceutical companies listed on the back cover of the document. The views of these funding entities did not influence the content of the guideline.

The editors of this guideline declare that they have received in the last two years fees for their participation in meetings, congresses or research activities organized by the following pharmaceutical companies: ALK, AstraZeneca, Bial, Boehringer-Ingelheim, Chiesi, Esteve, GlaxoSmithKline, Leti, Menarini, MSD, Mundipharma, Novartis, Orion, Pfizer, Sanofi, Teva and Zambón.

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List of abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
Ac	Antibody
ACE	Angiotensin-converting enzyme inhibitors
ACOS	Asthma-COPD overlap syndrome
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	Adverse effects
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Sanitary Products)
AEPap	Asociación Española de Pediatría de Atención Primaria (Spanish Association of Primary Care Pediatrics)
AERD	Aspirin-exacerbated respiratory disease
ALAT	Asociación Latinoamericana del Tórax (Latin American Chest Association)
API	Asthma Predictive Index
AR	Allergic rhinitis
ASA	Acetylsalicylic acid
ATS	American Thoracic Society
BAI	Breath-actuated inhaler
Bd	Bronchodilation
BDT	Bronchodilation test
BHR	Bronchial hyperresponsiveness
BMI	Body mass index
c-ACT	Childhood Asthma Control Test
CAN	Asthma Control Questionnaire in Children
CAL	Chronic airflow limitation
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CPG	Clinical practice guideline
CPK	Creatine phosphokinase
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps

CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
DAC	Difficult asthma control
DPI	Dry powder inhaler
EGPA	Eosinophilic granulomatosis with eosinophilia
EMH	Electronic medical history
ENT	Ear, nose and throat
Eos	Eosinophils
ERS	European Respiratory Society
ESS	Endoscopic sinus surgery
FDA	Food and Drug Administration
FENAER	Federación Española de Asociaciones de Pacientes Alérgicos y con Enfermedades Respiratorias (Spanish Federation of Associations of Patients with Allergic and Respiratory Diseases)
FE_{No}	Fractional exhaled nitric oxide
FEV₁	Forced expiratory volume in one second
FIO	Forced impulse oscillometry
FVC	Forced vital capacity
GC	Glucocorticoids
GEMA	Spanish guideline for asthma management
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GRAP	Sociedad de Respiratorio de Atención Primaria (Primary Care Respiratory Society)
HMW	High molecular weight
HR	Hazard ratio
HRQoL	Health-related quality of life
ICU	Intensive care unit
IGC	Inhaled glucocorticoids
IgE	Immunoglobulin E
IL	Interleukin
ILO	Inducible laryngeal obstruction
IMV	Invasive mechanical ventilation
INGC	Intranasal glucocorticoids
INPECS	Instituto para la Excelencia Clínica y Sanitaria (Institute for Clinical and Health Care Excellence)
ISAAC	International Study of Asthma and Allergens in Childhood
IT	Immunotherapy
i.v.	Intravenous
kg	kilogram
LABA	Long-acting β 2-adrenergic agonists
LAMA	Long-acting muscarinic antagonist
L-ASL	Lysine-acetylsalicylate
LLN	Lower limit of normal
LMW	Low molecular weight

LPT	Lipid transfer protein
LTRA	Leukotriene receptor antagonists
MA	Meta-analysis
MADM	Mean aerodynamic diameter mass
Mg	Magnesium
MR	Magnetic resonance
NAR	Non-allergic rhinitis
NEB	Nebulized
NIMV	Non-invasive mechanical ventilation
NIV	Non-invasive ventilation
NK	Natural killer
nNO	Nasal nitric oxide
NO₂	Nitric oxide
NP	Nasal (sinonasal) polyposis
NSAID	Non-steroidal anti-inflammatory drug
OA	Occupational asthma
OGC	Oral glucocorticoids
OR	Odds ratio
pACT	Pregnancy Asthma Control Test
pANCA	Perinuclear anti-neutrophil cytoplasmic antibody
PaCO₂	arterial partial pressure of carbon dioxide
PaO₂	arterial oxygen partial pressure
PEF	Peak expiratory flow.
pMDI	Pressurized metered-dose inhaler
PPI	Proton pump inhibitor
RADS	Reactive airways dysfunction syndrome
RCT	Randomized controlled trial
RR	Risk ratio
RSV	Respiratory syncytial virus.
SA	Severe asthma
SABA	Short-acting β 2-adrenergic agonists
SaO₂	Arterial oxygen saturation
SAS	Sleep apnea syndrome
SBPT	Specific bronchial provocation test
s.c.	Subcutaneous
SEAIC	Sociedad Española de Alergología e Inmunología Clínica (Spanish Society of Allergology and Clinical Immunology)
SEDISA	Sociedad Española de Directivos de la Salud (Spanish Society of Health Managers)
SEFAC	Sociedad Española de Farmacia Familiar y Comunitaria (Spanish Society of Family and Community Pharmacy)
SEFC	Sociedad Española de Farmacología Clínica (Spanish Society of Clinical Pharmacology)
SEFH	Sociedad Española de Farmacia Hospitalaria (Spanish Society of Hospital Pharmacy)

SEICAP	Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica (Spanish Society of Clinical Immunology, Allergology and Pediatric Asthma)
SEMERGEN	Sociedad Española de Médicos de Atención Primaria (Spanish Society of Primary Care Physicians)
SEMES	Sociedad Española de Medicina de Urgencias y Emergencias (Spanish Society of Urgent and Emergency Medicine)
SEMFYC	Sociedad Española de Medicina Familiar y Comunitaria (Spanish Society of Family and Community Medicine)
SEMG	Sociedad Española de Médicos Generales y de Familia (Spanish Society of General and Family Physicians)
SENP	Sociedad Española de Neumología Pediátrica (Spanish Society of Pediatric Pneumology)
SEORL-CCC	Sociedad Española de Otorrinolaringología y Cirugía de Cabeza y Cuello (Spanish Society of Otorhinolaryngology and Head and Neck Surgery)
SO₂	Sulfur dioxide
SEPAR	Sociedad Española de Neumología y Cirugía Torácica (Spanish Society of Pneumology and Thoracic Surgery)
SEPEAP	Sociedad Española de Pediatría Extrahospitalaria y Atención Primaria (Spanish Society of Outpatient and Primary Care Pediatrics)
SPP	Sociedad Portuguesa de Pneumologia (Portuguese Society of Pneumology)
SR	Systematic review
SUA	Severe uncontrolled asthma
TAI	Test of Adherence to Inhalers
Th2	Type 2 helper T cells
TL	T lymphocytes
TNF	Tumor necrosis factor
TPR	Therapeutic positioning report
TSLP	Thymic stromal lymphopoietin
USAA	Uncontrolled severe allergic asthma
VAS	Visual analogue scale

1. Introduction

1.1 Definition

Asthma is a syndrome that includes different clinical phenotypes that share similar clinical manifestations, but probably of different etiologies. Classically, it is defined as a chronic inflammatory disease of the airways, in which different inflammatory cells and mediators are involved, conditioned in part by genetic factors and associated with bronchial hyperresponsiveness (BHR) and variable degree of airflow obstruction that is totally or partially reversible by either the action of drugs or spontaneously¹. Being a chronic disease and included in the different current chronicity strategies, the objective of its approach is to achieve and maintain control of the disease and the prevention of future risk, especially exacerbations, which can be life-threatening for the patient and generate a burden for the society².

1.2 Prevalence

The prevalence of asthma is highly variable worldwide, ranging from 2% in Tartu (Estonia) to 11.9% in Melbourne (Australia). In addition, the prevalence of wheezing over the last 12 months varies from 4.1% in Mumbai (India) to 32% in Dublin (Ireland)^{3,4}.

According to the 2015 Global Burden of Disease study, the prevalence of asthma has increased worldwide by 12.6% from 1990 to 2015. On the contrary, the age-standardized mortality rate has decreased almost 59% during the same period⁵. This increase in prevalence affects mainly middle-aged people and women, and can be explained by an increase in allergic asthma, with stabilization of the non-allergic⁶.

In our country, The European Respiratory Health Study reported prevalence rates of 4.7% in Albacete, 3.5% in Barcelona, 1.1% in Galdakao, 1% in Huelva and 1.7 % in Oviedo⁷.

Other recent studies show very different prevalences based on different variables, such as: age (adolescents), between 10.6%⁸ and 13.4%⁹; the method used (self-reported by the patient), 13.5%¹⁰; or the study setting (work environment), 2.5%¹¹.

In Spain, a study carried out in Navarra showed a prevalence of 10.6% in adolescents⁸. In another study also conducted in Navarra, but designed and carried out in rural areas, a prevalence of asthma of 13.4% was found in adolescents, the latter being slightly higher in females (13.7% vs. 10.9%), with rhinitis, wheezing (especially associated with physical activity) and dry cough as related symptoms⁹.

A study carried out in Argentina showed a prevalence of asthma in adults (20 to 44 years old) of 6.4%¹² (Table 1.1).

1.3 Risk factors

Factors associated with the appearance of asthma syndrome should be distinguished from triggering factors of symptoms or asthma exacerbation episodes.

The most widely studied risk factors for asthma development, or those with a higher degree of association, are shown in Table 1.2. Many host-related factors are perinatal, while environmental factors vary greatly and can impact on patients of different age groups.

Table 1.1. Prevalence of asthma in adults and adolescents

Author	Area	Year	Prevalence	Comments
Álvarez ⁸	Navarra	2014	10.6%	Adolescents
Elizalde ⁹	Navarra (rural)	2018	13.4%	Adolescents
Vila-Rigat ¹¹	Barcelona	2014	2.5%	Working population 16-64 years
López ¹⁰	Madrid	2017	6.3%/13.5%	Current asthma/accumulated asthma
Arias ¹²	Argentina	2018	6.4%	Adults 20-44 years

Table 1.2. Factors associated with developing of asthma

Risk factors	Evidence	Association	Type of study	Reference
HOST-RELATED FACTORS				
Atopy	C	OR 3.5 (2.3-5.3)	b	Arbes 2007 ¹³
Early menarche	C	OR 1.08 (1.04-1.12)	b	Minelli 2018 ¹⁴
Obesity	B	RR 1.50 (1.22-1.83)	a	Egan 2013 ¹⁵
Bronchial hyperresponse	C	OR 4.2 (1.92-9.23)	b	Carey 1996 ¹⁶
Rhinitis	C	OR 3.21 (2.21-4.71)	b	Guerra 2002 ¹⁷
	C	OR 4.16 (3.57-4.86)	b	Burgess 2007 ¹⁸
	C	RR 3.53 (2.11-5.91)	b	Shaaban 2008 ¹⁹
PERINATAL FACTORS				
Maternal age	C	OR 0.85 (0.79-0.92) 1,4	b	Gómez 2018 ²⁰
Preeclampsia	C	OR 4.01 (1.11-14.43)	b	Stokholm 2017 ²¹
Prematurity	B	OR 2.81 (2.52-3.12) 2	a	Been 2014 ²²
	B	OR 1.37 (1.17-1.62) 3	a	Been 2014 ²²
	C	OR 4.30 (2.33-7.91)	b	Leps 2018 ²³
Cesarean section	C	HR 1.52 (1.42-1.62)	b	Tollánes 2008 ²⁴
Neonatal jaundice	C	OR 1.64 (1.36-1.98)	b	Ku 2012 ²⁵
Lactation	C	OR 0.88 (0.82-0.95) 4	b	Silvers 2012 ²⁶
	B	OR 0.70 (0.60-0.81) 4	a	Gdalevich 2001 ²⁷
Tobacco consumption during pregnancy	C	OR 1.72 (1.11-2.67)	b	Strachan 1996 ²⁸
	A	OR 1.85 (1.35-2.53)	a	Burke 2012 ²⁹
	C	OR 2.70 (1.13-6.45)	b	Cunningham 1996 ³⁰
	C	OR 1.65 (1.18-2.31)	b	Neuman 2012 ³¹
Maternal diet	C	OR 0.49 (0.27-0.90) 2,4	b	Litonjua 2006 ³²
	A	OR 0.54 (0.33-0.88) 5,4	a	Wolks 2017 ³³
	C	OR 0.33 (0.11-0.98) 4	b	Devereux 2007 ³⁴
	A	OR 0.86 (0.78-0.95) 6,4	a	García-Marcos 2013 ³⁵
Infant diet	A	RR 0.66 (0.47-0.94) 7,4	d	Hibbs 2018 ³⁶
Pulmonary function of the neonate	C	OR 2.10 (1.12-3.93)	b	Håland 2006 ³⁷
ENVIRONMENTAL FACTORS				
Aeroallergens	C	OR 0.49 (0.29-0.83) 8,4	b	Kerkhof 2009 ³⁸
	C	OR 0.68 (0.49-0.95) 9,4	b	Kerkhof 2009 ³⁸
Allergens in the workplace	C	RR 2.2 (1.3-4.0)	b	Kogevinas 2007 ³⁹
	C	OR 0.55 (0.43-0.70) 10,4	b	Hoppin 2008 ⁴⁰
Respiratory infections	C	OR 0.52 (0.29-0.92) 11,4	b	Illi 2001 ⁴¹
Tobacco	C	RR 3.9 (1.7-8.5)	b	Gilliland 2006 ⁴²
	C	HR 1.43 (1.15-1.77)	b	Coogan 2015 ⁴³
	C	HR 1.21 (1.00-1.45) 12	b	Coogan 2015 ⁴³
Environmental pollution	A	OR 1.34 (1.17-1.54)	a	Orellano 2018 ⁴⁴
DRUGS				
Paracetamol	C	OR 1.26 (1.02-1.58)	b	Sordillo 2015 ⁴⁵
Antacids	A	RR 1.45 (1.35-1.56)	a	Lai 2018 ⁴⁶
Antibiotics	B	OR 1.12 (0.88-1.42) 13	a	Marra 2006 ⁴⁷
	C	OR 0.6 (0.4-0.96) 4	b	Goksör 2013 ⁴⁸
	C	HR 1.23 (1.20-1.27) 14	b	Loewen 2018 ⁴⁹
	C	OR 1.75 (1.40-2.17) 15	b	Hoskin-Parr 2013 ⁵⁰
Hormone replacement therapy	C	HR (1.54 (1.13-2.09) 16	b	Romieu 2010 ⁵¹

HR: *hazard ratio*; OR: *odds ratio*. RR: risk ratio. Type of study: a meta-analysis-systematic review, b epidemiological prospective study, c epidemiological retrospective study, d clinical trial.

Comment: **1** female sex, **2** very preterm, **3** moderate preterm, **4** protective factor, **5** vitamin D level at initiation of pregnancy, **6** Mediterranean diet, **7** vitamin D supplement, **8** dog exposure, **9** cat exposure, **10** living in a farm, **11** non-respiratory viral infection, **12** passive tobacco consumption, **13** no association, **14** prenatal exposure, **15** postnatal exposure, **16** with estrogens only.

On the other hand, the most common triggers of asthma symptoms or exacerbations are shown in Table 1.3. It is important to be aware of them because they can lead to serious conditions and, therefore, should be avoided.

Genetic factors are becoming increasingly relevant with the progress of research. Current studies show their antagonism in the appearance of asthma, phenotypic expression of the disease, individual response to precipitating factors of asthma

Table 1.3. Precipitating factors of asthma symptoms and exacerbations

Environmental factors	Atmospheric	Pollution	- SO ₂ - NO ₂ - Ozone - CO - Particles in suspension
		Plants	- Grass pollen - Tree pollen - Weed pollen
	Domestic	Dust mites	- Animal epithelium - Cockroach
	Fungus and virus	- <i>Alternaria alternata</i> - <i>Cladosporium herbarum</i>	- <i>Penicillium</i> - <i>Aspergillus fumigatus</i>
Systemic factors	Drugs	- Antibiotics	Topical and systemic non-selective β-blockers
		- <i>Ácido acetilsalicílico</i>	- NSAID
	Food	- Cow milk	- Cereals
		- Egg	- Fish
		- Nuts	- Seafood
		- Sulfite-containing foods	Nuts, wine, lemon, lime and grape juices, dried potatoes, vinegar, seafood, beer, etc.
	Plant panallergens such as profillins or lipid transfer protein (LTP)		
Other	- Hymenoptera venom	- <i>Apis mellifera</i> (bee) - <i>Vespa</i> spp, <i>Polistes dominulus</i> (wasp)	
Occupational-related factors	Low molecular weight substances	Industry involved	
	Drugs	Pharmaceutical industry	
	Anhydrides	Plastic industry	
	Diisocyanates	Polyurethane, plastic, varnish and enamel manufacturing industries	
	Woods	Sawmills, carpentry, joinery	
	Metals	Foundries, nickel plating, silver industries, leather tanning, boiler cleaning	
	Other	Cosmetics industries, hairdressing salons, photography development, refrigeration, dyes	
	High molecular weight substances	Industry involved	
	Substances of plant origin, powder and flours	Farmers, dock workers, mills, bakeries, beer industry, soybean processing, cacao, coffee, tee industries, textile industry	
	Food	Food industry	
	Plant enzymes	Food industry, pharmaceutical industry	
	Plant gums	Food industry, printing, latex industry, sanitary	
	Fungi and spores	Bakeries, farms, farmers	
Animal enzymes	Mills, carmine manufacturing		

symptoms or exacerbations and, very especially, in the response to new therapies in cases of severe asthma⁵².

Finally, it should be emphasized the growing evidence of the importance of environmental pollution, both inside buildings from burning biomass and outdoors from burning fossil fuels^{53,54}. Environmental pollution is an associated factor to the development of asthma and a precipitating factor of asthma symptoms and exacerbations. Also, it contributes to an increase of asthma-related morbimortality as well as the incidence of other chronic respiratory diseases, cardiovascular diseases, and different types of cancer⁵⁵.

1.4 Pathogenesis

Inflammation affects the whole airways including the nasal mucosa, and is present even when symptoms are episodic. However, the relationship between severity of asthma and intensity of inflammation has not been consistently established⁵⁶. The epithelium initiates the

response to inhaled substances secreting cytokines, such as thymic such as *Thymic Stromal Lymphopoietin* (TSLP), IL-33 and IL-25, which are crucial for the activation of type 2 innate immune system (Table 1.4)^{59,60}. Once type 2 innate lymphoid cells have been activated, type 2 proinflammatory cytokines are released, such as IL-4, IL-5 and IL-13, which assume the role of starting and maintaining T2 response (Table 1.5). On the other hand, dendritic cells promote the development of T-helper lymphocytes (Th2) with secretion of type cytokines. Recent studies show that not all patients develop Th2 inflammation, since other molecules such as IL-17 and IF- γ are involved in the so-called, Th2-low asthma. Molecules that participate in this inflammatory cascade are summarized in Table 1.6.

Patients with asthma often exhibit characteristic structural changes, known as airway remodeling, which include thickening of the reticular layer of the basal membrane, subepithelial fibrosis, hypertrophy and hyperplasia of the bronchial smooth muscle, vascular proliferation and dilatation, mucosal gland hyperplasia and mucus

Table 1.4. Airway cells and structural elements involved in asthma

Bronchial epithelium: it is damaged, with loss of ciliated and secretory cells. Epithelial cells are sensitive to changes in their microenvironment, express multiple inflammatory proteins, and release cytokines, chemokines, and lipid mediators in response to physical modifications. Pollutants and viral infections can also stimulate its production. The repair process that follows epithelial damage can be abnormal, increasing the obstructive lesions that occur in asthma ⁵⁷ .
Airway smooth muscle: their cells show an increase in proliferation (hyperplasia) and growth (hypertrophy) expressing proinflammatory mediators, similar to those of epithelial cells ⁵⁸ .
Endothelial cells: participate in the recruitment of inflammatory cells from the vessels to the airway, through the expression of adhesion molecules.
Fibroblasts and myofibroblasts: stimulated by inflammatory and growth mediators, they produce components of the connective tissue, such as collagen and proteoglycans, which are involved in the remodeling of the airway.
Airway cholinergic system: it can be activated by nerve reflexes and cause bronchoconstriction and mucus secretion. Sensory nerves can cause symptoms such as cough and chest tightness, and can release inflammatory neuropeptides.

Table 1.5. Inflammatory cells involved in asthma

T lymphocytes (TL): are increased in number in the airways, with an imbalance in the Th1/Th2 ratio and predominance of Th2 that release specific cytokines, including IL-4, 5, 9 and 13. The cytokines orchestrate the eosinophilic inflammation and IgE production by B lymphocytes. Levels of TL regulators are decreased and TL NK increased ⁶¹ .
Mastocytes: are increased in the bronchial epithelium and infiltrate the bronchial wall smooth muscle. Their activation releases mediators with bronchoconstrictor and proinflammatory activity, such as histamine, leukotrienes and prostaglandin D2 ⁶² . They are activated by allergens, osmotic stimuli (such as exercise-induced bronchoconstriction) and neuronal connections.
Eosinophils: are increased in the airways and its number correlates with severity. They are activated and their apoptosis is inhibited. They release inflammatory enzymes that harm epithelial cells and generate mediators that amplify the inflammatory response ⁶³ .
Neutrophils: are increased in the airways of some patients with severe asthma during exacerbations and in smokers with asthma. Their pathophysiological role is not well defined and their increase may be due to treatment with glucocorticoids ⁶⁴ .
Dendritic cells: are antigen-presenting cells that interact with lymph node regulating cells and stimulate the production of Th2 lymphocytes ⁶⁵ .
Macrophages: these cells may be activated by allergens through the low affinity IgE receptors and release mediators that boost the inflammatory response, particularly in severe asthma ⁶⁶ .
Pulmonary neuroendocrine cells: contribute to Th2 response and stimulate mucus producing cells ⁶⁷ .

Table 1.6. Relevant molecules involved in the asthma inflammatory process

Chemokines. These are mainly expressed by epithelial cells and are important in the recruitment of inflammatory cells in the airways.

Cysteinyl leukotrienes. Potent bronchoconstrictors released by mastocytes and eosinophils.

Cytokines. They drive and modify the inflammatory response in asthma, and determine its severity⁶⁸:

- IL-1 β and TNF α : amplify the inflammatory response.
- GM-CSF: prolong survival of eosinophils in the airway.
- Epithelium-derived cytokines:
 - IL-33: promotes proallergic inflammatory properties of CD4 cells and acts as chemoattractant for Th2 cells.
 - IL-25: involved in eosinophilic inflammation, remodelling and bronchial hyperresponsiveness (this last most controversial).
 - TSLP: induces eosinophilia, increases IgE level, and airway hyperresponsiveness and remodelling.
- Th2-derived cytokines:
 - IL-4: important to the differentiation of Th2 lymphocytes, increased mucus secretion and IgE synthesis.
 - IL-5: necessary for the differentiation and survival of eosinophils.
 - IL-13: important for IgE synthesis and metaplasia of mucus cells.

Histamine. Released by mastocytes contributes to bronchoconstriction and inflammatory response.

Nitric oxide: A potent vasodilator predominantly produced in the epithelial cells by the inducible nitric oxide synthase enzyme.

Prostaglandin D2: A bronchoconstrictor mostly derived from mastocytes; it is involved in the recruitment of Th2 lymphocytes in the airways.

GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF: tumor necrosis factor.

Table 1.7. Mechanisms of airway obstruction in asthma

Bronchial smooth muscle contraction: it occurs in response to multiple mediators and neurotransmitters with bronchoconstrictor effects and is the main mechanism of airway narrowing. Monomeric G proteins (RhoA and Rac1) are involved contributing to contraction and proliferation of muscle cells. It is largely reversible with bronchodilators.

Edema of the airways: it is due to microvascular exudate in response to inflammatory mediators. It is particularly important during acute exacerbations.

Mucus hypersecretion: it is due to an increased number of epithelial goblet cells and an increased size of submucosal glands. It can cause a mucus plug, which is associated with severity of asthma⁷¹.

Structural changes of the airways: subepithelial fibrosis due to deposition of collagen fibers and proteoglycans under the basal membrane; smooth muscle hypertrophy and hyperplasia and increased circulation within the blood vessels of the bronchial wall, with enhanced permeability.

hypersecretion, all of which are associated with a progressive deterioration of pulmonary function⁶⁹. Some of these phenomena are related to the severity of asthma and may lead to a bronchial obstruction, which is occasionally irreversible⁶⁹. These changes may result from a repairing response to chronic inflammation or may occur independently of the inflammatory process⁷⁰.

Narrowing of the airways is the final event of all pathophysiological changes and the cause of most symptoms. However, airflow limitation and symptoms may resolve either spontaneously or in response to medication (reversibility) or even remain absent during some periods of time in a given patient. The different mechanisms contributing to bronchial obstruction are shown in Table 1.7.

Different triggering factors may cause severe narrowing of the airways leading to asthma exacerbation. The most severe episodes occur in relation to viral infections of the upper respiratory tract (rhinovirus and respiratory syncytial virus) or by allergenic exposure⁷². Other precipitating factors include

non-steroidal anti-inflammatory drugs (NSAID) in patients with hypersensitivity to these agents, exercise, exposure to cold air or certain non-specific irritants⁷³⁻⁷⁵. The intensity of the response to these stimuli is related to the underlying inflammation.

Bronchial hyperresponsiveness (HRB) is a characteristic component of asthma, which leads to airway narrowing in response to stimuli that are harmless to people without asthma. It is linked to airway inflammation and repair, and is partially or totally reversible with treatment. Mechanisms involved in BHR are shown in Table 1.8. The degree of BHR is partially correlated with clinical severity of asthma and inflammatory biomarkers⁷⁷. Anti-inflammatory treatment improves asthma control and reduces BHR but does not completely suppress it⁷⁸.

Variability is another important feature of asthma, and is defined as the variation or fluctuation of both symptoms and pulmonary function over time, even during the same day, beyond physiological circadian changes.

Table 1.8. Mechanisms of bronchial hyperresponsiveness

Excessive contraction of airway smooth muscle. It may result from increased volume and/or contractility of bronchial smooth muscle cells.
Uncoupling of airway contraction. It is a result of inflammatory changes in the airway wall that may lead to its narrowing and to loss of the maximum level of contraction, which can be found in healthy airways when a bronchoconstrictor substance is inhaled.
Thickening of the airway wall. Edema and structural changes amplify the bronchial wall narrowing due to airway muscle contraction ⁶⁹ .
Sensitized sensory nerves. Their sensitivity may be enhanced by inflammation, which results in excessive bronchoconstriction in response to sensorial stimuli ⁷⁶ .

1.5 Childhood asthma

Asthma is one of the most prevalent chronic diseases in childhood. According to the International Study of Asthma and Allergies in Childhood (ISAAC) the prevalence in Spain is 10%; similar to that of the European Union, being more prevalent in the coastal areas and in males, in the age group of 6-7 years⁷⁹⁻⁸².

It is estimated that more than half of adults with asthma had already asthma in childhood⁸³.

During the first three years of life, the definition, diagnostic criteria, and even classification of asthma are complicated and

are a matter of controversy⁸⁴, making it difficult to establish its prevalence at these ages.

This is because the usual asthma symptoms (cough, wheezing and respiratory difficulty) are frequent in children younger than 3 years of age without asthma and also due to the impossibility of routinely evaluating pulmonary function.

The definitive diagnosis requires the exclusion of other diseases that can present with similar signs and symptoms (Table 1.9)⁸⁷⁻⁹⁰. In fact, some of these disorders may be associated with asthma⁹¹.

The presence of personal and family history of atopy is the most important risk factor for the subsequent development of

Table 1.9. Differential diagnosis of childhood asthma

Cystic fibrosis	Airway anomalies. Tracheomalacia. Vascular ring
Bronchiectasis	Respiratory dysfunction. Induced laryngeal obstruction
Ciliary dyskinesia	Psychogenic cough
Chronic lung disease of prematurity	Pulmonary tuberculosis
Chronic aspiration. Dysphagia	Chronic interstitial disease
Foreign body aspiration	Congenital heart diseases
Gastroesophageal reflux	Primary or secondary tumors

Table 1.10. Phenotypes of children with wheezing in the Tucson study based on the long-term outcome

1. Transient early wheezing

- Wheezing started before the first year of age and disappeared around the age of 5.
- Negative IgE and/or patch tests, without features or atopy history.
- Decreased lung function at birth, with low values at 16 years of age.
- Bronchial hyperresponsiveness and variability of peak expiratory flow (PEF) negative at 11 years of age.
- Risk factors: maternal smoking during pregnancy, male sex, prematurity, exposure to siblings and/or children at daycare centers.

2. Persistent wheezing (non-atopic)

- Usually beginning before the first year of age and persist at 6 years of age.
- Males and females are equally affected.
- Negative IgE and/or cutaneous tests, without features or history of atopy.
- Normal lung function at birth and reduced at 6 and 11 years of age.
- Bronchial hyperresponsiveness decreases with age.
- Usually disappears at adolescence.

3. Late-onset wheezing (atopic)

- The first episode appears after the first year of age and predominates in males.
- Increased IgE and/or positive cutaneous tests, features and family history of atopy.
- Normal lung function at birth with decrease up to 6 years of age and subsequent stabilization below normal values.
- Bronchial hyperresponsiveness is present.
- It usually persists during adolescence.

D asthma. Other factors are: age at presentation, severity and frequency of episodes, male sex, and severe bronchiolitis (RSV, rhinovirus)⁹¹⁻⁹³.

C After the first description of phenotypes of childhood asthma based on the Tucson study (Table 1.10)⁹⁴, a number of prospective studies (cohorts followed from birth)⁹⁵⁻⁹⁷ or complex biostatistics analyses (grouping of populations without prior hypotheses)⁹⁸ have been conducted trying to identify different phenotypes of childhood asthma. Its clinical usefulness is controversial⁹⁶.

D Base on findings of these studies, tools or prediction models of future risk of asthma have been developed, but a few have been validated. The best known is the Asthma

Predictive Index (Table 1.11) developed from the Tucson cohort study⁹⁹.

Although other indexes or modifications have subsequently appeared, it continues to be the most useful, as it is simple to perform, has been more validated than other tools and has a better positive likelihood ratio¹⁰⁰.

The diagnosis of asthma in children under 3 years of age should be probabilistic, a probability that increases in the presence of atopy. The term asthma should not be avoided when there are more than 3 episodes per year, or severe episodes of cough, wheezing and difficult breathing, with a good response to maintenance treatment with inhaled corticosteroids and if a worsening occurs after its withdrawal.

Table 1.11. Asthma Predictive Index

Previous condition
<ul style="list-style-type: none"> • Infants with 3 episodes of wheezing per year during the first 3 years of life and 1 major or 2 minor criteria.
Major criteria
<ul style="list-style-type: none"> • Asthma in a parent, documented by a physician. • Atopic eczema in the child (at 2-3 years of age), documented by a physician.
Minor criteria
<ul style="list-style-type: none"> • Allergic rinitis in the child (at 2-3 years of age), documented by a physician. • Wheezing apart from colds, reported by the parents. • Peripheral eosinophilia greater than or equal to 4%.
Predictive values for asthma diagnosis at any time between 6 and 13 years of age
<ul style="list-style-type: none"> • Positive predictive value 77%. • Negative predictive value 68%.

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2. Diagnosis

2.1 Clinical features

C A diagnosis of asthma should be considered in the presence of suggestive clinical symptoms and signs, such as wheezing (the most characteristic)¹, dyspnea or breathing difficulty, cough, and chest tightness (key symptoms)^{2,3}. These clinical manifestations are usually variable, occur mainly at night or at early morning and are caused by different triggers (viral infections, allergens, tobacco smoke, exercise, emotions, etc.). Seasonal variations and family and personal history of atopy are important aspects to be considered⁴⁻⁷.

C Usually, several signs or symptoms appear at the same time; isolated clinical manifestations are poorly predictive of asthma^{4,8,9}. None of these symptoms and signs are specific of asthma¹⁰, hence the need to include some objective diagnostic test, usually respiratory function tests.

C The patient's clinical history should also include other aspects, such as the onset of symptoms, the presence of allergic rhinitis or eczema, and a family history of asthma or atopy⁵, all of which increases the probability to establish a diagnosis of asthma. Table 2.1 shows the key questions for the identification of patients with suspected asthma^{2,3}.

On physical examination, wheezing on auscultation is the most characteristic, and in some occasions, nasal obstruction on anterior rhinoscopy, and dermatitis or eczema. However, a normal unrevealing physical examination does not exclude the diagnosis of asthma. **C**

In the presence of acute symptoms at the onset of the disease, a short anamnesis and physical examination will be performed, and treatment will be started. Objective diagnostic tests will be performed once symptoms have been controlled⁸. **C**

If asthma is suspected, a differential diagnosis with other diseases, particularly chronic obstructive pulmonary disease (COPD) should be established as shown in Table 2.2. **C**

2.2 Pulmonary function in adults

2.2.1 Adults

The diagnosis of asthma is established when in a patient with suspected symptoms of disease, a pulmonary function test (preferably spirometry) objectively demonstrates an alteration compatible with asthma. **D**

Table 2.1. Key questions for the diagnostic suspicion of asthma

- Have you ever had “whistling” in the chest?
- Have you ever had cough especially at night?
- Have you had cough, wheezing, breathing difficulty in certain periods of the year or when in contact with animals, plants, tobacco or at the workplace?
- Have you had a cough, “whistling”, breathing difficulty after a moderate or intense physical exercise?
- Have you had colds lasting more than 10 days or “going down into the chest”?
- Have you used inhaled medications that relieve your symptoms?
- Do you have any kind of allergy? Do you have any relatives with asthma or allergy?

Modified from García Polo 2012 and Martín Olmedo 2001^{2,3}.

Table 2.2. Differential diagnosis of asthma in adults

	ASTHMA	COPD
Age at onset	Any age	After 40 years of age
Smoking	Irrelevant	Practically always present
Atopy	Common	Uncommon
Family history	Common	Not assessable
Symptom variability	Yes	No
Reversibility of bronchial obstruction	Significant	Usually less significant
Response to glucocorticoids	Very good, almost always	Indeterminate or variable
	Other possible conditions	Characteristic symptoms
Age between 15 and 40 years	<ul style="list-style-type: none"> • Inducible laryngeal obstruction • Hyperventilation • Inhaled foreign body • Cystic fibrosis • Bronchiectasis • Congenital heart disease • Pulmonary thromboembolism 	<ul style="list-style-type: none"> • Dyspnea, inspiratory stridor • Fainting, paresthesia • Sudden onset of symptoms • Excessive cough and mucus • Recurrent infections • Heart murmurs • Sudden onset of dyspnea, tachypnea, chest pain
Age older than 40 years	<ul style="list-style-type: none"> • Inducible laryngeal obstruction • Hyperventilation • Bronchiectasis • Parenchymal lung disease • Heart failure • Pulmonary thromboembolism 	<ul style="list-style-type: none"> • Dyspnea, inspiratory stridor • Fainting, paresthesia • Recurrent infections • Exertional dyspnea, non-productive cough • Exertional dyspnea, nighttime symptoms • Sudden onset dyspnea, tachypnea

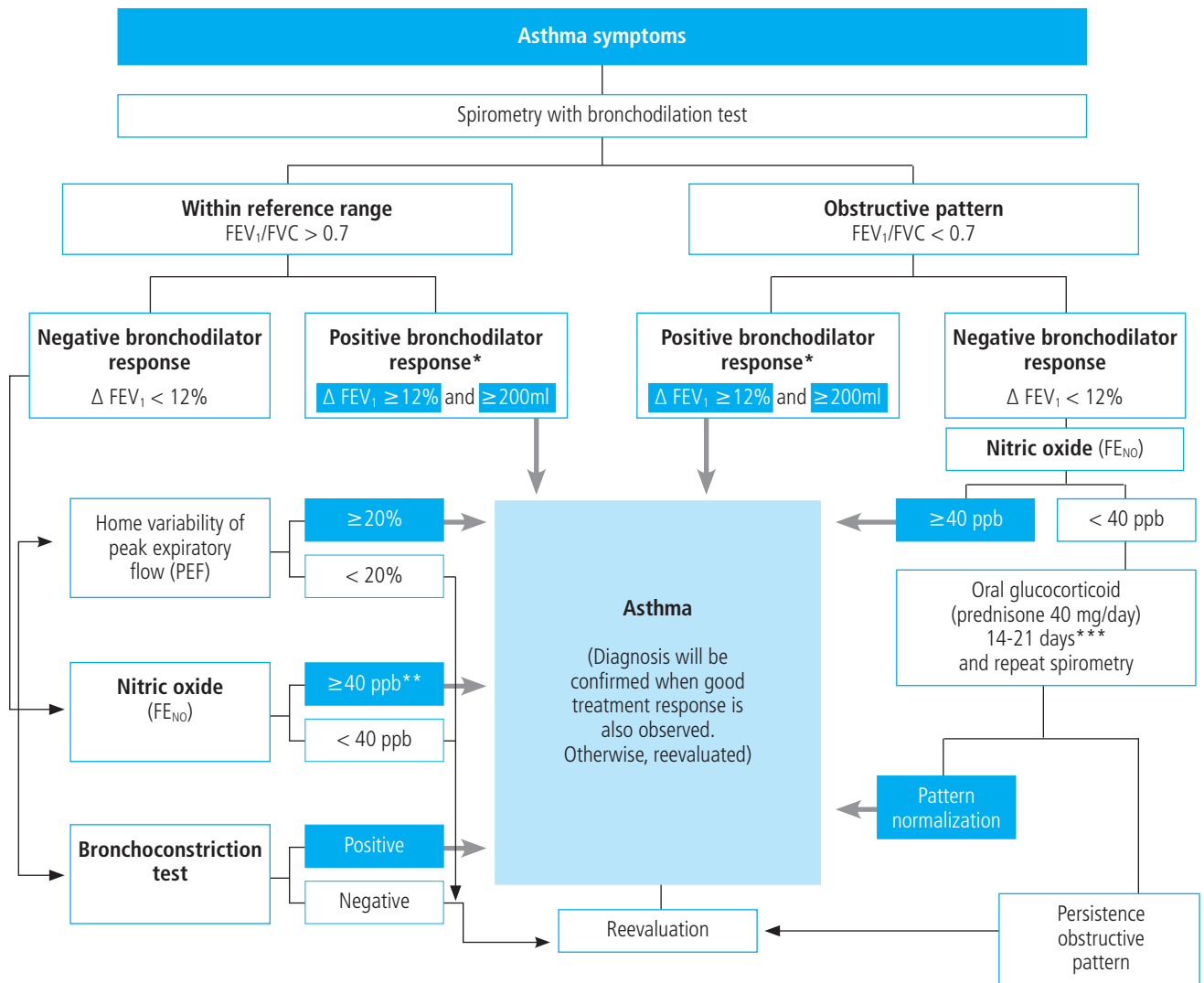
Modified from GINA 2019 and Plaza 2019^{6,10}.

The main functional alterations in asthma are airflow obstruction, reversibility, variability, and bronchial hyperresponsiveness.

Spirometry is the first-choice diagnostic test, as shown in the algorithm of the diagnostic process (Figure 2.1). The main parameters to be determined are forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC); their reference values should be adjusted to the age and ethnic group/race of each patient. Airway obstruction is defined as FEV₁/FVC ratio below the lower limit of reference values, which has been arbitrarily set at 0.77¹². This criterion, however, may lead to an overestimation of airway obstruction in patients of advanced age¹². For this reason, it is recommended to use international reference values, adequate for all ages, which allow to express results as deviations of the mean (z-score), with a lower limit or normal (LLN) of -1.64¹³. A reduced FEV₁ value confirms the obstruction, helps to establish its severity and indicates a greater risk of exacerbations¹⁴. On the

other hand, many patients with asthma may show spirometric values close to the reference range or even a non-obstructive (restrictive) pattern due to air trapping.

For the **bronchodilation test**, the administration of 4 successive/puffs of 100 µg *salbutamol*, or its equivalent, using a pressurized inhaler with a spacer chamber and repeating the spirometry after 15 minutes is recommended. A response is considered to be positive (or significant bronchodilation) when there is a ≥ 12% and a ≥ 200 ml increase in FEV₁ from baseline (Table 2.3)¹². An alternative criterion for bronchodilation is a > 60 l/min or > 20% rise in the peak expiratory flow (PEF)¹⁵. Reversibility can also be identified as an improvement in FEV₁ or PEF after 2 weeks of treatment with systemic glucocorticoids (prednisone 40 mg/day or equivalent) or 2-8 weeks of inhaled glucocorticoids (1500-2000 mg/day of fluticasone propionate or equivalent)¹⁶. Although reversibility of bronchial obstruction is a typical characteristic of asthma, it is not present in all patients.



*In children, a 12% increase is sufficient to consider this test as positive, even if < 200 ml. **In cases of a negative bronchoconstriction test, a diagnosis of eosinophilic bronchitis should be considered. ***Alternatively, inhaled glucocorticoids at very high doses, 1500-2000 µg of fluticasone, 3 or 4 times a day for 2-8 weeks may be used.

Figure 2.1. Diagnostic algorithm.

Table 2.3. Reversibility and daily variability criteria recommended for the diagnosis of asthma

Reversibility	Post-Bd FEV ₁ – pre-Bd FEV ₁ ≥ 200 ml and $\frac{\text{Post-Bd FEV}_1 - \text{pre-Bd FEV}_1}{\text{pre-Bd FEV}_1} \times 100 \geq 12\%$
Daily variability	$\frac{\text{Maximum PEF} - \text{minimum PEF}}{\text{Maximum PEF}} \times 100$ Variability ≥ 20 % during ≥ 3 days per week, in a 2-week recording

FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; Bd: bronchodilatation.

Variability, or excessive fluctuation of pulmonary function over time, is essential for the diagnosis and control of asthma. The most widely recommended daily variability index is the PEF amplitude in relation to the averaged mean over at least 1-2 weeks and recorded before the administration of medication (Table 2.3)¹⁷. A PEF variability ≥ 20 % is diagnostic for asthma¹⁸.

Bronchial hyperresponsiveness is the term that defines an excessive narrowing of the bronchial lumen in the presence of physical or chemical stimuli that usually only provokes little or no reduction of airway caliber¹⁹. The identification of this excessive response to a bronchoconstrictor by means of a **non-specific bronchoprovocation (challenge) test** may be useful in patients with clinical suspicion of asthma and normal

pulmonary function. Either direct agents, such as methacholine or histamine, or indirect agents, such as monophosphate adenosine, mannitol or hypertonic saline can be used²⁰. These latter agents show a better relationship with inflammation and a higher sensitivity to the effect of glucocorticoids²¹. Furthermore, mannitol offers the advantage of being administered via a dry powder inhaler²².

The analysis of bronchial hyperresponsiveness is carried out in terms of sensitivity or threshold, by determining the dose or concentration leading to a 20% decrease in FEV₁ as compared to the post-diluent value^{19,23}. In the case of methacholine, it has been recently recommended to use the cumulative dose associated with a 20% reduction of FEV₁ (PD20) in respect to the value obtained after administration of the diluent²⁴. This type of bronchial challenge test has a high sensitivity but a limited specificity²⁵, thereby being more useful for excluding than for confirming the diagnosis of asthma. Bronchial hyperresponsiveness is also present in other diseases, such as allergic rhinitis, COPD, bronchiectasis, cystic fibrosis or heart failure

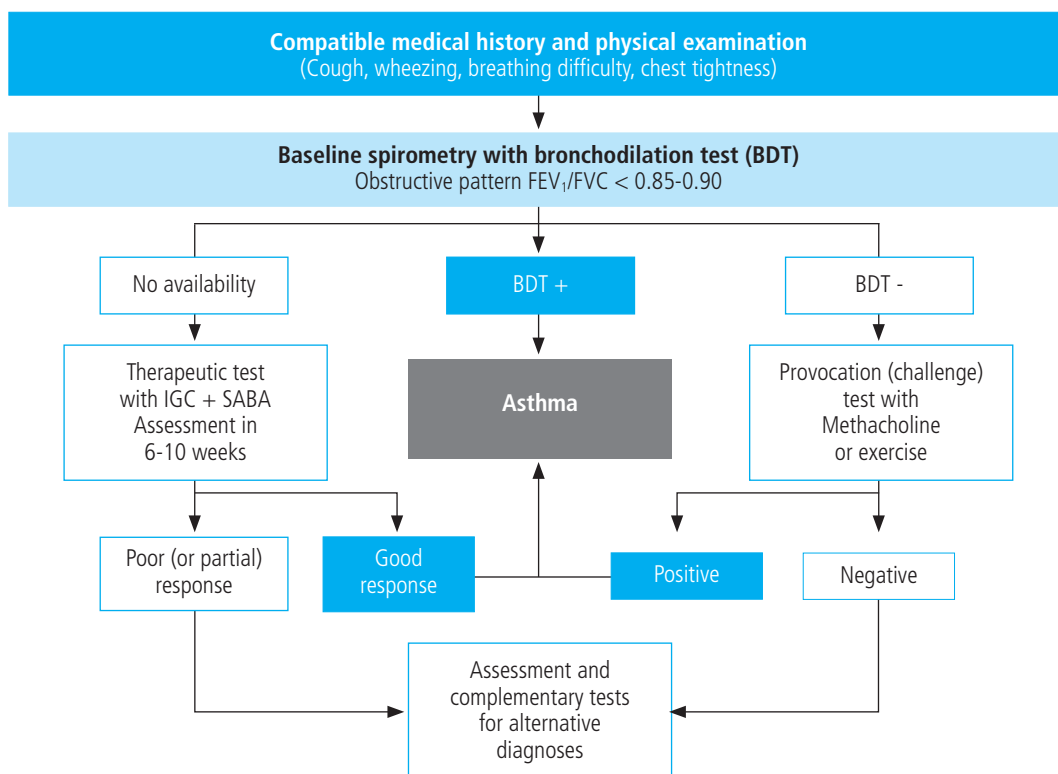
The mannitol test is considered to be positive when a 15% fall in FEV₁ from baseline (PD15) occurs or when there is an incremental decrease of FEV₁ of ≥ 10% between two consecutive doses¹⁹. This test is more useful to confirm the diagnosis of asthma (particularly in cases of exercise-induced bronchoconstriction) because its specificity is > 95%, although its sensitivity is of 60%.

The **fractional exhaled nitric oxide (FE_{NO})** is a non-invasive measurement of bronchial inflammation of allergic-T2 phenotype (see section 7.3) and related in part with eosinophilic inflammation. Although both FE_{NO} and eosinophils are involved in the T2 inflammatory cascade, the two biomarkers are regulated by different inflammatory pathways. The measurement procedure has been standardized²⁶ and the recently recommended cut-off point has been established at < 40 ppb in adults not being treated with glucocorticoids^{8,27}. FE_{NO} has a high sensitivity and specificity for the diagnosis of asthma in non-smoking patients not receiving inhaled glucocorticoids²⁸, particularly in association with reduced FEV₁²⁹. However, a normal FE_{NO} value does not exclude the diagnosis of asthma especially in non-atopic subjects³⁰.

2.3 Pulmonary function in children

The usefulness of pulmonary function tests in children for the diagnosis of asthma is lower than in adults, since most children (including moderate and severe forms) showed FEV₁ values within the reference range^{31,32}. Pulmonary function tests may contribute to the diagnosis, but normal results do not exclude the diagnosis. These tests do not sufficiently discriminate the level of severity³³.

With an appropriate method, it is possible to obtain reliable forced spirometries in children since the age of 3 years. From 5



Positive bronchodilation test (BDT): increase of FEV₁ >12 % as compared with baseline.

Figure 2.2. Asthma diagnostic algorithm in children.

C to 6 years onwards, functional diagnosis of asthma is similar to that made in adults. In children, FEV₁/FVC is better correlated with severity of asthma than FEV₁^{21,34}. In children, obstruction is defined by FEV₁/FVC ratio < 85-90 % (Figure 2.2).

C A bronchodilator test is considered positive when the increase of FEV₁ from baseline is equal or greater than 12%, although it is possible that an 8% increase from baseline or a 9% increase in relation to the predicted value may define better the bronchodilator response in children^{35,36}.

C As children can exhale all the air in 2-3 seconds, an expiration lasting this amount of time may be considered valid provided its validity can be confirmed by visual inspection of the correctness of the maneuver by an expert³⁷. Less strict reproducibility criteria are also acceptable: 100 ml or 10% of FEV₁³⁸.

C FEF_{25-75%} values do not provide relevant additional information and, therefore, do not contribute to clinical decision-making³⁹. At present, international reference values, *all ages equations*, which are suitable for all ages, are available¹³, allowing to express the results as deviations of the mean (z-score), with a lower limit or normal (LLN) of -1.64.

C If diagnosis is uncertain, methacholine and exercise challenge tests may be of special interest in children, since exercise challenge test is relatively easy to perform, reproducible and has a high specificity for the diagnosis of asthma, although its sensitivity is low⁴⁰.

D Between 3 and 5 years of age, it is indispensable to use adequate methodology and appropriate reference values and do not extrapolate values of older children⁴¹⁻⁴³. Since these children may occasionally have expiration times lower than 1 second, the most useful value would be FEV_{0.5} or FEV_{0.75} rather than FEV₁⁴⁴. In this age segment, the normal FEV₁/FVC value would be greater than 90%.

D As for the use of the bronchodilation test at this age, the cut-off point for both FEV₁ and FEV_{0.5} or FEV_{0.75} remains to be determined^{45,46}. Other tests that may be useful in the management of preschool children with asthma include forced impulse oscillometry (FIO)⁴⁷⁻⁴⁹, the measurement of airway resistance using the interrupter technique (Rint), the tidal flow-volume curve analysis or measurement of airway resistance by plethysmography. Any of these techniques must be adapted to ATS/ERS guidelines on pulmonary function in preschool children⁴⁴. For children under 2 years of age, the rapid thoracoabdominal compression is the most widely used technique.

D To perform reliable pulmonary function tests in children, particularly in those younger than 5-6 years of age, it is essential to have nursing staff specifically trained in these techniques as well as laboratories adapted for children.

D Measurement of FE_{NO} allows assessing the degree of bronchial inflammation also in children⁵⁰. The assessment of FE_{NO} in young children is not relevant for predicting a diagnosis of asthma at school age⁵¹. The diagnostic reliability of FE_{NO} for asthma is compromised by the wide confidence intervals and the overlapping of values between children without asthma and those with atopic dermatitis. Population-based studies⁵² have established cut-off values quite similar to those proposed by the ATS⁵³, with positivity in children above 35 ppb.

C Regarding the usefulness of FE_{NO} in the follow-up and treatment adjustment, it has not been possible to consistently demonstrate its benefits. It is necessary, a better knowledge of the personal value and to make therapeutic decisions based on changes in relation to this optimal value⁵⁴. Treatment with inhaled glucocorticoids reduces FE_{NO} concentration, so that measurement of FE_{NO} may be a predictor of response⁵⁵. In some cases (especially in the most severe), increasing trends as compared to the optimal value may be useful to estimate the future risk of relapse⁵⁶.

C Although potentially useful as guidance, the available evidence does not confirm the reliability of FE_{NO} to evaluate adherence to IGC treatment.

C FE_{NO} can be determined in young children using the multiple breath-exhalation technique, with reference values having been established for the age between 1 and 5 years⁵⁷. In this age group, although some study has shown an association between high levels of FE_{NO} and the risk of asthma⁵⁸, this correlation remains to be established.

C Overall, there is no consistent evidence to recommend the routine use of FE_{NO} in the follow-up of children with asthma, and its use should be limited to specialized consultation settings⁵⁹.

2.4 Allergy evaluation

C The aim of allergy testing is to determine the presence of a potential sensitization to aeroallergens that may influence the development of the allergic asthma phenotype or to trigger exacerbations. These tests can be performed in all patients with asthma regardless of their age. The anamnesis helps to evaluate personal and family history of atopy (rhinoconjunctivitis, eczema, food allergy) and the relationship between symptoms and allergen exposure. To make a diagnosis of allergic asthma,

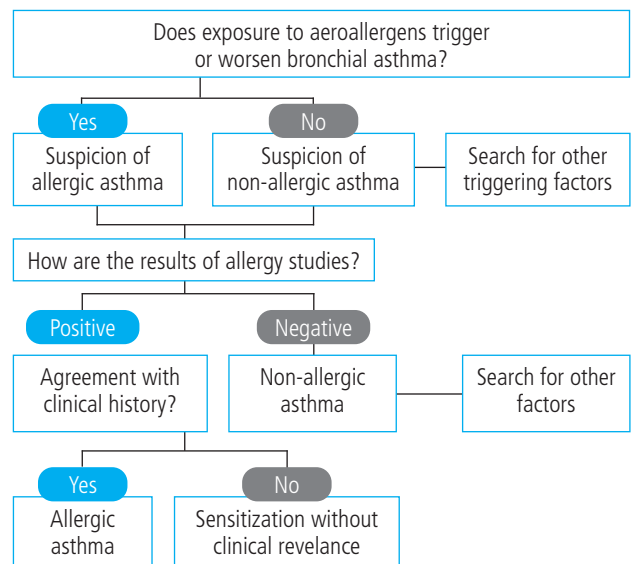


Figure 2.3. Allergy study: to establish the diagnosis of allergic asthma, there should be agreement between the medical history and the result of the allergic study.

C in addition to sensitization to inhaled allergens, it is important to assess the clinical relevance of the results obtained⁶⁰ (Figure 2.3).

B **C** The **intradermal puncture testing or prick test** with standardized extracts⁶¹ (Table 2.4) is the first-choice method because of its high sensitivity, low cost and immediate availability of results. It is necessary to be aware of the variables that may affect the results (drugs, dermatographism, etc.), and to have experience for a correct interpretation of results (false positives due to cross-reactivity)⁶².

B Measurement of **specific serum IgE against complete aeroallergens**, although having the same significance as the *prick* test, is less sensitive and more expensive⁶³. Specific serum IgE to allergenic components allows to differentiate primary sensitization from cross-reactivity⁶⁴, and in polysensitized patients improves the selection of the composition of specific immunotherapy with allergens⁶⁵.

C The **specific bronchial challenge test** may be useful when there is a discrepancy between clinical history and the results of sensitization tests, although it is not routinely recommended and should be performed by expert professionals

2.5 Classification of severity in adults

D Asthma has usually been classified according to its severity, although the definition and assessment of these characteristics has changed over time^{6,11,66}. Severity of asthma is an intrinsic property of the disease that reflects the intensity of its pathophysiological abnormalities⁶⁷.

D Traditionally, the classification of asthma based on clinical and functional parameters includes 4 categories: intermittent, mild persistent, moderate persistent, and severe persistent^{6,11,66}.

Table 2.4. Standard battery of aeroallergens used in intraepidermal puncture skin tests or prick*

Mites	<i>Dermatophagoides pteronyssinus/farinae</i> <i>Lepidoglyphus destructor</i> ; <i>Blomia tropicalis</i>
Dander	Cat, dog
Pollens	Grasses, <i>Olea europaea</i> , <i>Cupressus</i> spp, <i>Platanus</i> spp, <i>Salsola kali</i> , <i>Parietaria judaica</i> , <i>Artemisia vulgaris</i>
Molds	<i>Alternaria alternata</i> , <i>Aspergillus fumigatus</i>

*Extracts of other allergens according to environmental exposure (such as professional allergens) or geographical prevalence can be added.

D It should be remember that asthma severity involves both the intensity of the process and its response to treatment^{68,69}. Severity is usually evaluated while the patient is being treated and is classified according to the need for maintenance therapy to achieve control of symptoms and exacerbations^{68,69} (Table 2.5).

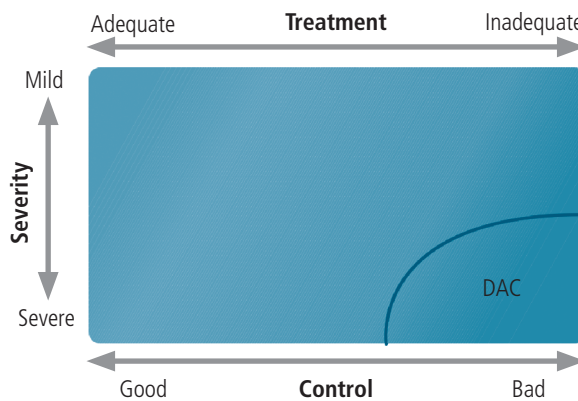
D Severity is not necessarily a constant characteristic of asthma and needs to be periodically reassessed since may vary with time (months or years).

A Most asthma populations suffer from intermittent or mild persistent asthma^{70,71}. The inflammatory features of these apparently non-severe forms of the disease should not be underestimated^{72,73}. Despite the absence of symptoms in mild and intermittent asthma, a correct clinical and functional evaluation of the patient is needed for proper classification and adjustment of treatment.

2.6 Control and measuring methods

D Asthma control is the extent to which manifestations of the disease can be either absent or maximally reduced by therapeutic interventions, and treatment goals are fulfilled^{67,69}, largely reflecting the adequacy of asthma treatment (Figure 2.4).

D Asthma has been arbitrarily classified according to the degree of disease control in: well-controlled asthma, partially controlled asthma and poorly controlled asthma, based on the criteria shown in Table 2.6. Some asthma patients may show a good control of both symptoms and pulmonary function, while simultaneously experiencing exacerbations, whereas other patients may have daily symptoms and very few exacerbations.



Modified from Osborne, et al.⁷⁴

Figure 2.4. Relationship between severity and control of asthma. The degree of control largely reflects the adequacy of treatment. Some patients have a difficult asthma control (DAC).

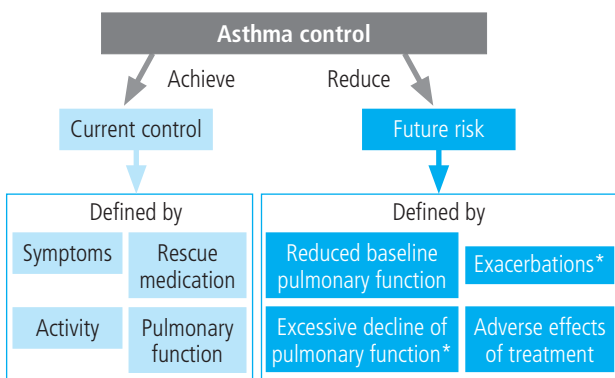
Table 2.5. Classification of asthma severity when it is well-controlled with treatment (stratified by steps)

Severity	Intermittent	Persistent		
		Mild	Moderate	Severe
Minimal treatment requirements to maintain control	Step 1	Step 2	Step 3 or Step 4	Step 5 or Step 6

Table 2.6. Classification of asthma control in adults

	Well-controlled (all of the following)	Partially controlled (any measure in a week)	Poorly controlled
Daytime symptoms	None or ≤ 2 days a month	> 2 days a week	If ≥ 3 characteristics of partially controlled asthma
Limitation of activities	None	Any	
Nighttime symptoms/ awakenings	None	Any	
Need for reliever medication (rescue) (short-acting β_2 -adrenergic agonist)	None or ≤ 2 days a month	> 2 days a week	
Pulmonary function FEV ₁ PEF	$> 80\%$ predicted value or z-score (-1.64) $> 80\%$ better personal value	$< 80\%$ predicted value or z-score (-1.64) $< 80\%$ better personal value	
Exacerbations	None	≥ 1 /year	≥ 1 in any week

FEV₁: forced expiratory volumen in one second; PEF: peak expiratory flow.



*Evaluate risk factors.

Figure 2.5. Domains and risk factors that determine the degree of asthma control.

D Thus, when trying to minimize the clinical expression of asthma two major domains should be take into account⁶⁹: on the one hand, the day-to-day disease manifestations (current control), and on the other hand, its possible consequences (future risk), as shown in Figure 2.5.

D Regarding the current control domain, control would be defined by the ability to prevent the presence of daytime and nighttime symptoms; the frequent use of rescue medication for the relieve of these symptoms; maintenance of pulmonary function within or close to normal limits; the absence of limitations of daily living activities, including family, social, work or school activities, and physical exercise; and finally, the fulfillment of expectations of both patients and their families regarding the quality of care received.

D As for the future risk domain, control includes: the absence of exacerbations; the absence of the need of using systemic glucocorticoids, visits to emergency departments and hospitalizations; the prevention of an excessive loss of

pulmonary function and the development of a fixed airway obstruction or, in the case of children, an anomalous lung development; and finally, the prescription of an optimal treatment with minimum or no adverse effects.

As defined in the control of asthma, a number of procedures should be used for its evaluation⁷⁵. The essential tool for assessing asthma control is **the continued follow-up medical visit**. In this visit, the domains of current control and future risk of exacerbations should be evaluated, together with possible presence of fixed airflow obstruction and treatment-associated adverse effects, and finally and most importantly, the adherence to treatment, including a reminder of the self-management plan and actions to be taken in case of disease decompensation, and trying to reinforce the patient-healthcare professional relationship at each visit.

In order to facilitate and standardize the evaluation of the domain of current control of asthma, different simple questionnaires and easy to be completed by the patient have been developed. The Asthma Control Test (ACT)^{76,77} and the Asthma Control Questionnaire (ACQ)^{78,79} have been validated and culturally adapted for use in Spain. Validation of the ACT questionnaire is more detailed for its use in clinical practice with well-defined cut-off points, so that a score equal to or greater than 20 is highly consistent with well-controlled asthma, between 19 and 16 with partially controlled/not well-controlled asthma, and equal to or lower than 15 with poorly controlled asthma^{76,77}. The minimum clinically relevant difference is 3 points⁸⁰. Also, the Spanish version of the ACQ questionnaire has been validated, with cut-off values based on actual clinical practice^{81,82} with < 0.5 for well-controlled asthma, between 0.5 and 0.99 for partially controlled asthma, and ≥ 1 for poorly controlled asthma. Nevertheless, the reliability of both questionnaires to detect poorly controlled asthma is low⁸³, and for this reason they should never be used as single tools to evaluate asthma control.

Factors associated with the risk of exacerbations include the presence of uncontrolled asthma symptoms and history

Table 2.7. Main risk factors for exacerbations

- Poor current control: ACT < 20 or ACQ > 1.5.
- History of exacerbations: ≥ 1 severe exacerbation in the previous year or history of almost life-threatening asthma
- Undertreatment with inhaled steroids: not prescribed, poor adherence or critical errors with the use of inhalers.
- Excessive use of rescue medication: ≥ 3 inhalers per year (≥ 2 puffs/day).
- Type 2 inflammation: increased peripheral blood/sputum eosinophils, increased FE_{NO}.
- Pulmonary function: low baseline FEV₁, reversibility with the bronchodilator.
- Psychosocial problems, low socioeconomic level.
- Exposures: tobacco smoke, allergens, pollution.
- Comorbidities: obesity, sleep apnea-hypopnea syndrome, chronic rhinosinusitis, gastroesophageal reflux, food allergy, pregnancy.

Adapted from GINA 2019⁶.

C of severe exacerbations. Other factors that may increase the risk of exacerbations in the absence of uncontrolled asthma or previous severe exacerbations are shown in Table 2.7.

C Assessment of biomarkers of type 2 inflammation may contribute to stratify the patient's risk, and taking into account that peripheral blood eosinophilia⁸⁴⁻⁸⁶ or sputum eosinophilia⁸⁷ as well as increased FE_{NO} in a patient treated with inhaled glucocorticoids⁸⁸ are additional factors that increase the risk of exacerbations.

A In the patient with severe asthma, adjustment of treatment with inhaled glucocorticoids has been recommended, taking into account results of sputum eosinophils or FE_{NO}, since this strategy is associated with a lower risk of exacerbations, although it has no effect on symptoms or pulmonary function⁸⁹.

C Forced spirometry is another tool that can help in the assessment of future asthma control, since a low baseline FEV₁ value, in particular < 60%⁹⁰, and the presence of reversibility have been reported as factors that increase the risk of exacerbations.

D Asthma control should be evaluated at each medical visit. Once asthma treatment is started, clinical and therapeutic management of the disease should be directed toward achieving and maintaining control (including symptoms, exacerbations, and lung function). Therefore, the degree of control will determine the decisions on maintenance treatment and dose adjustment, according to the therapeutic steps shown in the corresponding section.

2.7 Control and classification of severity in children

2.7.1 Clinical severity

D The classification of severity is different according to the moment at which asthma is evaluated: at the onset, at the time of diagnosis or thereafter once control of the disease has been achieved. In the first case, the level of severity depends on the frequency and intensity of symptoms (number of attacks and between-attack status: mainly exercise tolerance and nighttime symptoms), the need for a rescue bronchodilator and the values of respiratory function tests. In small children in whom lung function testing is not feasible, severity is only classified according to symptomatology.

D Some children with asthma present symptoms intermittently, episodically, more or less frequently, while others suffer from more persistent symptoms. The character of moderate or severe asthma is determined by the frequency and intensity of the symptoms. In any case, the classification of severity is established once treatment is started, based on the medication necessary to keep the child well controlled.

C In this way, the patient who requires step 5 or 6 treatment will have severe asthma, the one who needs step 3 or 4, a moderate asthma, the one who requires step 1 or 2, a mild asthma.

D Childhood asthma varies substantially over time, even during a single year, which makes its classification difficult. Most young children experience asthma symptoms during viral infections only; they may experience, therefore, moderate or severe asthma in the winter and remain asymptomatic in spring and summer seasons. In order to typify correctly a case of asthma in children, it is necessary to specify, in addition to severity, the triggering factors in the individual patient and the degree of control of asthma.

2.7.2 Control

C Asthma control is defined by the extent to which clinical manifestations have declined or disappeared with the treatment prescribed⁹². It includes the two components: current symptom control and future risk (future consequences of such control)⁶.

C The **current control of symptoms** is evaluated by the presence and frequency of symptoms, both at daytime and nighttime, the need of rescue medication and the presence of some limitation for daily life activities. The criteria established to define the degree of control vary from one guideline to another, but generally it is classified as good or poorly controlled asthma, although some guidelines also introduce the concept of partially controlled⁶.

To facilitate symptom control evaluation, there are available specific Spanish validated questionnaires. One of these questionnaires is the CAN questionnaire (Control de Asma en Niños, Asthma Control Questionnaire in Children) with a version for 9-14 year-old children and another version for parents (2-8 year-old children). This instrument evaluates nine questions about clinical manifestations within the last 4 weeks and is scored between 0 (good control) and 36 (poor control). A patient is considered to be poorly controlled when scores are equal to or higher than 8⁹⁵ (Table 2.8). Also available is the Childhood Asthma Control Test (c-ACT), validated in Spanish^{95,96} for 4-11 year-old children, which includes 7 questions (4 for the child and 3 for the parents/caregivers). A patient is considered to be poorly controlled when the score is lower than 20 (Table 2.9).

The **future risk** assesses the presence of risk factors for exacerbations (Table 2.10), to develop a fixed airflow limitation (undertreatment with IGC, prematurity⁹⁷, environmental exposure to tobacco smoke, low FEV₁, severe asthma, previous hospitalizations) and for suffering treatment-related side effects (frequent courses of oral glucocorticoids, high doses of IGC)⁹⁸.

In addition to the control of clinical symptoms and pulmonary function, measurement of FE_{NO} has been advocated as an approach to assess the control of inflammation. Although potentially useful in some patients, this procedure does not seem to add any relevant benefits to the aforementioned follow-up and treatment strategies⁹⁹.





Table 2.8. Asthma Control Questionnaire in Children (CAN)⁹³

<p>1. In the last 4 weeks, how often have you coughed during the day without having a cold?</p> <p>4. More than once a day 3. Once a day 2. 3 to 6 times a week 1. Once or twice a week 0. Never</p>	<p>4. In the last 4 weeks, how often have you had wheezing at night?</p> <p>4. More than once a night 3. Once a night 2. 3 to 6 times a week 1. Once or twice a week 0. Never</p>	<p>7. When the child exercises (plays, runs, etc.) or bursts out laughing, does he/she coughs or wheezes?</p> <p>4. Always 3. Almost always 2. Sometimes 1. Almost never 0. Never</p>
<p>2. In the last 4 weeks, how often have you coughed at night without having a cold?</p> <p>4. More than once a night 3. Once a night 2. 3 to 6 times a week 1. Once or twice a week 0. Never</p>	<p>5. In the last 4 weeks, how often have you had breathing difficulty during the day?</p> <p>4. More than once a day 3. Once a day 2. 3 to 6 times a week 1. Once or twice a week 0. Never</p>	<p>8. In the last 4 weeks, how many times has he/she had to visit the emergency department because of his/her asthma?</p> <p>4. More than 3 times 3. 3 times 2. Twice 1. Once 0. Never</p>
<p>3. In the last 4 weeks, how often have had wheezing/whistling sounds in your chest during the day?</p> <p>4. More than once a day 3. Once a day 2. 3 to 6 times a week 1. Once or twice a week 0. Never</p>	<p>6. In the last 4 weeks, how often have you had breathing difficulty during the night?</p> <p>4. More than once a night 3. Once a night 2. 3 to 6 times a week 1. Once or twice a week 0. Never</p>	<p>9. In the last 4 weeks, how many times has the child been admitted to hospital because of her/his asthma?</p> <p>4. More than 3 times 3. 3 times 2. Twice 1. Once 0. Never</p>





Table 2.9. Childhood Asthma Control Test (ACT) validated in Spanish^{95,96}

Have your child complete these questions




1. How is your asthma today?

 0 Very bad	 1 Bad	 2 Good	 3 Very good
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2. How much of a problema is your asthma when you run, exercise or play sports?

 0 It's a big problem, I can't do what I want to do	 1 It's a problem and I don't like it	 2 It's a little problem but it's okay	 3 It's not a problem
---	---	--	---

3. Do you cough because of your asthma?

 0 Yes, all of the time	 1 Yes, most of the time	 2 Yes, some of the time	 3 No, none of the time
---	--	--	---

4. Do you wake up during the night because of your asthma?

 0 Yes, all of the time	 1 Yes, most of the time	 2 Yes, some of the time	 3 No, none of the time
---	--	--	---

Please complete the following questions on your own

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5 Not, at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday
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6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5 Not, at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday
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7. During the last 4 weeks, how many days did your child wake up during the night because of the asthma?

5 Not, at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday
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Table 2.10. Risk factors for asthma exacerbations in children^{98,99}

-
- At least one exacerbation in the previous year.
 - Previous care in the ICU or need of intubation.
 - Excessive use of SABA.
 - Persistent and/or uncontrolled symptoms.
 - Lack of adherence to treatment*, inadequate inhalation technique.
 - Low FEV₁. Positive bronchodilation test.
 - Exposure to allergens in case of allergy/atopy.
 - Exposure to tobacco smoke.
 - Comorbidities: obesity, allergic rhinitis, food allergy.
 - Important psychological or socioeconomic problems.
 - Other: peripheral blood or sputum eosinophilia; increase of FE_{NO} in routine control visits.
-

*The ratio between the number of control medications administered and control medications prescribed is < 0.5.

RECOMMENDATIONS

- 2.1. Asthma should be suspected in a patient with wheezing, dyspnea (or breathing difficulty), cough and chest tightness of variable intensity and frequency. R2
- 2.2. In case of suspected asthma, seasonal variations and personal or family history of asthma or atopy are important aspects to be considered, although none of these or none of the signs or symptoms, especially isolated, are specific of asthma. R2
- 2.3. **The diagnosis** of asthma should be based on objective measures of functional involvement. Spirometry with a bronchodilation test is the diagnostic study of choice. R2
- 2.4. The diagnosis of asthma should be considered in the presence of daily **variability** of peak expiratory flow (PEF) > 20 %, or an **increased fractional exhaled nitric oxide (FE_{NO})** > 40 ppb in patients who have not been treated with glucocorticoids, particularly in association with reduced FEV₁. R2
- 2.5. **Non-specific bronchial challenge** test should be considered to exclude the diagnosis of asthma. R2
- 2.6. Periodic spirometry tests (at least once a year) are recommended for children with asthma requiring continuous treatment. R2
- 2.7. In children, except for specialized consultation, it is not necessary to measure FE_{NO} routinely. R2
- 2.8. Allergy studies are especially indicated when aeroallergens are suspected to be involved in the development of asthma or its exacerbations, or when other associated atopic diseases are present. R2
- 2.9. The diagnosis of allergic asthma will be based on the agreement between the patient's clinical history and the results of diagnostic studies. R2
- 2.10. The severity of asthma (in adults and children) will be established according to the minimum maintenance treatment needed to achieve control. In untreated patients, the severity of asthma should be established at the beginning of treatment, with further re-evaluations once control is attained. R2
- 2.11. The severity of asthma (in adults and children) is not necessarily a constant feature that can change over time (months or years), so that periodic re-evaluation is required. R2
- 2.12. Control of asthma (in adults and children) should be evaluated at each consultation, and treatment should be adjusted to achieve and maintain control. Control has two main components that should be identified: current control and future risk. R2
- 2.13. In the objective assessment of the degree of current control of asthma (in adults and children), it is recommended using validated questionnaires for symptoms (preferably ACT in adults, and cACT and CAN in children). In the assessment of future risk of exacerbations, recommendations include questioning on previous events, spirometry, use of inhaled glucocorticoids and reliever/rescue medication, comorbidities and, in selected cases, inflammatory biomarkers (peripheral blood or sputum eosinophils and FE_{NO}). R2

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3. Maintenance treatment

3.1 Objectives

The main objective of asthma management is to achieve and maintain control of the disease as quick as possible, in addition to prevent exacerbations and chronic airflow obstruction and to maximally reduce mortality. With a properly designed treatment plan, therapeutic targets (Table 3.1) can be achieved in the majority of patients in terms of daily symptom control (current control domain) and prevention of both exacerbations and excessive loss of pulmonary function (future risk domain).

To attain these objectives a global and individualized long-term strategy must be followed based on an optimally adjusted pharmacological treatment along with supervision measures, environmental control and asthma education activities¹. Pharmacological treatment should be adjusted according to the degree of control, considering the most effective therapeutic options, safety and cost of the different alternatives, and taking into account the patient's satisfaction with the degree of control achieved. Patients should be periodically evaluated to determine whether objectives are being met. Clinical inertia and causative factors on the part of the patient, the physician and the healthcare system should be avoided.

Table 3.1. Asthma treatment goals

In the domain of current asthma control

- To prevent daytime, nighttime and exercise-related symptoms.
- Use of short-acting β_2 -agonists no more often than twice a month.
- To maintain a normal or near-normal pulmonary function.
- No restrictions on daily life activities and physical exercise.
- To fulfil the expectations of both patients and their families.

In the domain of future risk

- To prevent exacerbations and mortality.
- To minimize progressive loss of pulmonary function.
- To avoid treatment-related adverse effects.

Avoid therapeutic inertia

3.2 Pharmacological treatment

Asthma treatment should follow an overall plan, established by consensus of the physician and the patient (and eventually by the patient's family), in which the goals, the interventions to achieve them and the criteria for their modification or adaptation according to changing disease circumstances must be made clear. Distinguishing between the 'current control' domain and the 'future risk' domain in the control of the disease is relevant, because it has been documented that these domains may respond differently to treatment^{2,3}. For example, some patients may have a good daily control of asthma symptoms and yet experience exacerbations, and viceversa.

Treatment should be adjusted continuously, so that the patient remains always in a well-controlled status. This cyclic treatment adjustment means that asthma control should be objectively assessed (chapter 2.6), that the patient is being treated to achieve control and that treatment is periodically checked to maintain asthma control (Figure 3.1). That is, if a patient is not well controlled, treatment must be stepped up as needed in order to regain control, always taking into account non-pharmacological measures, treatment adherence and risk factors susceptible to be modified.

If asthma has been controlled for at least 3 months, maintenance therapy may be gradually decreased in order to determine minimum treatment needs that are required to maintain control⁴. A simple scoring system that includes data of different clinical (ACT, previous exacerbations) and functional (spirometric values) variables has been developed, to determine the risk after stepping down treatment in patients with controlled asthma⁵.

Drugs used to treat asthma are classified as controller or maintenance medications and reliever medication, also called "rescue" medication. **Controller or maintenance medications** should be administered continuously during prolonged periods of time, include inhaled glucocorticoids (IGC) or systemic glucocorticoids, leukotriene receptor antagonists (LTRA), long-acting β_2 -agonists (LABA), tiotropium and monoclonal antibodies (omalizumab, mepolizumab, reslizumab and dupilumab). Chromones and sustained-release theophylline have fallen into disuse because of their lower efficacy.

Reliever medications are used on-demand for rapid treatment or prevention of bronchoconstriction, and include

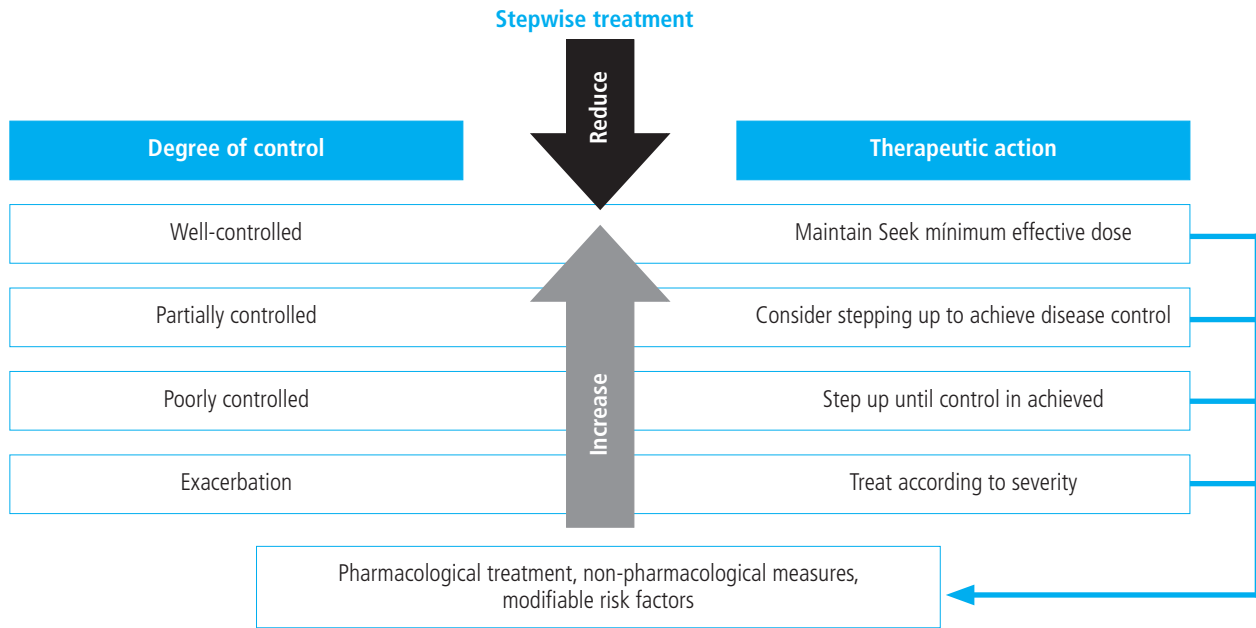


Figure 3.1. Cyclic adjustment of treatment according to periodic assessment of control of asthma.

Table 3.2. Characteristics of inhaled β_2 -adrenergic agonists

Drug	Amount per puff (μg)		Time of effect (minutes)		
	Pressurized inhaler	Dry powder	Onset	Maximum	Duration
Short-acting					
Salbutamol	100	100	3-5	60-90	180-360
Turbutaline	-	500	3-5	60-90	180-360
Long-acting					
Formoterol	12	4.5 – 9 - 12	3-5	60-90	660-720
Salmeterol	25	50	20-45	120-240	660-720
Vilanterol	-	22	3-5	-	1440

inhaled short-acting β_2 -agonists (SABA) (Table 3.2) and inhaled short-acting anticholinergics (*ipratropium bromide*). Also, the combinations *budesonide/formoterol*, *beclomethasone/formoterol* or *beclomethasone/salbutamol*, used on-demand can be considered reliever medications.

The six treatment steps (Figure 3.2) aimed at achieving asthma control are the following:

3.2.1 Steps

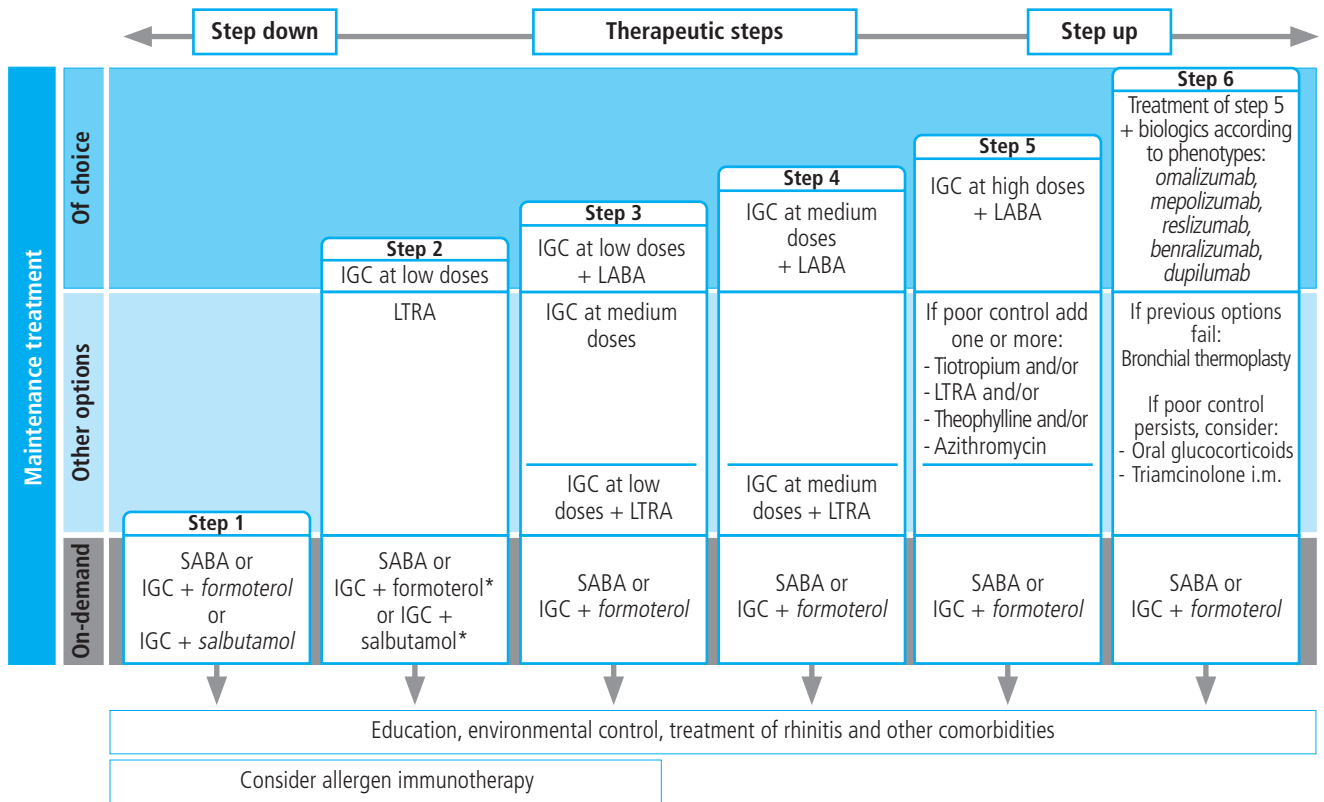
Step 1

Different treatment options can currently be considered for this step. A correct clinical and functional assessment of the patient is required for an adequate selection of treatment.

Inhaled SABA (*salbutamol* or *terbutaline*), exclusively on-demand, can be used in those patients with mild and occasional daytime symptoms (maximum twice a month) and without nighttime symptoms^{6,7}. The patient should

remain asymptomatic between episodes, maintain a normal pulmonary function, and neither having had exacerbations in the previous year nor presenting risk factors for exacerbations (Table 2.7)⁶.

The association *budesonide/formoterol* on-demand can also be used⁸. In a randomized study on adult asthma patients with approximately half of patients having intermittent asthma and in which an open-label design was used to reflect clinical practice conditions⁹, the use of *budesonide/formoterol* on-demand was superior to salbutamol on-demand in the prevention of exacerbations. In a small study of patients with intermittent asthma and increased fractional exhaled nitric oxide (FE_{NO}) in which both *budesonide/formoterol* and *formoterol* on-demand were compared, the combination showed a higher reduction of FE_{NO} levels¹¹. However, these indications are not included in the technical specifications of these drugs. In addition, cost-benefit studies have not been carried out.



*Without maintenance treatment.

IGC: Inhaled glucocorticoid; LABA: Long-acting β_2 -agonist; LTRA: Leukotriene receptor antagonist; SABA: Short-acting β_2 -agonist

Figure 3.2. Therapeutic steps for maintenance treatment in adult asthma.

Table 3.3. Equipotent doses of inhaled glucocorticoids

	Low dose (mg/day)	Medium dose (mg/day)	High dose (mg/day)
Budesonide	200-400	401-800	801-1..600
Beclomethasone dipropionate	200-500	501-1000	1001-2000
Extrafine beclomethasone*	100-200	201-400	> 400
Ciclesonide	80-160	161-320	321-1280
Fluticasone propionate	100-250	251-500	501-1000
Fluticasone furoate	-	92	184
Mometasone furoate	100-200	201-400	401-800

*Extrafine beclomethasone dipropionate.

A The use of an inhaled SABA on-demand, more than twice a month, for the treatment of symptoms (excluding its preventive use before exercise), or having had exacerbations in the previous year, or a FEV₁ value < 80 % indicates an inadequate asthma control and prompts the initiation of maintenance therapy¹²⁻¹⁴.

A Inhaled SABAs administered 10-15 minutes before exercise are the drugs of choice to prevent exercise-induced bronchoconstriction¹⁵.

D An inhaled anticholinergic is only recommended as a reliever medication in those rare cases of intolerance to SABA agents⁸.

Step 2

A The treatment of choice at this step is an inhaled glucocorticoid (IGC) (*beclomethasone, budesonide, ciclesonide, fluticasone or mometasone*) at low doses and administered daily¹⁶⁻¹⁹. In general, this is the first step for most patients with persistent asthma who have not been previously treated. The usual dose ranges between 200 and 400 $\mu\text{g/day}$ of budesonide or equivalent. Continuous administration of IGC is the most effective treatment for persistent asthma, both for the control of daily symptoms and to reduce the risk of exacerbations^{13,19-21}. The equipotent doses of the most common IGC are shown in Table 3.3.

B Two clinical trials showed that a strategy of using a combination of *budesonide/formoterol* in a single inhaler on-demand compared to continuous IGC treatment in mild persistent asthma, was not inferior in preventing exacerbations (the rate of which was similarly low); however, it was inferior in the maintenance of asthma control and in the increase of pulmonary function^{22,23}. In a randomized open-label study⁹, *budesonide* twice a day plus salmeterol on-demand and *budesonide/formoterol* on-demand were similar regarding annualized exacerbation rates.

Also, a similar result with *beclomethasone/salbutamol* has been observed.

D Results of the aforementioned studies may provide indirect evidence of a possible indication of the combinations of low dose IGC with LABA or SABA (e.g. *budesonide/formoterol*, *beclomethasone/formoterol* or *beclomethasone/salbutamol*), administered exclusively on-demand, in the treatment of step 2 in patients with low treatment adherence and in which specific educational interventions have been unsuccessful. However, no studies have been specifically designed to assess this therapeutic indication.

A At this level, an alternative treatment includes leukotriene receptor antagonists (LTRA) or anti-leukotrienes (*montelukast* and *zafirlukast*)^{24,25}, although IGC are more effective for long-term treatment²⁴. Patients who are well controlled on IGC at low doses fail to maintain the same level of asthma control with *montelukast*²⁶.

B LTRA would be particularly indicated as alternative drug in patients who are unable or unwilling to receive IGC or have adverse effects with IGC, have difficulties with the inhaler technique, or suffer from concomitant allergic rhinitis^{27,28}.

A In patients who have not previously received maintenance treatment with IGC, the combination of IGC at low doses and LABA as initial treatment as compared with IGC at low doses, improves symptoms and pulmonary function but has a higher cost and it does not reduce the risk of exacerbations²⁹.

B Sustained-release *theophylline* is not recommended for use at this step since it have been shown to be modestly effective as both bronchodilator and anti-inflammatory drug^{30,31} and may cause mild to serious adverse events.

A Chromones (*disodium cromoglycate* and *nedocromil sodium*) show low efficacy, although they have a good tolerability³². Currently, they are not commercialized in Spain for this indication.

Step 3

A First-line treatment at this step is a combined inhaled treatment with IGC at low doses and a LABA (*salmeterol* or *formoterol* or *vilanterol*)³³⁻³⁸, which can be administered using a single device (preferred option) or separate inhalers. By using this combination a more pronounced reduction of symptoms, improvement of pulmonary function, and reduction of exacerbations and use of reliever medications is obtained as compared to increasing the dose of IGC. However, an appropriate individualized risk/benefit assessment for both strategies is required.

A Treatment with LABA should be always accompanied by an IGC. LABA agents must never be used as monotherapy because of a higher risk of hospitalizations and life-threatening exacerbations^{40,41}. IGC/LABA combinations

commercialized in Spain include *fluticasone propionate* with *salmeterol*, *budesonide* with *formoterol*, *beclomethasone dipropionate* with *formoterol*, and *fluticasone furoate* with *vilanterol*.

Formoterol is a rapid-onset LABA. For this reason, if *budesonide/formoterol* or *beclomethasone/formoterol* combinations are chosen, they can be used as both maintenance and reliever therapy (MART strategy). This strategy leads to reduced exacerbations and a better asthma control, despite requiring a lesser amount of IGC^{20,42-49}. It may be assumed that other IGC combinations (*fluticasone propionate*) with *formoterol* may be effective as MART strategy, although there is no evidence of its use as maintenance and on-demand treatment and the indication is not included their technical specifications.

In any case, MART therapy always should be administered using a single inhaler device.

A further option at this step includes increasing IGC doses up to medium doses, but this approach is less effective than adding a LABA⁵⁰⁻⁵². Alternatively, IGC at low doses associated with a LTRA may be used. This option has been found to be superior to IGS monotherapy and although it is not as effective as the IGS and LABA combination, has an excellent safety profile⁵³⁻⁵⁶. However, the addition of an LTRA does not appear allowing to reduce the IGC dose⁵⁷.

Step 4

The first-line treatment at this step is the combination of IGC at medium doses with a LABA^{29,34,36,58}.

A For patients who have had at least one exacerbation in the previous year, the combination of a IGC at low doses (*budesonide* or *beclomethasone*) and *formoterol*, using the MART strategy, is more effective in reducing exacerbations than the same dose of an IGC and LABA in a fixed schedule, or higher doses of IGC^{49,59}.

B Alternatively, the combination of an IGC at medium doses with a LTRA can be used, although the addition of LABA to the IGC is more effective in preventing exacerbations, control of daily symptoms and improving pulmonary function⁵⁴.

Step 5

B The next step consists of up-titrating IGC dosage and using it in combination with LABA^{34,36,60}. IGC at medium and high doses are usually administered twice daily, although a greater therapeutic efficacy can be achieved with *budesonide* by increasing the dosing frequency up to 4 times a day⁶¹.

C Other drugs can be added for maintenance therapy, with a subgroup of patients improving with the addition of LTRA^{62,63} or sustained-release *theophylline*⁶⁴.

B In patients not well controlled with the combination of an IGC at low doses and a LABA, who show post-bronchodilator FEV₁/FVC ≤ 70 %, the addition of *tiotropium* as maintenance therapy has shown to improve pulmonary function and to reduce exacerbations^{65,66}.

B Macrolide antibiotics, particularly *azithromycin* administered 3 days/week for several months, may play a role as an add-on medication in patients with severe non-eosinophilic asthma and frequent exacerbations^{67,68}, as well as in eosinophilic asthma⁶⁹ (see chapter 7).

Step 6

A For asthma patients who remain uncontrolled and with frequent exacerbations, the addition of biologic drugs should

A be considered after a specialized evaluation and according to the endophenotype of the patient.

A In cases of uncontrolled severe allergic asthma (USAA), the anti-IgE monoclonal antibody (*omalizumab*) by the subcutaneous route can be added, which improves daily symptoms and decreases exacerbations⁷⁰⁻⁷³, increasing the overall control of the disease (see chapter 7).

A In patients with eosinophilic USAA, independently of the presence of allergy, biologic drugs targeting interleukin-5 (IL-5) pathway can be used. Currently, anti-IL-5 monoclonal antibodies, *mepolizumab* y *reslizumab*, and the anti-IL-5 receptor α chain (IL-5R α), *benralizumab*, are approved as additional treatment of eosinophilic USAA (severe refractory eosinophilic asthma)⁷⁴⁻⁸⁰ (see chapter 7).

A *Dupilumab*, a human monoclonal antibody directed against the interleukin-4 receptor subunit α (IL-4R α) of IL-4 that blocks the effects of IL-4 and IL-13 is approved as additional treatment in patients older than 12 years of age with USAA with increased eosinophils and/or FE_{NO} (see chapter 7).

In cases in which the administration of biologic agents has failed, the indication of enbronchial thermoplasty may be considered⁸³ (see chapter 7).

The last therapeutic option when all other alternatives have failed is the administration of systemic glucocorticoids (always used at the lowest effective dose and for the minimum period of time possible)^{84,85} even though they are also associated with adverse effects, occasionally serious (see chapter 7).

3.2.2 Inhalers and nebulizers

Inhaled therapy is the preferred administration route for the treatment of asthma as it acts directly on the lungs, delivers a greater amount of drug into the airways, elicits a rapid response and is associated with few or no systemic effects⁸⁶⁻⁹¹.

The main disadvantage of this route is the difficulty of the inhalation technique of the different devices⁹²⁻⁹⁵.

Table 3.4. Aerodynamic properties provided by inhalers (based in part on Giner 2013)⁹⁶

	Pulmonary deposition (%)		Oropharyngeal deposition (%)		MADM (μ m)
	in vivo	in vitro	in vivo	in vitro	
pMDI					
Conventional pMDI	7.8-34	-	53.9-82.2	-	1.4-8
Conventional pMDI with spacer	11.2-68.3	-	31.2	40	2-3.2
Breath-actuated pMDI	50-60	-	30	-	-
Modulite [®]	31-34	-	33-58	-	1-2
Alvesco [®]	50-52	-	32,9	-	-
BAI					
k-haler [®]	44.7 ⁹⁷	-	23-30	-	-
SMI					
Respimat [®]	40-53	-	19.3-39	-	-
DPI (by alphabetical order)					
Accuhaler [®]	7.6-18	15-30	-	-	3.5
Aerolizer [®]	13-20	21.7-28	73	-	1.9-7.9
Breezhaler [®]	36	39	-	45	2.8
Easyhaler [®]	18.5-31	29	-	-	2.2-3.0 ⁹⁸
Ellipta [®]	-	-	-	-	2-4.8
Genuair [®]	30.1	-	54.7	-	-
Handihaler [®]	17.8	17.3-22	-	71	3.9
Ingelheim [®] inhaler	16	-	59	-	-
Nexthaler [®]	56	-	43	-	1.4-1.5
Spinhaler [®]	11.5	-	30.9	-	-
Turbuhaler [®]	14.2-38	28	53-71.6	57.3-69.3	1.7-5.4
Twisthaler [®]	36-37	-	-	-	2-2.2

MADM: mean aerodynamic diameter mass; BAI: breath-actuated inhaler; DPI: dry powder inhaler; pMDI: pressurized metered-dose inhaler; SMI: soft miss inhaler. The comparison of values among devices should be considered with caution because of differences in the methods and drugs used for estimating the corresponding values, as well as differences in human studies, which were performed in diverse clinical settings (healthy and ill subjects with different diseases and degrees of severity), inspiratory flows and ages.

Currently available inhalation devices include: the conventional pressurized inhaler (pMDI) and the the Modulite® system, which can be used with or without a spacer, the breath-actuated inhaler (BAI) k-haler® and Easy-breathe®, the soft mist inhaler (SMI) Respimat®, the dry powder inhalers (DPI) (Accuhaler®, Aerolizer®, Breezhaler®, Easyhaler®, Ellipta®, Forspiro®, Genuair®, Handihaler®, Nexthaler®, Spiromax®, Turbuhaler®, Twisthaler® and Zonda®) and the nebulizers (*jet*, ultrasonic or vibrating mesh). Each of them has their own technical characteristics that should be considered when prescribed (Table 3.4)⁹⁰.

All inhaler devices if correctly used provide an efficient deposition of the drug in the lung⁸⁸.

The use of spacers is recommended for pMDI. Spacers circumvent coordination issues, improve the distribution and the amount of drug reaching the bronchial tree, reduce the deposition of drug particles in the oropharynx, decrease cough and the possibility of oral candidiasis (that may be associated with the use of IGC), decrease systemic bioavailability and, hence, the risk of systemic effects⁹⁹⁻¹⁰².

Healthcare professionals involved in the care of patients with asthma should know the inhalation techniques of each of the devices; knowledge, however, is still insufficient¹⁰³⁻¹⁰⁴.

Given that the proper use of inhalers is a crucial aspect in the treatment of patients with asthma, all healthcare professionals involved, doctors, nurses and pharmacists especially those from the community due to their accessibility, should be involved in the instruction and review of the inhalation technique¹⁰⁵⁻¹¹².

The patient should be periodically trained and controlled in the use of the prescribed inhaler device, explaining its characteristics, the appropriate technique, demonstrating how it is used, then asking the patient to perform the maneuvers (with a placebo device) and correcting the possible mistakes^{91,113-115}.

Whenever pharmacologically possible, a single type of inhaler device should be used^{116,117}.

After the instruction in the use of the device, the patient should be given a brochure with description of the technique and receive information on how to find demonstration videos showing the correct technique^{89,90,92,114,115}.

It is important to take advantage of control visits, performance of pulmonary function tests and admissions to the hospital to check the patient's inhalation technique¹¹⁴.

3.3 Other treatments

3.3.1 Smoking and environmental control

Smokers with asthma have more severe symptoms, a poorer response to IGC treatment, even in patients with mild asthma¹¹⁸, and an accelerated loss of pulmonary function^{119,120}, so that a step-up in treatment is often required¹²¹. The proportion of asthmatic smokers is high and similar to that in the general population. Moreover, since longitudinal studies have found a relationship between tobacco use and asthma in both adults and adolescents¹²², the main objective in environmental control is getting the patient to stop smoking. To this end, smokers should receive full information of the most appropriate quit smoking methods¹²³. Exposure to both environmental contaminants and passive smoking aggravates the course of asthma and constitute a risk factor for asthma development

in childhood¹²⁴. Administrative regulations banning smoking in public spaces are having a highly positive impact^{125,126}. Also, passive exposure to smoke of electronic cigarettes has been related with a higher risk for exacerbations and asthma symptoms^{127,128}, and active exposure to severe effects of respiratory health¹²⁹, so that vaping cannot be recommended as a method to quit.

Some asthma patients, particularly those with sinonasal polyposis, may experience exacerbations when administered *acetylsalicylic acid* or other non-steroidal anti-inflammatory drugs (NSAID). Many of these reactions are serious or even fatal¹³⁰, so that it is necessary that patients are correctly diagnosed based on evident data in the medical history (several reactions to different NSAID) or by means of an oral challenge test which, in severe cases, can be replaced with bronchial or nasal inhalation challenge testing^{131,132}. This issue is more comprehensively explained in chapter 8.5 (*acetylsalicylic acid*-exacerbated respiratory disease). These patients, however, among their environmental measures, should avoid the use of analgesic or anti-inflammatory treatments with drugs of the NSAID therapeutic class.

Specific recommendations should be considered in allergic asthma, once sensitizations to different allergens had been confirmed in each patient. The most effective measures are those enabling a dramatic decrease of exposure levels, such as those applicable to many patients with occupational asthma (job change) or asthma due to animal dander (removal of animals from the patient's home) or cockroach allergy (wise use of pesticides)¹³³⁻¹³⁸.

Isolated individual interventions, such as the use of mattress covers or acaricides have not shown to be effective, not even in reducing exposure levels¹³⁹⁻¹⁴¹.

However, in a recent randomized study, the use of impermeable bed covers was effective for preventing exacerbations in children and adolescents with allergic asthma triggered by dust mites¹⁴².

The use of combined specific measures has been associated with a significant reduction in the level of allergen exposure and, in consequence, of benefits in clinical efficacy^{133,143,144}. In a randomized trial of 937 patients with uncontrolled moderate to severe asthma and sensitization to at least one domestic allergen, in which combined measures were applied (impermeable covers, vacuum cleaners and air purifiers in the bedroom both with HEPA filters, cockroach disinsection plans), associated with a general education program, for one year, obtained a significant reduction in symptoms and unscheduled medical visits¹³³.

Finally, the two more recent systematic reviews of the effect of combined interventions showed favorable outcomes^{137,145}.

3.3.2 Allergen immunotherapy

Subcutaneous immunotherapy with allergen extracts is an effective treatment in well-controlled allergic asthma with low or medium treatment levels (steps 2 to 4), provided that a clinically relevant IgE-mediated sensitization against common aeroallergens has been demonstrated and well-characterized and standardized allergen extracts are used^{146,147}, avoiding complex mixtures^{148,149}. However, many patients with mild intermittent asthma (step 1) suffer from moderate or severe allergic rhinitis concomitantly, which would justify the

A

prescription of immunotherapy¹⁵⁰. Immunotherapy should not be prescribed to patients with uncontrolled severe asthma, because its efficacy is not well documented and entails a high risk of serious, even fatal, adverse reactions^{149,151}. For this reason, subcutaneous immunotherapy should only be prescribed by specialist physicians with experience in this type of treatment and administered in centers equipped with the basic resources for the immediate treatment of a possible adverse reaction.

B

The search for safer and more convenient options for the patient has led to investigate the efficacy of sublingual immunotherapy. Some systematic reviews conclude that oral immunotherapy with capsules or lyophilized extracts can significantly reduce clinical manifestations and the use of rescue medication in children, adolescents and adults with allergic asthma^{147,152-154}.

B

Most clinical trials showing clinical efficacy were performed with well-characterized extracts at much higher doses than those usually prescribed for subcutaneous immunotherapy. The tolerability profile of sublingual immunotherapy is optimal and fatal reactions have not been reported^{147,154}.

B

Sublingual immunotherapy with an oral lyophilized mite extract when added to regular pharmacological maintenance treatment is able to reduce the number of moderate to severe exacerbations¹⁵⁵ and to improve control of the disease, with a very favorable safety profile. Therefore, its use is recommendable for adult patients with moderately controlled or partially controlled asthma¹⁵⁰.

B

No comparative studies on the cost-effectiveness of immunotherapy versus conventional pharmacotherapy are yet available, and they are not likely to be performed since their complex design makes them still unfeasible.

B

However, immunotherapy is not only useful in controlling disease manifestations, but it also offers additional advantages over pharmacotherapy, such as the maintenance of clinical benefits for several years after treatment discontinuation^{156,157}, a decrease in the risk of developing asthma in patients with allergic rhinitis^{157,158} or the occurrence of new sensitizations in monosensitive patients¹⁵⁹. Finally, immunotherapy has been found to be cost-effective in comparison with pharmacotherapy alone in patients with the coexistence of allergic rhinoconjunctivitis and asthma¹⁶⁰⁻¹⁶².

B

3.3.3 Influenza and pneumococcal vaccinations

A

Influenza^{163,164} and pneumococcal¹⁶⁵ vaccines have not been shown to be effective in preventing asthma exacerbations.

D

However, since it is a cost-effective approach, and due to the high risk of complications in patients with chronic diseases^{166,167} and a higher risk of therapeutic failure in children¹⁶⁸, annual influenza vaccination should be considered in patients with moderate and severe asthma, both in adults and children. Similarly, and given that asthma population have a high risk of invasive pneumococcal disease^{169, 170}, different international¹⁷¹ and national¹⁷² consensus documents as well as the National Healthcare System¹⁷³ recommend the administration of pneumococcal vaccine in patients with severe asthma.

3.4 Education

3.4.1 Objectives

Education of asthma patients is an essential component of treatment, because reduces the risk of exacerbations, improves quality of life and decreases healthcare costs¹⁷⁴, thus becoming an indispensable part of the overall management of asthma^{8,175-180}. The main goal of education is to provide patients with the knowledge and skills they need to improve self-care and treatment compliance. This results in a better adherence to treatment and, in consequence, in an optimal control of the disease. In addition, education promotes patient's self-control of asthma. Self-control is the situation in which the patient monitors their symptoms and applies self-management following a plan agreed with his/her doctor. Self-control supported by a healthcare professional reduces the number of consultations and exacerbations, and improves quality of life without increasing costs^{181,182}.

A

3.4.2 Knowledge and skills

From a practical point of view¹⁸³, education should consider two major aspects: transmission of knowledge and acquisition of skills and competences (Table 3.5).

A

Regarding the information that the patient should receive about asthma, their needs, previous knowledge, beliefs¹⁸⁴, age, severity of asthma, and the degree of involvement necessary in their self-control and treatment should be considered.

A

These interventions should include¹⁸⁵: symptom self-management or PEF monitoring, written action plans, and regular assessments of asthma control, asthma treatment and abilities of the healthcare personnel¹⁸¹.

A

Interventions without written action plans are less effective^{185,186}. Actions that are exclusively informative are ineffective^{178,185}.

B

Regarding the skills to be developed, patients will be trained in taking the prescribed medication, particularly in the technique of their inhalation devices^{89,90,92,93,187}, in the recognition of exacerbations and how to act early, and in the avoidance of allergenic triggers^{188,189}.

B

Table 3.5. In Information and basic skills that should be learned by a patient with asthma

1. **To know** that asthma is a chronic disease requiring continuous treatment even if symptoms are absent.
2. **To know** the differences between inflammation and bronchoconstriction.
3. To be able to **differentiate** between inflammation "controller" drugs and obstruction "reliever" drugs.
4. **To recognize** the symptoms of the disease.
5. **To use** inhalers correctly.
6. **To identify** triggers and avoid triggering factors as much as possible.
7. **To monitor** symptoms and peak expiratory flow (PEF).
8. **To recognize** the signs and symptoms of asthma worsening (loss of control).
9. **To act** in case of asthma worsening in order to prevent an attack or exacerbation.

Table 3.6. Asthma action plan

A. Standard**I. USUAL TREATMENT**

- 1.- Take daily _____
 2.- Before Exercise, take _____

II. WHEN SHOULD YOUR TREATMENT BE INCREASED

1. Assessment of the degree of asthma control

- Do your asthma symptoms occur more than twice a day? No/Yes
 Do your activity of physical exercise is limited by asthma? No/Yes
 Do you wake up at night because of asthma? No/Yes
 Do you need to take your bronchodilator more than twice a day? No/Yes
 If you use a peak flow meter (PEF), are PEF values lower than _____? No/Yes

If your answers have been Yes to three or more questions, your asthma is not well controlled and your usual treatment needs to be increased.

2. How to increase treatment

Increase your treatment as follows and assess your improvement daily:

_____ (Write down the increase of your new treatment)

Maintain this treatment for _____ days (specify the number).

3. When should I call the doctor/hospital for help

Call your doctor/hospital _____ (Provide phone numbers)

If your asthma does not improve _____ days (specify the number)

_____ (lines for Complementary instructions)

4. EMERGENCY: severe loss of asthma control

If you have a severe breathlessness attack that you can only speak short sentences.

If you have a severe breathlessness or asthma attack.

If you have to use your reliever or rescue bronchodilator every 4 hours without any improvement.

1. Take 2 to 4 puffs _____ (rescue bronchodilator)
2. Take ___ mg of _____ (oral glucocorticoids)
3. Ask for medical assistance: go to _____ : Address _____ : Call phone number _____
4. Continue using your _____ (rescue bronchodilator) until you get medical help

B. REDUCED (mini-action plan), based in part on Plaza 2015¹⁹⁰**FRONT**

Name _____

Date _____

If your asthma has worsened in the last 24 hours due to having:

- Difficult breath or whistling more than twice or
- Difficult breath or whistling in the last night or
- Need to take your rescue inhaler more than twice

Increase treatment as follows:

1. Increase _____ and maintain for ___ days
2. If no improvement start _____ (prednisone) 30 mg. 1 tablet a day, and maintain for _____ days (maximum 3-5).*
3. If no improvement, ask for a visit with your doctor.

BACK**The 4 basic advices**

1. **Asthma is a chronic inflammatory disease.**
For this reason, do not stop taking daily your maintenance or usual treatment. It is the best way to prevent crisis or asthma attacks.
2. **Do not smoke**, or be in the presence of other people smoking.
3. **If you lose control of your asthma, take action!** If you have an action plan, implement it; if not, seek for medical help.
4. If you have allergy (mites, pets, pollens, etc..), **avoid exposure.**
5. **If you repeat the use of cortisone*...**

*Review and put notes to avoid overdosing or uncontrolled repeated treatment.

C Minimal educational interventions reduced to the essentials (mini-action plan, avoidance behaviors and revision of inhalation technique) have shown efficacy if they are administered repeatedly at follow-up visits¹⁹⁰.

3.4.3 Action plan

B The education program should consider setting up an action plan, which consists of a set of individualized written instructions in which asthma severity, disease control and the usually prescribed treatment are taken into account. The main objective of the education program is the early detection of asthma worsening and the rapid adoption of measures to achieve quick remission. Depending on the patient's and the physician's preferences¹⁹¹⁻¹⁹³, the level of control on which the action plan should be based can be assessed in terms of severity and frequency of asthma symptoms, as well as through daily home recording of PEF. This plan should include two basic components¹⁹⁴⁻¹⁹⁶: usual treatment in situation of clinical stability and actions to be implemented in case of asthma worsening (Table 3.6). This action plan will be reviewed at every visit, either scheduled or unscheduled, as well as on hospital admissions or at visits to the emergency department.

B Action plans improve the patient's quality of life, but a systematic review did not find other beneficial or detrimental effects of using a written action plan¹⁹⁷.

3.4.4 Treatment adherence

B Patient's adherence to treatment is a critical factor for achieving and maintaining disease control. It is estimated that adherence in asthma patients is lower than 50%^{198,199}. Low adherence is associated with increased morbimortality as well as with a greater use of healthcare resources^{200,201}.

D Three types of patients with low adherence or non-adherence have been described: erratic (due to forgetfulness to take medication), deliberated (or intentionally non-adherence where the patient decides not to take medications) and involuntary or unwitting (due to failure in understanding the disease and/or its treatment)^{202,203}.

B Treatment adherence should be evaluated at each medical visit using a reasonably validated method, such as the Test of

Adherence to Inhalers (TAI), pharmacy dispensing medication, or the combination of both²⁰⁴⁻²⁰⁶.

The education program should include the assessment of the level of adherence, promoting the appropriate corrective measures in case of low adherence and adapting them to the patient's pattern of non-adherence.

Participation of the patient in the choice of the inhaler provides greater therapeutic adherence and control of the disease. Therefore, patients should be involved in the selection of the inhaler device^{102,104,116,117,207-210}.

Non-adherence to control medication in severe asthma can be detected by the FE_{NO} suppression test²¹¹.

3.4.5 Other aspects to be considered

D For education to be effective, a confidence relationship between the healthcare team and the patients should be established, so that patients can raise their doubts, concerns and fears. The healthcare provider should use a simple and understandable language towards both the patients and their relatives, ensure that all concepts have been understood and encourage the patients to put forward their doubts and queries.

Also, written personalized goals shared by patients and physicians must be established.

An appropriate agreement between the patient's opinions and expectations and his/her physician is one of the factors related to asthma control²¹².

Patients and their families should be encouraged to raise doubts and queries regarding the information received or emerging from the medical interview, and sufficient time should be allocated so that they can be sorted out at the next visit⁸.

B Since education is a continuous process and not an isolated event, each visit should give the opportunity to review, strengthen and increase patients' knowledge and skills; hence, it is indispensable that education should be agreed on and accepted by the whole team¹⁷⁸.

B Table 3.7 describes the educational tasks that should be undertaken at each visit. Once properly trained, the nursing and pharmacy staff should actively participate in the organization and management of education programs^{106,213-215}.

Table 3.7. Educational tasks to be implemented at each visit

	Communication	Information	Instruction
Initial visit	Assess expectations Agree on common targets Discuss adherence issues	Basic concepts on asthma and its treatment	Inhalation technique Self-monitoring
Control visits	Evaluate achievements concerning expectations and objectives Discuss adherence issues	Reinforce information provided at the initial visit. Inform about environmental avoidance measures	Reinforce inhalation technique How to avoid triggers Interpretation of records Self-management plan
Reviews	Evaluate achievements concerning expectations and objectives Discuss adherence to treatment and environmental avoidance measures	Reinforce the whole information	Review and reinforce inhalation technique Review and reinforce self-monitoring and the self-management plan

A Individualized discharge programs assisted by trained nursing personnel prevent readmissions for exacerbations²¹⁶.

C Educational interventions carried out in the primary care setting reduce unscheduled visits and the inappropriate use of drugs, such as antibiotics²¹⁷.

A In the interventions to potentiate self-care, sociocultural differences of the patients should be considered¹⁸⁴.

B Educational interventions cannot exclusively develop in the clinical setting. Interventions of self-care in schools or by other patients with asthma provide a better control, a reduction of exacerbations and a better quality of life. Also, they can positively influence on adolescents to quit smoking^{218,219}.

B The use of telemedicine improved adherence to treatment²²⁰ through inhaler monitoring devices²²¹ or reminder alarms²²².
A It also improves symptoms and decreases the use of medical care²²³. Teleconsultation improves asthma control and quality of life²²⁴ (see section 9.4).

A The effectiveness of the patient's self-control in asthma is very positive. For interventions on the patient's self-management to be effective, it is necessary to combine the active participation of the patient, with training and motivation of professionals integrated into a healthcare system that values the self-control in asthma patients²²⁵.

C Educational workshops are a useful tool as a complement to individualized care, being more profitable when performed during the periods of time when patients present more symptoms²²⁶.

A The community pharmacist, due to its accessibility and frequent use by the patient, can identify poorly controlled patients especially those who abuse SABA agents or have low adherence to anti-inflammatory maintenance treatment. The community pharmacist can offer health education improving adherence, asthma control and obtaining better clinical and economic outcomes. If necessary, he/she can refer the patient to medical consultation^{112,227-230}.

RECOMMENDATIONS

- | | |
|--|----|
| 3.1. SABAs, when administered 10-15 min before the exercise, are the drugs of choice to prevent exercise-induced bronchoconstriction. | R1 |
| 3.2. In step 1 <i>budesonide/formoterol</i> , <i>beclomethasona/formoterol</i> or <i>beclomethasona/salbutamol</i> on-demand can be used, although this strategy is not approved in technical specifications and the cost-effectiveness is unknown. | R2 |
| 3.3. First-choice treatment (step 2) is an IGC at low doses used on a daily basis. LTRA can be considered as alternative treatment. | R1 |
| 3.4. In step 2 , an alternative could be the use of IGC at low doses with LABA or SABA (e.g. <i>budesonide/formoterol</i> , <i>beclomethasona/formoterol</i> , or <i>beclomethasona/salbutamol</i>) on-demand in patients with low adherence to treatment in whom a specific education had previously failed. However, this strategy is not approved in the products technical specifications and the cost-effectiveness is unknown. | R2 |
| 3.5. For moderate persistent asthma, the first-line treatment is the combination of an IGC at low doses (step 3) or medium doses (step 4) with inhaled LABA. | R1 |
| 3.6. For moderate persistent asthma, an IGC at low doses (step 3) or medium doses (step 4) associated with an LTRA can be considered as an alternative treatment. | R1 |
| 3.7. The combination of <i>budesonide/formoterol</i> or <i>beclomethasona/formoterol</i> can be used as maintenance and on-demand (reliever) treatment. | R1 |
| 3.8. In severe persistent asthma (step 5) first-line treatment is an IGC at high doses in combination with a LABA. | R1 |
| 3.9. In patients with severe <i>persistent asthma</i> (step 5 or 6) uncontrolled with the combination of an IGC at high doses and a LABA, with post-bronchodilation FEV ₁ /FVC ≤ 70 %, the addition of tiotropium has shown to improve pulmonary function and reduce exacerbations. | R2 |
| 3.10. SABA, <i>budesonide/formoterol</i> or <i>beclomethasona/formoterol</i> combinations and, in selected cases, short-acting anticholinergics (ipratropium bromide), are the drugs that can be used as reliever medications (in all therapeutic steps). | R1 |
| 3.11. Inhalation is the route of choice in the management of asthma. | R1 |
| 3.12. All healthcare professionals taking care of asthma patients should be involved in the instruction and control of inhaled therapy. | R1 |
| 3.13. The patient should participate in the selection of the inhaler device. | R1 |
| 3.14. It is recommendable the use of a single type of inhaler or at least similar inhalers. | R2 |
| 3.15. Patients should be trained on the inhalation technique of inhaler devices and their technique should be periodically supervised. | R1 |
| 3.16. Smoking cessation is recommended in smokers with asthma. | R1 |
| 3.17. In allergic asthma, specific combined measures of environmental control according to sensitization of the patient are recommended. | R2 |
| 3.18. In well-controlled allergic asthma with low or medium treatment levels (steps 1 to 4), allergen immunotherapy is recommended when clinically relevant IgE-mediated sensitization against common aeroallergens has been demonstrate, and well standardized extracts are used. | R1 |
| 3.19. Allergen immunotherapy should be prescribed by experienced specialized physicians. All administration of subcutaneous immunotherapy and the first of sublingual immunotherapy should be carried out in centers with available basic resources for immediate treatment of a possible adverse reaction. | R2 |
| 3.20. When different alternatives of immunotherapy are available, the use of those that have the consideration of registered medicines with well established efficacy, safety and quality should be prioritized. | R2 |
| 3.21. Patients with asthma should follow a fomal education program of their disease. Informative actions alone have not been shown to be effective. | R1 |
| 3.22. Patients with asthma should be provided with a written action plan in order to detect early asthma worsening and to be able to implement actions for rapid remission. | R1 |
| 3.23. It is indispensable to determine the level of adherence to treatment in each individual patient. To this purpose, the use of validated methods such as the TAI questionnaire or electronic registry of pharmacy dispensing medicines is recommended. | R2 |
| 3.24. Self-control interventions to be effective should combine the active participation of the patient, the healthcare professional and the healthcare system. | R1 |

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4. Assessment and treatment of asthma exacerbations

4.1 Introduction and life-threatening risk factors

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- **Concept:** an asthma exacerbation is defined by an episode of deterioration of the baseline clinical status of a patient that implies the need of administering specific treatment.
- **Synonyms:** in addition to exacerbations, it can receive other names such as crisis, agudization, or asthma attack.
- **Identification:** it can be clinically identified by an increase of symptoms, need of reliever medication, or worsening of pulmonary function in comparison of usual daily variation in a given patient¹.
- **Onset:** depending on how fast exacerbations occur, two types are identified: rapid-onset with progression in less than 3 hours, and slow-onset (usually developing in days or weeks). The identification of the type of exacerbation is important because of differences in causative factors, pathogenesis and prognosis^{2,3}.

Rapid-onset exacerbations develop by a mechanism of bronchoconstriction, are associated with a higher initial severity and vital risk than slow-onset exacerbations, although therapeutic response is usually more rapid and favorable. Triggering factors include inhaled allergens, drugs (NSAID or β -blockers), food (due to food allergy, particularly milk and egg in childhood, and panallergens related to lipid transfer proteins in dried fruits, fruits and vegetables; or additives and preservatives), or emotional stress.

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

- **Severity:** the intensity of exacerbations is variable with some attacks occasionally showing mild or symptoms that may be undetectable by the patient, while other episodes are very severe and life-threatening.
- **Vital risk:** a series of factors that increase the probability of suffering from life-threatening exacerbations have been reported. These factors are related to the characteristics of the current and past exacerbation episodes, adequate control of the disease, and presence of a specific comorbidity (Table 4.1)^{4,6}.

Table 4.1. Risk factors for life-threatening asthma exacerbation

- Related to the asthma exacerbation:
 - Current exacerbation of rapid-onset.
 - Previous episodes requiring medical consultation or hospital admission:
 - a. Multiple visits to the emergency department in the previous year.
 - b. Frequent hospitalizations in the previous year.
 - c. Previous episodes of ICU admission, intubation or mechanical ventilation.
- Related to chronic asthma disease and its adequate control:
 - Absence of periodic control.
 - Abuse of a short-acting β_2 -adrenergic agonist.
- Cardiovascular comorbidity.
- Psychological, psychiatric and social conditions that difficult treatment adherence: alexithymia, denial attitudes, anxiety, depression, psychosis.

ICU: intensiv care unit.

4.2 Assessment of severity

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

- *Initial or static (pre-treatment)* evaluation: aimed at identifying signs and symptoms and objectively measuring the degree of airflow obstruction by determining FEV₁ or PEF and their impact on gas exchange. in order to establish the level of severity of the exacerbation episode (Table 4.2).
- *Dynamic (post-treatment)* evaluation: aimed to measure changes in the degree of airflow obstruction versus initial values, and to assess the need of other diagnostic studies.

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

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

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Table 4.2. Assessment of severity of asthma exacerbation

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

FEV₁: forced expiratory volumen in one second; PEF: peak expiratory flow; x': per minute; SaO₂: oxyhemoglobin saturation; PaO₂: arterial oxygen partial pressure; PaCO₂: arterial partial pressure of carbon dioxide.

C The objective assessment of the degree of airflow obstruction by spirometry (FEV₁) or using a peak expiratory flow (PEF) meter is crucial to ascertain the initial severity and evaluate treatment response. It is preferable to use the percentage value of the previous best value of the patient in the last two years, but if this datum is unknown, the percentage value in relation to the predicted value can be used. According to the values obtained, exacerbations are classified as mild, if FEV₁ or PEF are equal to or greater than 70%; moderate, if FEV₁ or PEF values range between 70 and 50%; and severe, if these values are lower than 50%. Life-threatening asthma attack is usually associated with values lower than 33%. The initial therapeutic response of airflow obstruction is the main prognostic factor in the assessment of the exacerbation episode⁹⁻¹².

D Measurement of oxygen saturation by pulse oximetry is easy to obtain in all patients and has a complementary role. Values lower than 90-92%, with or without supplemental oxygen therapy, can be associated with hypercapnia respiratory arrest; therefore in these cases, arterial blood gases analysis is indicated¹³.

D Other complementary studies at the beginning of an asthma attack, such as chest X-rays and an electrocardiogram, are indicated in case of symptoms, such as fever or suspicion of infection (pneumonia), pain or intense breathlessness that may suggest the presence of pneumothorax or pneumomediastinum, or when therapeutic response, as shown by objective parameters, is not appropriate and in the presence of a life-threatening asthma attack¹⁴⁻¹⁶.

4.3. Treatment

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

4.3.1. Mild exacerbation

In clinical practice, it is difficult to differentiate a mild exacerbation from a transient loss of asthma control, since changes observed will be close to the normal range of variation for a given patient¹.

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

Asthma patients who have been provided with written action plans, including home PEF monitoring and how to act in case of loss of control, have an excellent and readily usable tool for managing mild exacerbations¹⁷. In order to quickly implement the adequate measures, patients should be trained in identifying the early markers of exacerbations and be ready to act immediately according to their assigned action plan,

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

Therapeutic groups	Drugs	Doses
First-choice		
β_2 -adrenergic agonists	Salbutamol	pMDI + spacer: 200-800 μg (2-8 puffs of 100 $\mu\text{g}/\text{puff}$) every 10-15 min during the first hour NEB intermittent: 2.5-5 mg every 20 min during the first hour NEB continuous: 10-15 mg/hour
Anticholinergics	Ipratropium bromide	pMDI + spacer: 80-160 μg (4-8 puffs of 20 $\mu\text{g}/\text{puff}$) every 10-15 min NEB intermittent: 0.5 mg every 20 min
Systemic glucocorticoids	Prednisone	Oral route on discharge: 50 mg every/24 hours (5-7 days) Oral route on admission: 20-40 mg every/12 hours
	Hydrocortisone	i.v.: 100-200 mg every/6 hours
Inhaled glucocorticoids	Fluticasone propionate	pMDI + spacer: 500 μg (2 puffs of 250 $\mu\text{g}/\text{puff}$) every 10-15 min
	Budesonide	pMDI + spacer: 800 μg (4 puffs of 200 $\mu\text{g}/\text{puff}$) every 10-15 min NEB: 0.5 mg every 20 min during the first hour
Magnesium sulfate i.v.		i.v.: 2 g infused over 20 min (one time only)
Alternative in case of previous failure		
β_2 -adrenergic agonists i.v.	Salbutamol	i.v.: 200 μg in 30 min followed by 0.1-0.2 $\mu\text{g}/\text{kg}/\text{min}$
Magnesium sulfate inhaled		NEB: 145-384 mg in isotonic solution

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

which must include the measures to be adopted depending on treatment response.

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

Inhaled SABA are the most effective and rapidly acting bronchodilators for treating asthma exacerbations. Salbutamol at doses of 200 to 400 μg (2 to 4 puffs) with spacer is used^{18,19}.

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

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

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

The use of **systemic glucocorticoids** accelerates resolution of exacerbations and prevents relapses²⁰. Except for very mild attacks, systemic glucocorticoids should always be administered as early as possible^{21,22}, particularly if:

- Pulmonary obstruction cannot be reversed with inhaled SABA.

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

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

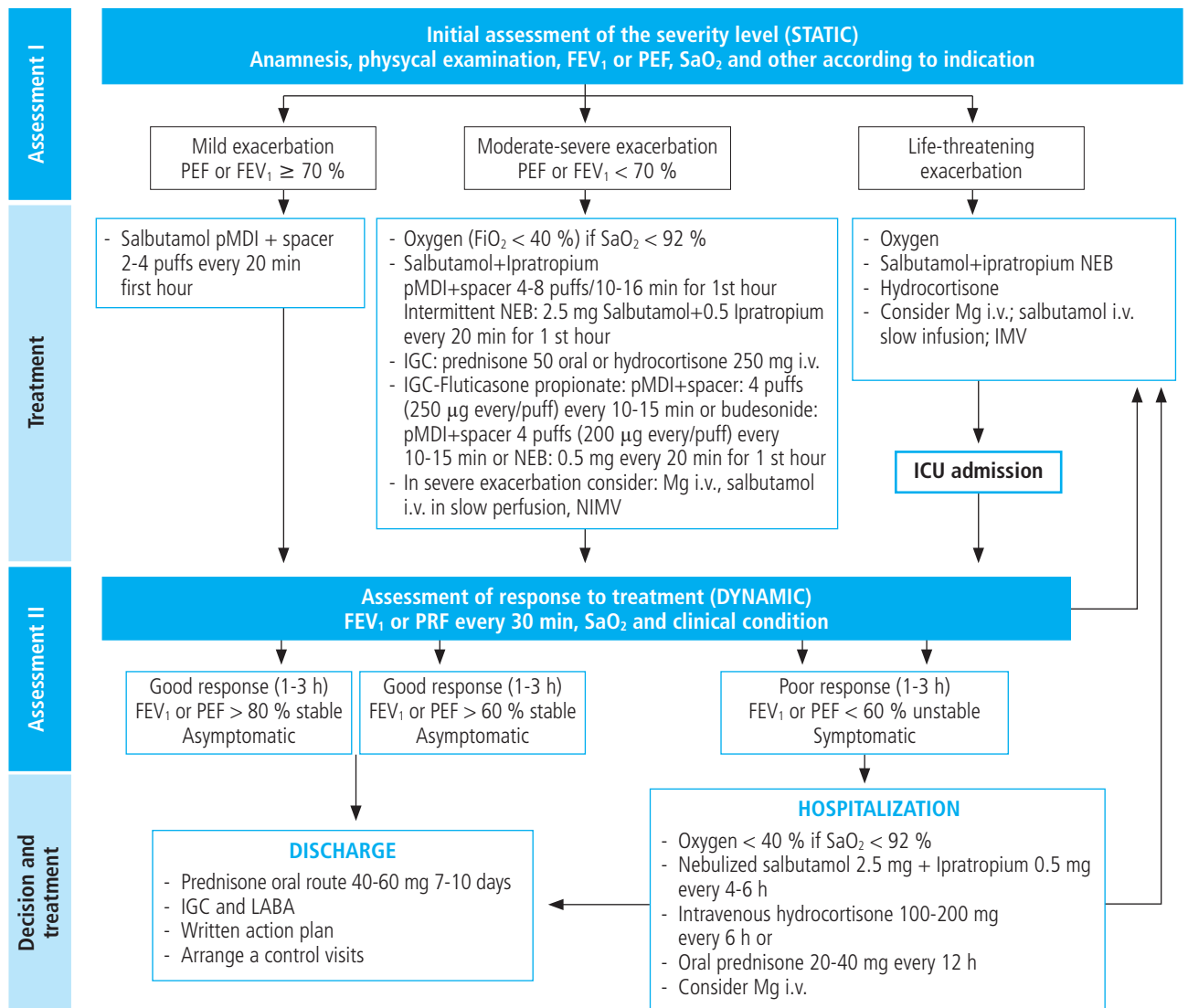
The administration of glucocorticoids by the oral, intramuscular or intravenous route provides similar biological results, but the oral route is less invasive and cheaper^{22,24-26}.

If response to inhaled bronchodilator treatment within the first hours is satisfactory, no hospital referral is required. Patients should be instructed on the need for adequate adherence to the treatment prescribed, their maintenance treatment plan should be reviewed, and a minimal asthma education intervention should be provided^{27,28}.

4.3.2 Moderate and severe exacerbations

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

In severe exacerbations with greater obstruction and risk of hypercapnia, the use of oxygen with controlled FiO_2 to



FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; SaO₂: oxyhemoglobin saturation; pMDI: pressurized metered-dose inhaler; NEB: nebulized; i.v.: intravenous route; IGC: inhaled glucocorticoid; NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation; min: minute; Mg: magnesium; h: hour; µg: micrograms; 1st: first.

Figure 4.1. Therapeutic management of asthma exacerbation in adults.

B obtain saturations around 93-95% is preferable than the use of high-flow oxygen therapy with which saturations around 100% can be achieved^{29,30}.

D In patients with severe exacerbations, the use of capnography to assess the trend to hypercapnia can be considered³¹.

A **Inhaled short-acting β₂-agonists (SABA)** are the first-choice bronchodilator treatment. Both the dose and the dosing intervals should be individualized according to the choice of the administration system and the therapeutic response.

A There is evidence that the use of a pressurized inhaler with spacer is the most cost-effective system³²; however, it is lower in patients with very severe exacerbations.

It has been shown that the administration of SABA using a nebulizer or a pMDI inhaler with spacer have a similar clinical efficacy in terms of pulmonary function, length of stay in the emergency department and risk of hospitalization. However, the dose used by pMDI is lower³²⁻³⁶.

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

There is no evidence to support the use of a route other than inhalation for the administration of bronchodilator medication³⁹. The intravenous route, with a very slow

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

B Similarly, no beneficial effects have been obtained when adding intravenous medication to inhaled therapy³⁹.

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

B When administered in aerosol form, doses higher than 2 mg, equivalent to 5 mg *salbutamol* are required as lower doses are ineffective⁴³.

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

A The use of *ipratropium bromide* during the initial phase of moderate or severe exacerbations concomitantly with a SABA is associated with a greater increase in pulmonary function (estimated by FEV₁ or PEF) and a decrease in hospitalizations as compared to the use of a SABA alone^{46,47}.

A **Systemic glucocorticoids** accelerate the resolution of asthma attacks and prevent relapses^{22,46,48}. They should be prescribed early, within the first hour of treatment in the emergency room, since their effect starts 4-6 hours after administration. They are especially indicated if no improvement is seen after the first dose of a SABA, if the patient was already receiving them or if previous exacerbation episodes requiring these drugs had occurred.

The preferred administration route of glucocorticoids is the oral route, as it is very effective⁴⁹, less invasive and cheaper than the intravenous route^{24,25}. The latter is reserved for cases in which patients are unable to swallow because of breathlessness, vomiting or are under mechanical ventilation.

B Daily dose is 50 mg of prednisone, as a single morning dose²¹ for 5-7 days, with no down-titration being necessary^{50,51}.

A Early use of **IGC** within the first hour of treatment reduces the need for hospital admission as in the case with systemic administration of glucocorticoids⁴⁸.

B The use of IGC together with systemic glucocorticoids provides even a higher reduction in the number of hospital admissions⁴⁸.

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

A Routine administration of **magnesium sulfate** is not indicated, although in selected patients experiencing severe obstruction (FEV₁ 25-30% predicted) or persistent hypoxemia, a single dose of 2 g administered by infusion reduces the need for hospitalization⁵³⁻⁵⁵.

A A systematic review of patients with severe exacerbations treated with intravenous **magnesium sulfate** only showed a mild improvement of pulmonary function⁵⁶.

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

SABA or SABA plus *ipratropium bromide*, reducing hospital admissions, in addition to a mild improvement of pulmonary function⁵⁷.

B **Heliox**, a mixture of helium and oxygen, in 80/20 70/30 proportion, has no place in the routine management of exacerbations due to the lack of consistent data regarding the efficacy of this compound. However, it may be considered in patients who do not respond to the usual treatment^{58,59}, particularly to nebulizing SABA⁶⁰.

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

4.3.3 Treatment failure

The use of non-invasive mechanical ventilation may be an option in severe exacerbations resistant to treatment. It allows improvement of the respiratory rate, dyspnea, and, in particular, airflow obstruction due to a direct effect of positive pressure, or indirectly contributing to a better distribution of aerosols⁶¹.

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

4.4 Criteria for hospitalization

The rate of hospital admission in asthma patients attended in the emergency setting is around 20%⁶², although there is a large variability among different countries^{63,64}. It is well known that adherence to guidelines is associated with a lower risk of hospitalization⁶³. In a systematic review, the degree of pulmonary function impairment was the most important risk factor for in-patient care⁶².

The decision to hospitalize a patient should be made within the first three hours after the start of treatment of the exacerbation episode, given that decision-making is rarely modified by longer periods of monitorization⁶⁵.

However, assessment of the patient's clinical condition and pulmonary function within the first hour after admission to the emergency room already enables to predict the need for in-patient care^{66,67}.

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

4.5 Criteria for hospital discharge

There are no functional parameters that allow a patient to be discharged with complete safety, so the decision is usually the result of the doctor's clinical observation of the patient's condition and results of arterial oxygen saturation⁷¹.

Patients may be discharged from hospital if they are capable of following their prescribed treatment at home, are paucisymptomatic or there is a reduced need for reliever medication⁷⁰.

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

D determination. FEV₁ or PEF values > 70% and with minimal symptoms can be criteria for discharge⁷². If the FEV₁ or PEF values are between 50% and 70%, possible risk factors should be considered (Table 4.4).

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

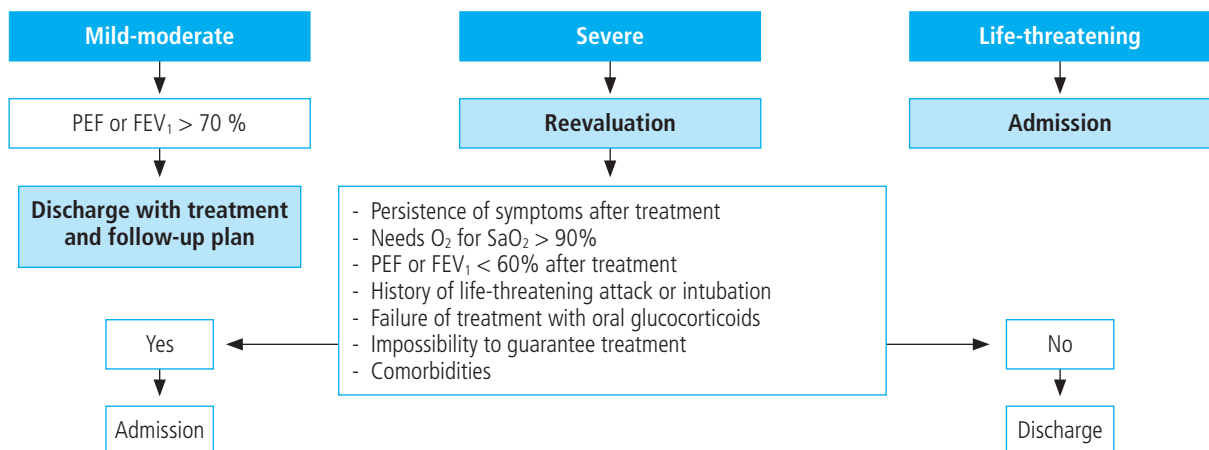
implemented and a written action plan will be provided (section 3.4.3). Also, an appointment with the patient's attending physician will be scheduled within the next five days²⁸.

Figure 4.2 shows an algorithm for hospital admission or discharge.

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

Criteria for hospital admission	Criteria for ICU admission
Remain symptomatic after treatment	Respiratory arrest
Need O ₂ for maintaining SaO ₂ > 92% <ul style="list-style-type: none"> – PEF or FEV₁ < 50-60 % after treatment⁶⁹ – PEF or FEV₁ = 50-70 % on arrival. A minimum observation period of 12 hour is advisable. – There is no functional parameter that defines when a patient should be discharged, although PEF < 75 % and variability higher than 25% are associated with a high rate of re-admissions⁷⁰ 	Decrease in the level of consciousness Progressive functional deterioration despite treatment
Previous life-threatening exacerbation with history of intubation and ventilation, hospital admission or visit to the emergency department due to recent asthma	SaO ₂ < 90 % despite supplemental O ₂ PaCO ₂ > 45 mm Hg = alarm sign of muscle exhaustion
Failure of treatment with oral glucocorticoids in the outpatient setting	Hypercapnia, need of ventilatory support or pneumothorax
Impossibility to ensure necessary care measures at home	
Respiratory (pneumonia, pneumothorax, pneumomediastinum) or non-respiratory comorbidities	

ICU: intensive care unit; SaO₂, arterial oxygen saturation; PEF, peak expiratory flow; FEV₁, forced expiratory volume in one second; PaCO₂, arterial partial pressure of carbon dioxide.



FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow.

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

4.6 Referral and control after discharge

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

All patients should be evaluated by his/her family physician within five days after discharge, as well as those who had suffered from a severe exacerbation by the pneumologist or allergologist within one month⁷¹. Table 4.5 shows criteria for referral to the next healthcare level.

D

Table 4.5. Criteria indicating specialized assessment of patients within one after an asthma exacerbation episode⁷¹

- Severe or life-threatening exacerbation.
- Repeated exacerbations requiring care in the emergency department^{13,16}.
- Exacerbations that require in-patient care^{16,73}, uncontrolled severe asthma, particularly in corticosteroid-dependent asthma, allergic bronchopulmonary aspergillosis, vasculitis.
- Pregnancy⁷⁴.
- Exacerbations triggered by NSAID, aeroallergens, food allergens or presenting with anaphylaxis.
- Known associated comorbidities.
- Clinical suspicion of vocal cord dysfunction, nasal, rhinosinusitis, gastroesophageal reflux, sleep apnea-hypopnea syndrome, asthma-COPD overlap syndrome.

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

RECOMMENDATIONS

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

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5. Treatment of childhood asthma

5.1 Education

A The education of the child with asthma and his/her family increases the quality of life, reduces the risk of exacerbations and the cost of healthcare, the reasons for which education is one the fundamental pillars of treatment. Its objective is for the child to achieve a normal life for his/her age including physical exercise and sport activities¹.

A Education is essential to improve treatment adherence and to achieve control of the disease^{2,3}.

Table 5.1. Key aspects of the education of a child with asthma

Topic area	Key aspects
Asthma	<ul style="list-style-type: none"> – Concept of asthma (chronic disease, variability) – Symptoms exacerbation/between exacerbations – Bronchoconstriction – Inflammation
Environmental measures	<ul style="list-style-type: none"> – Counseling against smoking – Triggering factors (allergens, virus, exercise, etc.) – How to identify and avoidance measures
Treatment	<ul style="list-style-type: none"> – Bronchodilators (rescue treatment) – Anti-inflammatory drugs (maintenance treatment) – Side-effects – Exacerbation (how to recognize initial symptoms and early action) – Immunotherapy
Inhalers	<ul style="list-style-type: none"> – Importance of inhaled medication – Inhalation technique – Maintenance of the system – Errors/forgetfulness
Self-control	<ul style="list-style-type: none"> – PEF. Best personal value – Symptoms registry – Personalized written action plan
Lifestyle	<ul style="list-style-type: none"> – School attendance – Practice of sports – Autonomy

PEF: peak expiratory flow.

Education should be developed in all healthcare settings in which children with asthma are attended⁴.

Education will be primary addressed to the family during early childhood and, from 8-9 years, should be especially addressed to the child, in order to promote personal autonomy and to achieve the maximum degree of self-care⁵.

Home education programs may be beneficial for children with poorly controlled asthma and are potentially profitable⁶.

For education to be effective, it is essential to identify the educational needs and the factors that affect the behavior of the patient and/or his/her family⁷.

Key aspects of education are shown in Table 5.1¹.

The education of children with asthma is more effective when accompanied by personalized written action plans (Table 5.2)^{8,9}, which addresses maintenance treatment (Table 5.3)¹⁰ and the management of asthma exacerbations (Table 5.4)¹¹. Every educational plan must be associated with periodic reviews.

In children, written action plans based on measurement of PEF do not provide benefits as compared with plans based on monitoring of symptoms, so that PEF-based plans are not generally recommended^{8,12}. However, on an individual basis, children and adolescents with severe asthma and low perception of symptoms could benefit from plans based on PEF monitoring^{13,14}.

5.2 Maintenance treatment

5.2.1 Drugs

Inhaled glucocorticoids (IGC). IGC are the first-line of treatment. In children older than 3 years of age, the efficacy of daily IGC is well established, with improvement of clinical and functional parameters, bronchial inflammation, better quality of life, and decrease in the risk of both exacerbations and hospitalizations^{15,16}.

Infants and preschool children treated with IGC daily experience fewer asthma/wheezing episodes^{17,18} a better treatment response being obtained by those showing risk factors of developing persistent asthma (Asthma Predictive Index [API])^{19,22}, while viral-induced episodic wheezing shows limited response²³. A treatment trial followed by evaluation of response is recommended²⁴.

B Treatment with IGC, either continuously or intermittently, does not modify the natural history of the disease²¹⁻²⁵.

B In preschool and children, the use of controller drugs (IGC or montelukast) at regular doses or intermittently at the onset of symptoms is not recommended²⁶⁻²⁸.

B Early intermittent therapy with IGC at high doses given to infants and preschool children with moderate-severe episodic wheezing and risk factors (API +) at the onset of symptoms have shown to be effective in reducing severity and duration of

exacerbations^{16,29,30}, but further studies are needed to establish the recommendation of this therapy.

When administered at usual doses, IGC are safe drugs for the management of childhood asthma. There is usually a decrease in the growth rate at the beginning of treatment (1-3 years), although this is a transient effect and does not influence final growth or final height. However, the final height of children treated with IGC over prolonged periods is lower, an effect proved to be dose-dependent^{31,32}.

B

B

Table 5.2. Components of a personalized action plan

Action plan for treating asthma exacerbation at home

- Recognize asthma symptoms and the onset of an exacerbation for using early short-acting bronchodilators and on-demand when symptoms appear.
- Recognize alarm signs and when to seek help from the doctor or go to the emergency department.

Self-controlled/family-controlled action plan

- Rules for avoiding specific asthma triggers in children.
- Daily use of preventive medication: doses, frequency and route of administration.
- Changes of preventive medication according to severity and frequency of symptoms (**symptom diary**) and/or measurement of peak expiratory flow (**home PEF recording**).
- When to go to his/her pediatrician because asthma is not controlled.
- Prevention and treatment of exertional asthma.

PEF: peak expiratory flow.

Table 5.3. Written action plan to maintain asthma control

Your usual treatment (preventive):

Every day I take: _____

Before exercise I take _____

When to Increase Preventive Treatment

Assess your level of asthma control:

In the last week you have had:

Asthma symptoms more than twice a day? No Yes

Activity or physical exercise limited by your asthma? No Yes

Night awakenings due to asthma? No Yes

Need of rescue medication more than twice a day? No Yes

If you measure (PEF), your PEF is lower than No Yes

If you have answered **“Yes” to 3 or more questions**, your asthma is not well controlled and **to increase a step in your treatment may be necessary**

How to Increase Treatment

Increase treatment from _____

to _____

and assess improvement every day. Maintain this treatment for _____ days.

In case of an exacerbation, **treatment in the action plan for the management of exacerbations** will be started and will attend a medical consultation for a new assessment.

Modified from GINA www.ginasthma.com

D It is difficult to establish the equivalent doses of the IGC mostly used in pediatric age³³. Comparable doses of IGC drugs for use in the pediatric age are tentatively shown in Table 5.5,

Table 5.4. Action plan for treating an asthma exacerbation at home

What is an ASTHMA EXACERBATION EPISODE and HOW TO ACT AT HOME?

An asthma exacerbation episode is a sudden or progressive worsening of symptoms:

- Increased cough (continuous, nocturnal or with exercise).
- Whistling sound.
- Fatigue (difficult breathing).
- Feeling of chest tightness.
- Decrease of PEF (if you use the pek-flow meter).

There are **symptoms** that warn us that **an exacerbation can be severe** (warning signs):

- Bluish color of the lips.
- Ribs sink when breathing.
- Difficulty speaking.
- Numbness.

Warning signs indicate that medical assistance should be immediately requested!

What to do at home in the presence of an exacerbation?

- Keep calm.
- Treat symptoms as early as possible.
- Start medication at home.
- Never wait to see if symptoms disappear spontaneously.
- After starting medication, observe for 1 hour and assess response.

USE OF MEDICATION:

Take your rapid rescue medication: salbutamol _____ with spacer, 2-4 puffs, separated by 30-60 seconds. This dose can be repeated every 20 minutes, up to a maximum of 3 times. If symptoms does not improve in 1 hour, start taking oral corticoids _____ (1 mg/kg/day, maximum 40 mg/day), for 3-5 days.

Take your anti-inflammatory medication _____ times a day, all days, according to the indications given by your pediatrician

ASSESS RESPONSE TO TREATMENT

If you improve in one hour and improvement is maintained for 4 hours, continue with salbutamol: 2-4 puffs every 4-6 hours (depending on symptoms) and visit your pediatrician in 24-48 hours.

If you do not improve or the improvement is not maintained and you relapse again: go to an emergency department

If you know how to control exacerbations, the duration of symptoms will be lower and your quality of life will improve.

taking into account that the lowest dose that maintains control of the patient should be sought.

Leukotriene receptor antagonists (LTRA). In preschool children with virus-induced asthma/weezing, LTRA are associated with a modest reduction of symptoms and need of oral glucocorticoids as compared with placebo^{27,34,35}. Although a definite beneficial effect remains unclear, a clinical trial to assess response to LTRA may be conducted, which could be stopped if the expected response is not obtained³⁴. More evidence is needed to determine whether there is a responder phenotype to *montelukast*³⁶.

If asthma symptom cannot be controlled with IGC at low doses, increasing IGC at medium doses is more effective than the association with *montelukast*³⁷.

Association of long-acting β_2 -adrenergic agonists (LABA) and IGC. It has been approved for use in children over 4 years of age. LABAs are safe when administered with an IGCs, but never as monotherapy^{38,39}.

A decrease in the number of exacerbations and the need for systemic glucocorticoids was observed in a study of children treated with *formoterol/budesonide* in a single inhaler as both maintenance and reliever therapy (MART approach)⁴⁰, although some authors consider that there is limited evidence for this age segment⁴¹.

In children aged between 6 and 11 years with persistent asthma not controlled with low doses of IGC, doubling the IGC dose has a similar effect to adding a LABA on clinical control and lung function⁴². However, the clinical phenotype and the heterogeneity of the individual response to IGC, LTRA and LABA should be assessed^{43,44}, therefore, it is necessary to closely monitor the response to treatment in children with asthma not controlled using IGC.

Tiotropium. It is a long-acting muscarinic antagonist. It can be used in children from 6 years of age with poorly controlled severe asthma treated with IGC at high doses plus LABA. The dose is 5 μ g once a day⁴⁵. A study in children aged 1 to 5 years concluded that tolerability of tiotropium is good in preschool children and can reduce the number of exacerbations⁴⁶.

Theophyllines. These drugs are less effective than IGCs as maintenance monotherapy, even though their anti-inflammatory activity enables their use in association with IGC in individual cases of severe asthma⁴⁷.

Anti-IgE monoclonal antibody (omalizumab). Omalizumab has shown therapeutic efficacy (decrease in the doses of IGC, quality of life improvement, reduction of exacerbations and hospitalizations) in children over 6 years of age with moderate or severe persistent allergic asthma inadequately controlled with IGC at high doses and LABA⁴⁸⁻⁵⁰. It is administered subcutaneously every 2-4 weeks at doses tailored to total IgE levels and body weight. A number of studies carried out in daily practice conditions in children with

Table 5.5. Comparable doses of inhaled glucocorticoids commonly used in pediatric age (mg/day)

Children under 12 years of age			
	Low doses	Medium doses	High doses
Budesonide	100-200	> 200-400	> 400
Fluticasone propionate	50-100	> 100-250	> 250

A severe allergic asthma, omalizumab was found to improve asthma control, reduce exacerbation and hospital admission rates, and decrease IGC doses at the fifth month of treatment⁵⁰.

C **Anti-IL5 monoclonal antibody (mepolizumab).** It is recommended in children from 6 years of age with severe eosinophilic asthma insufficiently controlled with high doses of IGC and LABA^{51,52}. In children 6 to 11 years of age, the recommended dose is 40 mg subcutaneously every 4 weeks and 100 mg every 4 weeks from 12 years of age.

A **Immunotherapy (IT).** When biologically standardized extracts are used and sensitized patients are appropriately selected, immunotherapy has been shown to provide a beneficial effect by reducing symptoms, the need of reliever and maintenance medication, and decreasing bronchial hyperresponsiveness (both specific and non-specific)⁵³.

B Also, IT prevents the development of new sensitizations and asthma in children with rhinitis^{54,55}.

5.2.2 Treatment according to the level of severity, control and future risk

D In naïve patients, the choice of treatment is determined by the initial severity. Subsequently, modifications will be carried out in a stepwise approach, adjusting the medication according to the current degree of control, assessing future risk and taking into account the child's age (Figure 5.1).

B Children with occasional episodic asthma should be prescribed bronchodilators on-demand without any

maintenance treatment. Children with frequent episodic asthma should start treatment at step 2, whereas children with persistent symptoms and/or impairment of pulmonary function should start treatment at step 3 or 4. For children with severe asthma, treatment should preferably be started at step 5 with a further decrease to a lower step (step down) when control is reached and trying to find the minimum effective dose^{38,56}. The degree of control and the treatment step should be assessed every three months.

5.3 Evaluation and treatment of exacerbations

5.3.1 Evaluation of severity

D The following factors should be considered: time course of the exacerbation episode, pharmacological treatment administered, presence of associated diseases and possible risk factors (previous intubation or ICU admission, hospitalizations in the preceding year, frequent need of admission to the emergency department in the previous year and/or use of oral glucocorticoids, excessive use of SABA in the preceding weeks).

C Severity assessment is mainly based on clinical criteria (respiratory rate, presence of wheezing and sternocleidomastoid retractions). Although no clinical scale is considered to be well validated^{57,58}, the Pulmonary Score (Table 5.6)⁵⁹ has been found

	Stepwise treatment	Maintenance treatment		R E S C U E M E D I C A T I O N
		> 3-4 years	< 3-4 years	
Assessment of adherence and inhalation technique	1	Without controller medication		
Environmental control	2	IGC at low doses or LTRA	IGC at low doses or LTRA	
	3	IGC at medium doses or IGC at low doses + LABA or IGC at low doses + LTRA	IGC at medium doses or IGC at low doses + LTRA	
Assessment of comorbidities	4	IGC at medium doses + LABA or IGC at medium doses + LTRA	IGC at medium doses + LTRA	
	5	IGC at high doses + LABA If not control add: LTRA, tiotropium, theophylline	IGC at high doses + LTRA	Short-acting bronchodilator on-demand
	6	IGC at high doses + LABA + omalizumab*, mepolizumab*, alternative: oral GC	If not control consider adding: LABA**, macrolides, tiotropium**, oral GC	

IGC: inhaled glucocorticoids; LTRA: leukotriene receptor antagonist; LABA: long-acting β_2 -adrenergic agonist; GC: glucocorticoid; *: from 6 years of age; **: Off-label.

Figure 5.1. Stepwise treatment of asthma in the pediatric age according to the level of control.

Table 5.6. Pulmonary Score for the clinical assessment of asthma exacerbation in children*

Score	Respiratory rate		Wheezing	Use of sternocleidomastoid muscle
	< 6 years	≥ 6 years		
0	< 30	< 20	No	No
1	31-45	21-35	End of expiration	Slight increase
2	46-60	36-50	Throughout expiration (stethoscope)	Increased
3	> 60	> 50	Inspiration and expiration without stethoscope**	Maximum activity

*It is scored from 0 to 3 in each of the sections (minimum 0, maximum 9)

**If wheezing is absent and the sternocleidomastoid activity is increased, the wheezing section should be scored 3.

Table 5.7. Overall evaluation of the severity of asthma exacerbation in children by integrating the Pulmonary Score and the arterial oxygen saturation

	Pulmonary Score	SaO ₂
Mild	0-3	>94%
Moderate	4-6	91-94 %
Severe	7-9	<91%

SaO₂: arterial oxygen saturation. In case of disagreement between clinical score and arterial oxygen saturation, the score indicating higher degree of severity will be used.

to be easy-to-use and applicable to all ages. The combination of symptoms and arterial oxygen saturation (SaO₂) allows completing an estimation of the severity of the exacerbation episode (Table 5.7).

5.3.2 Drugs

Inhaled short-acting β_2 -adrenergic agonists (SABA).

These agents constitute the first-line treatment due to their higher effectiveness and lower incidence of side effects⁶⁰. They should preferably be administered via a pressurized inhaler with a spacer chamber, since this way of administration is as effective as nebulizers for treating an acute asthma episode⁶¹⁻⁶⁴.

Recommended doses and dosing intervals depend on the severity of the exacerbation episode and the response to the initial doses⁶⁵. The most commonly used drug is *salbutamol*, which is available as a solution for use with a nebulizer and a pressurized inhaler. The latter must be administered in sequences of 2-10 puffs of 100 μ g until response is obtained. For mild attacks, a series of 2-4 puffs may be sufficient, although up to 10 puffs may be necessary for severe exacerbations.

Nebulized SABA should be restricted to those cases in which the patient requires oxygen supply for SaO₂ normalization, although a recent randomized clinical trial showed that even in severe exacerbations, the administration of salbutamol and ipratropium bromide with spacer chamber and facimask with oxygen by means of a nasal cannula was more effective than using a nebulizer⁶⁶.

Continuous nebulization does not offer greater advantages compared to intermittent nebulization at the same total administered doses^{67,68}.

Ipratropium bromide. The use of frequent doses, every 20 minutes, of ipratropium bromide for the first 2 hours in case of severe asthma exacerbations or moderate exacerbations not responding to initial treatment with SABA, has been shown to be effective and safe^{69,70}. The nebulized dose is 250 μ g for children weighing less than 30 kg and 500 μ g for those weighing more than 30 kg. The dose for inhaled use with a spacer chamber is 40-80 μ g (2-4 puffs). The maximum effect, which tends to decrease gradually, is observed with the first doses, so this agent should only be used during the initial 24-48 hours⁷¹.

In infants, the use of ipratropium bromide combined use with inhaled SABA has been shown to be effective in treating more severe exacerbations⁷². The effect of this association using an inhaler seems to be superior than that administered by nebulization⁶⁶.

Systemic glucocorticoids. The efficacy of systemic glucocorticoids in preschool children with mild to moderate acute episodes of wheezing induced by viral infections has been questioned; hence, its use should be restricted to more severe exacerbations (1-2 mg/kg/day)^{35,73,74}. In children aged over 5 years, these agents have shown benefit after early use⁷⁵, with the oral route being preferred over intravenous or intramuscular routes, except for circumstances in which oral intake may be inappropriate^{76,77}. Systemic glucocorticoids should be administered in moderate-severe exacerbations, and may be considered for mild exacerbations when sufficient improvement with bronchodilators has not been achieved or the child has a history of severe attacks. Prednisolone at doses of 1-2 mg/kg/day (maximum 40 mg) for 3 to 5 days until resolution is commonly administered^{78,79}.

Dexamethasone is being used as an alternative. The effect of administering a single dose of dexamethasone orally (at 0.3 mg/kg) is not inferior to that of administering prednisolone orally (at 1 mg/kg/day) during 3 days of treatment⁸⁰⁻⁸³.

Inhaled glucocorticoids. There is insufficient evidence to recommend the use of IGC as an alternative⁸⁴ or additional treatment to systemic glucocorticoids^{85,86} in the management of asthma exacerbations. Larger studies are required, with better methodological quality and cost-effectiveness analysis⁸⁷, as well as safety studies⁸⁴.

Magnesium sulfate. It can be used in severe exacerbations failing to respond to initial treatment^{88,89}. The drug is administered intravenously as a single dose of 40 mg/kg (up to 2 g) over 20 minutes.

C Nebulized magnesium sulfate together with a β_2 -adrenergic agonist in the treatment of an asthma exacerbation seems to have benefits in the improvement of pulmonary function^{90,91}.

5.3.3 Therapeutic regimens

C Treatment of an asthma exacerbation episode depends on its severity and follows the scheme shown in Figure 5.2. Doses of drugs and duration of administration should be modified according to the severity of the exacerbation and the response to treatment.

A When SaO_2 is below 94%, oxygen therapy is required to maintain SaO_2 between 94-98%^{92,93}. An $\text{SaO}_2 < 92\%$ after initial treatment with inhaled bronchodilators can be used as a marker to select the more severely ill patients who should be hospitalized for starting intensive treatment^{92,94}.

C In children with moderate/severe exacerbations refractory to first-line treatment, high-flow nasal cannula oxygen therapy appears to be superior to conventional

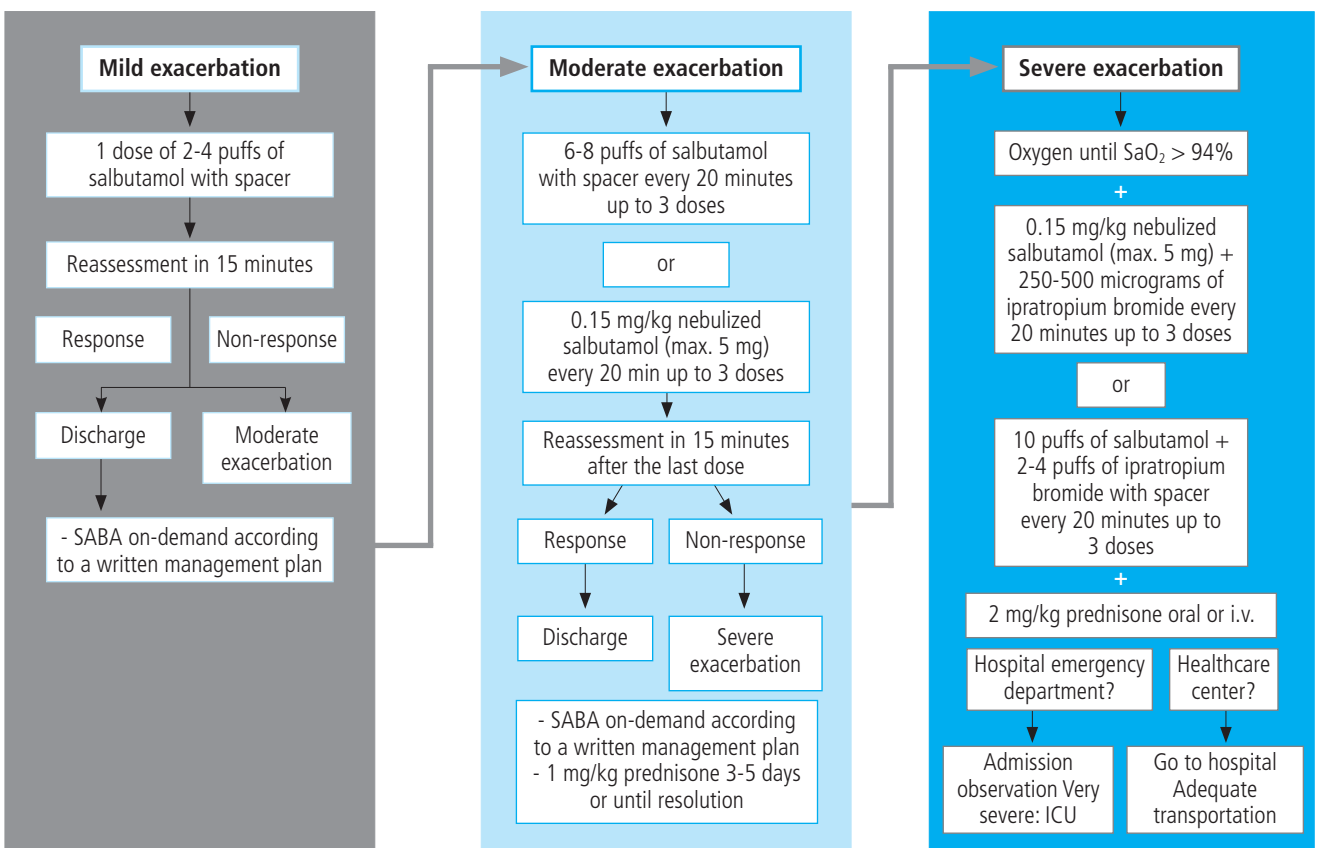
oxygen therapy to reduce breathing difficulty^{95,96}. However, more studies are needed to show its general efficacy for treating asthma and respiratory failure in the emergency setting⁹⁷.

Regarding non-invasive ventilation (NIV), the current available evidence does not allow us to confirm or exclude its use in exacerbation episodes refractory to the usual treatment⁹⁸.

Mild and moderate exacerbations can be treated in the primary care setting.

In the presence of severe exacerbation or suspicion of complications, history of high-risk exacerbations or lack of response to treatment, patients should be referred to the hospital in a medicalized ambulance.

Follow-up. It is necessary to evaluate the degree of the control of symptoms in the previous weeks, the presence of risk factors, possible triggering factors and previous treatment. Also, it is important to assess the level of therapeutic adherence and to supervise that the inhalation technique is correct. A written action plan must be reviewed or provided and a follow-up visit arranged¹⁰.



kg: kilogram; mg: milligram; SaO_2 : oxyhemoglobin saturation; max: maximum; SABA: short-acting β_2 -adrenergic agonist.

Figure 5.2. Treatment of asthma exacerbation in children.

RECOMMENDATIONS

- 5.1. The education of the child with asthma and his/her family is recommended because increases the quality of life and reduces the risk of exacerbations and healthcare costs. **R1**
- 5.2. In the education of children with asthma, it is recommended to include written personalized management action plans, addressing maintenance treatment and how to treat exacerbations. **R1**
- 5.3. Inhaled IGC is recommended as first-line treatment for the control of persistent asthma in children of all ages. **R1**
- 5.4. Montelukast can be tried as an alternative to IGC for maintenance therapy. **R2**
- 5.5. Treatment with LABA can be considered in children older than 4 years of age but always combined with IGC. LABA monotherapy should never be administered. **R1**
- 5.6. In the treatment of children with allergic asthma, immunotherapy should be considered provided that biologically standardized extracts are used and patients are appropriately selected. **R1**
- 5.7. In children aged 6 years or older with insufficiently controlled severe persistent asthma with high doses of IGC and LABA and/or LTRA and/or tiotropium, the use of biological agents or monoclonal antibodies is recommended. **R1**
- 5.8. Before considering that an asthma patient is poorly controlled and stepping up treatment, the diagnosis of asthma should be confirmed, treatment adherence and inhalation technique should be evaluated, and other comorbidities excluded. **R1**
- 5.9. Early and repeated administration of SABA at high doses is the first-line of treatment of asthma exacerbations in children. **R1**
- 5.10. It is recommended to individualize drug doses according to severity of exacerbations and the response to treatment. **R2**
- 5.11. Early use of systemic glucocorticoids is recommended in moderate and severe exacerbations; in mild exacerbation, an individualized assessment is recommended. **R1**
- 5.12. In the presence of $\text{SaO}_2 < 92\%$ after an initial treatment with inhaled bronchodilators, admission to the hospital to start intensive therapy is recommended. **R2**
- 5.13. A pMDI with spacer chamber is recommended for the administration of bronchodilators, particularly in mild-moderate exacerbations. **R1**
- 5.14. It is necessary to evaluate the degree of control, risk factors, adherence to treatment and inhalation technique, as well as to offer a written action plan and guarantee the follow-up of children with exacerbations. **R2**

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6. Asthma-associated rhinitis and rhinosinusitis

6.1 Definition and epidemiology

D The term rhinitis defines the inflammatory process of the nasal mucosa, which is characterized by the following clinical symptoms: anterior or posterior rhinorrhea, sneezing, block of nasal passages or congestion and/or nasal pruritus/itching. These symptoms should be present for two or more consecutive days and for more than one hour on most of the days¹⁻³.

C Rhinitis is a syndrome that includes several phenotypes. Rhinitis has the highest prevalence of all diseases, and it has been estimated that 100% of the population (children and adults) suffer from 1 to 10 episodes of infectious rhinitis annually⁴ (Table 6.1). Allergic rhinitis (AR) is the most prevalent of all chronic diseases, affecting 22-41% of the European population⁵ and 12.6% of children aged 0-18 years⁶. The prevalence of non-allergic rhinitis (NAR) is not so well estimated, with the highest rates in children under 6 years (up to 24.9%) and around 10% in children older than 15 years of age⁷.

C In Spain, rhinitis is the most common reason for consultation in Allergology (62% in adults and 53.8% in children)^{8,9}. The ISAAC study reported a prevalence of rhinoconjunctivitis of 7.9% in Spanish children aged 6-7 years (with an annual increase of 0.33) and 15% among those aged 13-14 years (annual increase of 0.10)¹⁰.

C AR-associated costs are high. A study carried out in Spain (FERIN project) established that the cost per patient per year was 2,326.70€ (direct costs 553.80€; indirect costs 1,772.90€)¹¹.

6.2 Diagnosis and classification

B By definition, AR diagnosis is mainly clinical, although symptoms do not enable to assess the cause, pathophysiology or the specific rhinitis phenotype; therefore, complementary diagnostic tests are necessary to establish the etiological diagnosis in cases of rhinitis of moderate to severe intensity¹.

D An initial approach to the classification (phenotyping) of rhinitis should establish whether the patient presents an infectious or non-infectious rhinitis, and subsequently classify rhinitis based on positivity of allergy tests and the correlation with the patient's symptoms. Two main rhinitis phenotypes are defined: AR and NAR. NAR includes a heterogeneous group of phenotypes of different pathologic conditions¹² (Table 6.1).

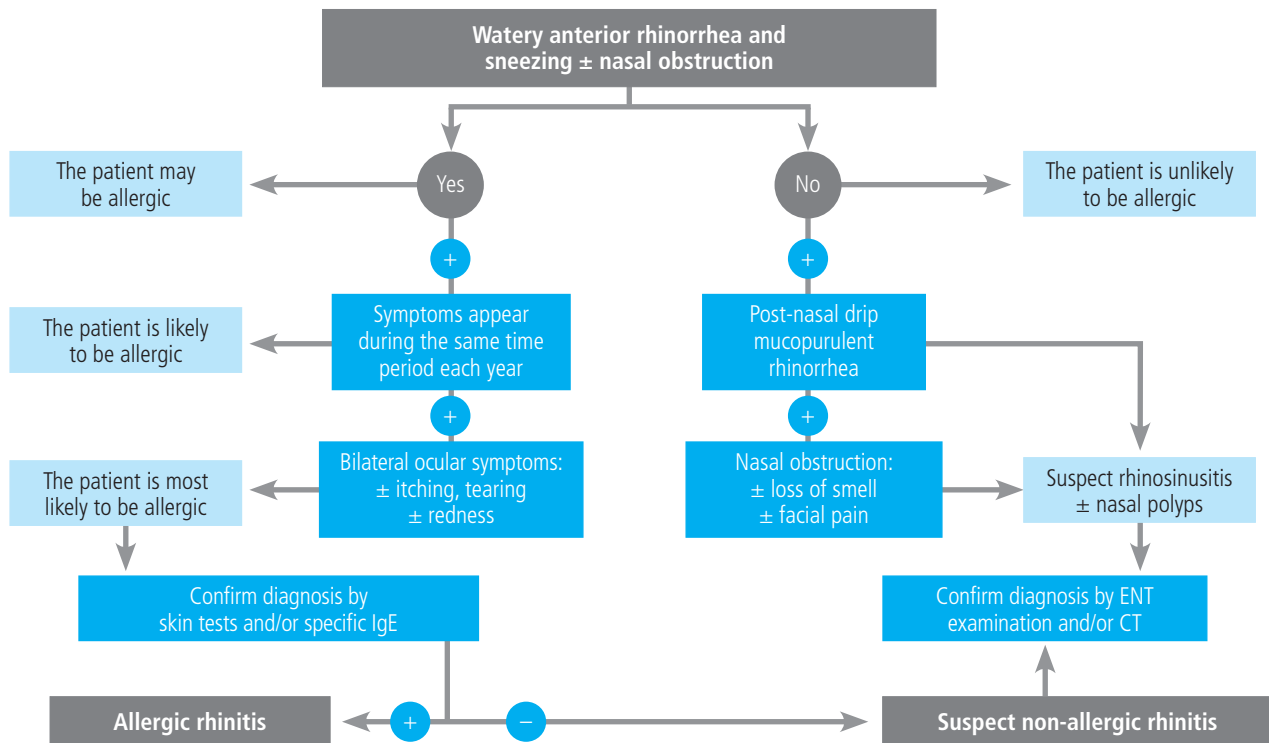
B Family history of allergy, seasonal manifestation of symptoms, concomitant ocular and nasal symptoms and an association with exposure to aeroallergens are clinical data with a high predictive value for the diagnosis of suspected AR¹³ (Figure 6.1).

B The most efficient complementary tests for the diagnosis of AR are allergic tests: intraepidermal puncture or skin prick testing with standardized allergic extracts and determination of specific serum IgE against allergens, preferably against recombinant allergens¹². A high percentage of patients with positive allergic tests does not have the disease or positive allergens are not clinically relevant, so that clinical correlation is indispensable to establish the diagnosis¹⁴.

B The specific nasal challenge (or provocation) test with allergens is the reference test for the diagnosis AR and can

Table 6.1. Rhinitis phenotypes

Infectious			Non-infectious
Viral	Bacterial	Local allergic/allergic	Non-allergic
		<ul style="list-style-type: none"> – Intermittent/persistent – Seasonal/perennial – Occupational – Mild/moderate/severe 	<ul style="list-style-type: none"> – Occupational rhinitis – Drug-induced rhinitis – Gustatory rhinitis – Hormonal rhinitis – Reactive rhinopathy (nasal hyperreactivity/old vasomotor rhinitis) – Dry/atrophic/sicca rhinitis – Idiopathic rhinitis



ENT: ear, nose and throat; CT: computerized tomography.

Figure 6.1. Diagnostic algorithm of allergic rhinitis.

B be necessary in cases of high clinical suspicion and negative results of intraepidermic testing or specific serum IgE^{15,16}.

B A specific AR phenotype, named local AR, has been described, which is characterized by negativity of systemic allergic tests (intraepidermic tests or specific serum IgE) and positive specific nasal challenge test¹⁷.

D Other complementary tests that can be useful in the study of nasal function include an objective assessment of obstruction (acoustic rhinometry, active anterior rhinomanometry, measurement of peak nasal inspiratory flow)¹⁸, assessment of nasal inflammation (nasal nitric oxide [nNO], nasal cytology, biopsy)¹⁹ and assessment of olfactory function by dynamic olfactometry²⁰.

D AR is an IgE-mediated chronic inflammatory immunological disorder of the nasal mucosa that causes a myriad of symptoms, including nasal obstruction/congestion, sneezing and rhinorrhea after inhalation of environmental allergens²¹.

B AR can be classified according to different criteria. On the basis of triggering allergens, AR can be classified into seasonal (outdoors such as pollens and fungal spores mainly) or perennial (indoors such as dust mites, insects, animal dangers or other fungal spores), and on the basis of temporal criterium as intermittent or persistent (symptoms present for more than 4 days a week and for more than 4 consecutive weeks). This last classification has been validated and has been shown to better reflect the actual clinical condition of patients²².

B The severity of AR is evaluated on the basis of the impact on the quality of life (sleep disturbance, impairment of daily

life activities, leisure and/or sport activities, impairment of school or job tasks, and the consideration of symptoms as bothersome), differentiating into mild (none affected) moderate (one to three) or severe (all affected). This classification has been validated in children and adults, with and without treatment²³⁻²⁵ (Table 6.2). A visual analogue scale can also be used to assess severity of AR²⁶.

In recent years, and in a similar way to that established in asthma, it has been proposed to evaluate rhinitis control using validated questionnaires (such as the Rhinitis Control Assessment Test)²⁷ or using a visual analogue scale (available as applications for mobile devices)²⁸.

6.3 Rhinitis and asthma

Multiple epidemiological, pathophysiological and therapeutic studies have demonstrated the association between rhinitis and asthma¹.

Factors determining why some patients with AR will develop asthma are unclear (Table 6.3), although it is known that both AR and NAR are risk factors for asthma^{29,30}.

Sensitization to different types of aeroallergens and specific profiles are associated with different allergic clinical features (rhinitis with/without conjunctivitis with/without asthma) and different levels of severity^{23,31}.

According to some studies, the association with asthma would be greater in cases of more severe and prolonged

Table 6.2. Classification of allergic rhinitis

According to duration		
Intermittent	Persistent	
Symptoms are present for ≤ 4 days a week or for ≤ 4 consecutive weeks	Symptoms are present for > 4 days a week and for > 4 consecutive weeks.	
According to severity		
Mild	Moderate	Severe
None of the following items is present: - Sleep disturbance - Impairment of daily, leisure and/or sports activities - Impairment of school and job tasks - Symptoms are bothersome	- One, - Two, - or three of the aforementioned items are present	The four items are present

Modified from (Bousquet 2008)¹ according to (Valero 2007)²⁵.

Table 6.3. Interrelationship between rhinitis and asthma: risk factors for asthma

- Allergic rhinitis.
- Non-allergic rhinitis.
- Characteristics of aeroallergens.
- Number of sensitizations.
- Intensity of sensitization.
- Severity and duration of rhinitis.
- Number of associated allergic diseases (rhinitis, conjunctivitis, dermatitis).

B AR^{32,36}, higher number of sensitizations^{32,37,38}, higher specific IgE levels³⁹ and in the presence of various associated allergic diseases (rhinitis, conjunctivitis, dermatitis)^{40,41}.

B The prevalence of rhinitis in patients with asthma is high and much higher than in the general population⁴². In Spain, two studies showed a prevalence of rhinitis in patients diagnosed with asthma of 71% and 89.5%, respectively⁴³. A parallel increase in the prevalence of asthma and rhinitis has been demonstrated⁴⁴.

B Suffering from rhinitis aggravates asthma⁴⁵, worsens asthma control⁴⁶ and asthma symptoms⁴⁷, and increases the use of healthcare resources^{48,49}.

B Inflammatory changes in the bronchial mucosa of non-asthmatic patients with AR have been observed⁵⁰, as has been the case with nasal eosinophilic inflammation in asthma patients without nasal symptoms⁵¹.

A Treatment of AR with intranasal glucocorticoids may improve some aspects of asthma, such as pulmonary function⁵², symptom score, quality of life or the use of reliever or rescue medication⁵³, the level of asthma control⁵⁵ and exacerbations in children^{34,54}.

6.4 Treatment of allergic rhinitis

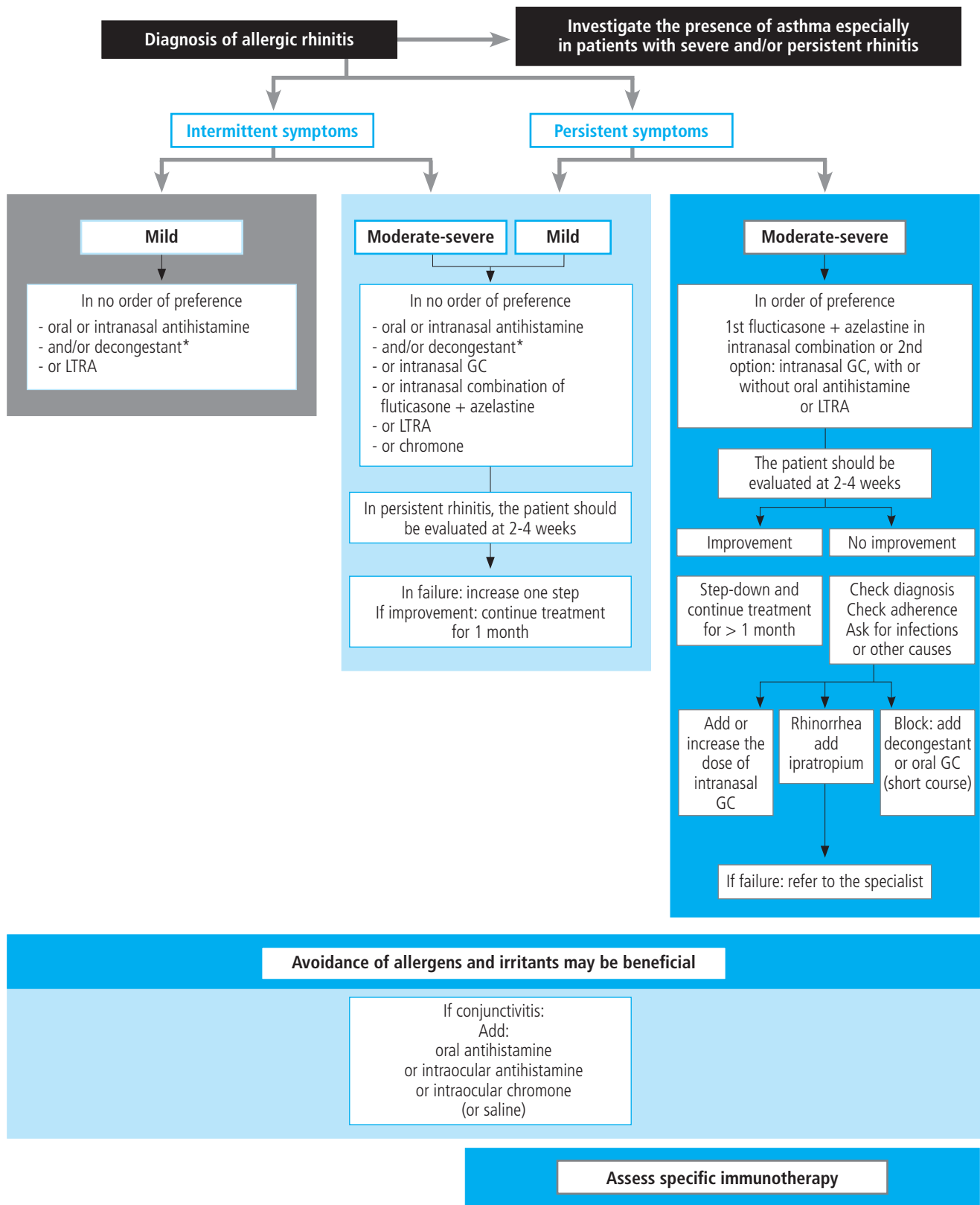
The treatment strategy of allergic rhinitis includes patient education, avoidance of allergens and contaminants, pharmacotherapy and allergen-specific immunotherapy. At the time of selecting the pharmacological treatment, efficacy, safety, cost-effectiveness relationship, patients' preferences, severity of disease and the presence of comorbidities should be evaluated. Pharmacological treatment of allergic rhinitis should include clear-cut recommendations that will have to be implemented in a stepwise approach according to severity (Figure 6.2).

Second generation H1-antihistamines (non-sedating) (*bilastine*, *cetirizine*, *desloratadine*, *ebastine*, *fexofenadine*, *levocetirizine*, *loratadine*, *mizolastina* and *rupatadine*) administered by the oral route, improve symptoms both in adults and children, rhinorrhea, sneezing, nasal itching and ocular symptoms, although are less effective to relieve nasal obstruction, and should be preferred over sedating antihistamines for their favorable risk-benefit ratio¹².

Topical H1-antihistamines (*azelastine*, *emedastine*, *epinastine*, *levocabastine* and *olopatadine*) have a rapid effect on symptoms, are more effective for nasal congestion than oral antihistamines and more effective for ocular symptoms, although are less effective for nasal congestion than intranasal glucocorticoids (INGC), and have been shown to reduce symptoms and improve quality of life versus placebo, without relevant side effects except for a bitter taste¹².

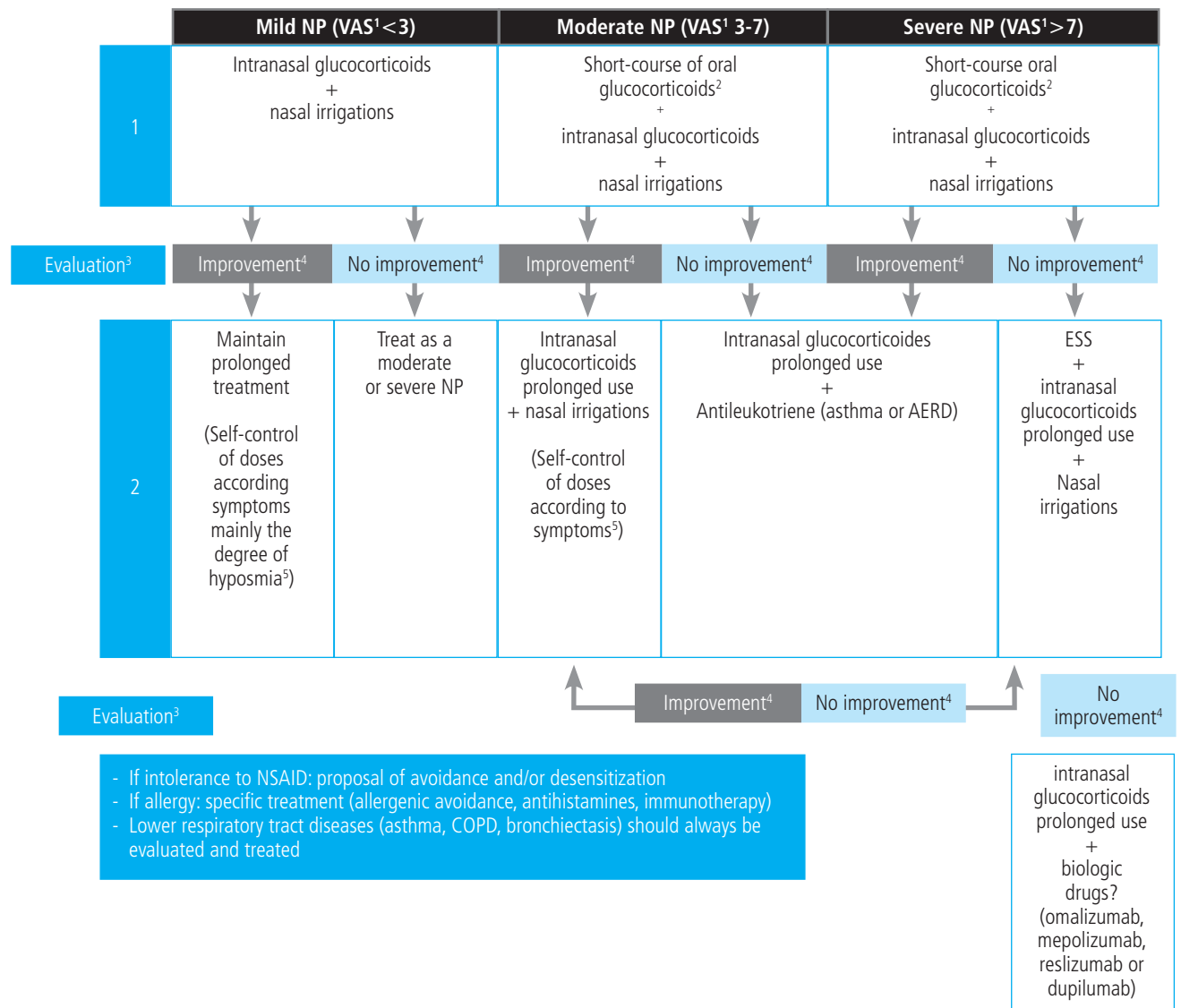
INGC (*budesonide*, *ciclesonide*, *fluticasone*, *mometasone* and *triamcinolone*) are very effective drugs for reducing nasal and ocular symptoms, even when administered intermittently, and are superior to oral antihistamines and *montelukast*. Their use may be associated with some minor adverse effects, such as epistaxis or headache, but a relevant effect neither on the hypothalamic-pituitary axis nor on the growth of children has been demonstrated¹².

The combination of topical intranasal fluticasone *propionate* and *azelastin* in a single device has shown a rapid



LTRA: leukotriene receptor antagonist; GC: glucocorticoids; *in short time periods, usually less than 5 days.

Figure 6.2. Treatment algorithm of allergic rhinitis^{1,52,53}.



VAS: visual analogue scale; AERD: aspirin-exacerbated respiratory disease; ESS: endoscopic sinus surgery; COPD: chronic obstructive pulmonary disease; ²short time periods, usually less than 5 days.

Figure 6.3. Treatment algorithm of sinonasal polyposis (NP).

A and more effective effect than the use of INGC or intranasal antihistamines in monotherapy, with the only relevant adverse effect of its bitter taste. It is recommended in more severe or uncontrolled cases or as a second-line treatment after failure of monotherapy¹².

A *Montelukast* has consistently shown to reduce symptoms and to improve quality of life as compared with placebo, although to a lower extent than INGC and similarly to oral antihistamines, with good safety data. It is neither recommended as monotherapy nor as first-line treatment¹².

B Decongestants, both oral and intranasal, have shown to be effective to reduce nasal congestion in the short-time, but adverse effects outweigh the benefits especially in the

presence of other comorbidities, and their generalized use is not recommended. Intranasal decongestants used for more than 5 days may cause rhinitis medicamentosa¹².

B Oral or parenteral glucocorticoids can improve the symptoms of RA, but should not be prescribed routinely because of their adverse effects on the hypothalamic-pituitary axis, growth and the musculoskeletal system, digestive system, control of glycemia, blood pressure and emotional status¹².

A Intranasal chromones (*cromoglycate* and *nedocromil*) have shown efficacy for reducing sneezing, rhinorrhea and nasal congestion with fewer adverse effects, although are less effective than INGC¹².

B Intranasal anticholinergics (*ipratropium bromide*) decrease rhinorrhea, although are associated with some adverse effects, such as nasopharyngeal irritation, headache, and nasal or oral dryness. They are recommended to be added to INGC for improving excessive rhinorrhea¹².

A The anti-IgE monoclonal antibody, *omalizumab*, has shown to reduce symptoms and the use of rescue medication as well as to improve quality of life as compared with placebo, with a low risk of local reactions at the site of injection or anaphylaxis. Its use could be considered as an add-on treatment in severe uncontrolled cases or to reduce the risk of anaphylaxis in patients treated with allergenic vaccines, although at the present time AR is not included as an indication in the technical specifications of the product¹².

A Allergen immunotherapy is effective and cost-effective for the treatment of adult and pediatric AR caused by pollens and dust mites when administered both subcutaneously and orally (sublingual route). It may alter the natural course of the respiratory allergic disease, decreasing the development of asthma and preventing new sensitizations, and is effective for the improvement of symptoms in patients with concomitant asthma and rhinitis¹².

A The combination of several avoidance measures of indoor allergens added to baseline pharmacological treatment is also effective¹².

D The principles of treatment of rhinitis in childhood are the same than in adulthood, but special attention should be paid to adverse effects. Doses should be adequate and, in some cases, the age of the patient should be considered when prescribing certain drugs⁵⁷⁻⁵⁹.

6.5 Rhinosinusitis. Nasal polyposis

D Chronic rhinosinusitis (CRS) is defined as an inflammatory disorder of the nasal passages and paranasal sinuses, characterized by the presence of at least two out of four cardinal symptoms: nasal obstruction and/or nasal drainage, and/or facial pain/pressure, and/or hyposmia/anosmia for at least 12 consecutive weeks⁶⁰. There are two phenotypes of CRS, with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP), which present differences in the inflammatory profile and response to treatment^{60,61}.

C In Europe, the prevalence of CRS is 10.7%⁶².

A Patients with CRS have a 3.5-fold higher risk for asthma⁵. Aspirin-exacerbated respiratory disease (AERD) or NSAID-exacerbated respiratory disease associated with asthma, CRSwNP and NSAID intolerance is more severe and has a

A poorer prognosis⁶³. In patients with asthma, the prevalence of AERD is 7-15%, which increases with a greater severity of asthma⁶⁴.

B Severity of CRS can be evaluated using a visual analogue scale, nasal endoscopy to assess the size of polyps, and/or using validated questionnaires to assess the impact on the quality of life such as SNOT-22⁶⁰⁻⁶⁵.

B Imaging studies do not add value to endoscopic diagnosis⁶⁶ and should be reserved for surgical planning (computerized tomography), suspicion of complications or nasosinusal tumor (magnetic resonance)⁶⁷.

A Medical treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) is based on the continuous and prolonged use of INGC (*beclomethasone*, *mometasone*, *budesonide*, *triamcinolone*) (Figure 6.3)⁶⁸. A greater efficacy of one active principle compared to another has not been demonstrated, although high doses are more effective than low doses⁶⁹⁻⁷¹.

A Short courses of oral glucocorticoids (*prednisone*, *methylprednisolone* or *deflazacort*, 2 to 4 weeks) associated with intranasal glucocorticoids significantly improve nasal congestion and reduce the size of polyps⁷².

B Endoscopic sinus surgery should be indicated in patients in which medical treatment has been unsuccessful to achieve an adequate control of the disease^{73,74}.

B INGC should be used after surgery for the prevention of relapses and to improve outcome⁷⁵. The need of revision surgery depends on the previous surgical procedures and postoperative medical treatment, being greater in AERD^{49,76}.

A An adequate medical/surgical control of CRS improves clinical and functional parameters of asthma^{77,78}.

B Other treatment options associated with the use of INGC that have shown some efficacy are: *montelukast* (particularly in allergic patients or AERD)⁷⁹ and *clarithromycin*⁸⁰.

B Up to 40% of patients have poor control of the disease⁸¹, evidencing the need to identify specific phenotypes that allow predicting therapeutic success⁶¹. Recent studies with different monoclonal antibodies, such as *omalizumab* (anti-IgE)⁸², *mepolizumab*⁸³, *reslizumab* (anti-IL5)⁸⁴ and *dupilumab* (anti-IL4-receptor α)⁸⁵⁻⁸⁷ have shown an improvement in the size of nasal polyps, nasal symptoms including olfaction, and quality of life. *Mepolizumab* and *dupilumab* have demonstrated a mild to moderate reduction in the indication of surgery^{83,87}. Treatment with biologic drugs is a highly promising approach to achieve good control of CRSwNP alone or associated with asthma especially in the most severe uncontrolled cases^{85,88}. However, this indication is not included in the technical specifications of the products (except for *dupilumab*) and its cost-effectiveness is unknown.

RECOMMENDATIONS

- 6.1. It is recommended to classify allergic rhinitis according to duration into intermittent and persistent, and according to severity into mild, moderate and severe. **R1**
- 6.2. The diagnosis of rinitis is established by clinical criteria and allergy tests. **R1**
- 6.3. Patients diagnosed with asthma should be assessed for the presence of chronic rhinitis and rhinosinusitis with nasal polyps and vice versa, to implement an integral treatment strategy. **R1**
- 6.4. For the pharmacological treatment of allergic rhinitis, it is recommended the use of oral and/or topical nasal second-generation antihistamines, intranasal glucocorticoids, or the association of these medications in case of lack of response or moderate to severe disease. **R1**
- 6.5. In appropriately selected patients (adults and children), immunotherapy with allergen extracts is recommended for the treatment of allergic rhinitis. **R1**
- 6.6. In patients with chronic rhinosinusitis with nasal polyposis, continuous use of intranasal glucocorticoids is recommended. The use of short-courses of oral glucocorticoids is indicated in severe cases and exacerbations. **R1**
- 6.7. In patients with poor control of chronic rhinosinusitis with nasal polyposis despite maximum medical treatment, it is recommended to consider the surgical option followed by post-surgical treatment with intranasal glucocorticoids. **R1**

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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.

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 (FEV₁/FVC ratio < 0.7 or FEV₁ < 80% predicted) after the use of an adequate treatment (as long as the better FEV₁ will be higher than 80%).

- Chronic airflow limitation (forced expiratory volume in one second/forced vital capacity [FEV₁/FVC] ratio < 0.7 or FEV₁ < 80% predicted) after the use of an adequate treatment (as long as the better FEV₁ 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 FEV₁ $\leq 75\%$ 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

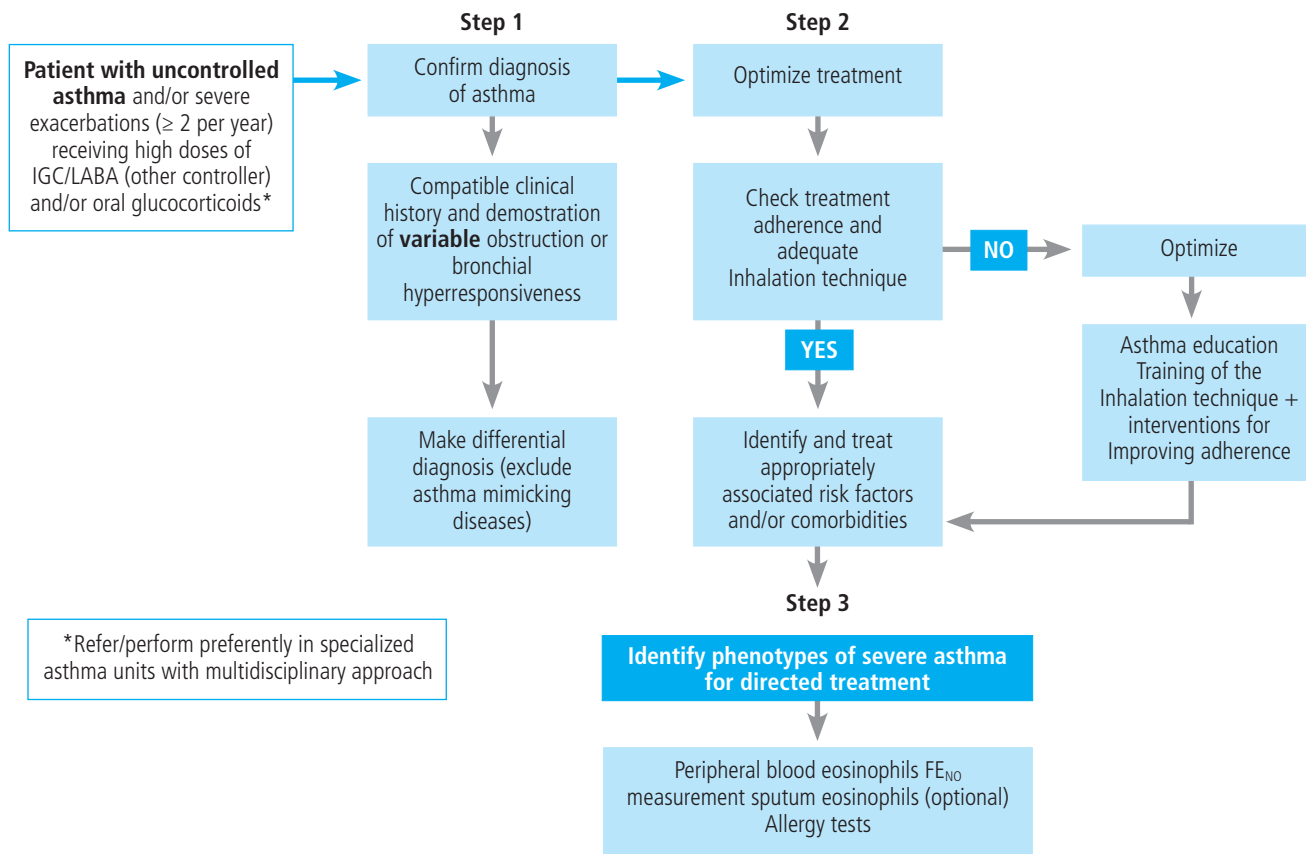


Figure 7.1. Diagnostic algorithm based on sequential step decision for SUA.

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).

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

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}.

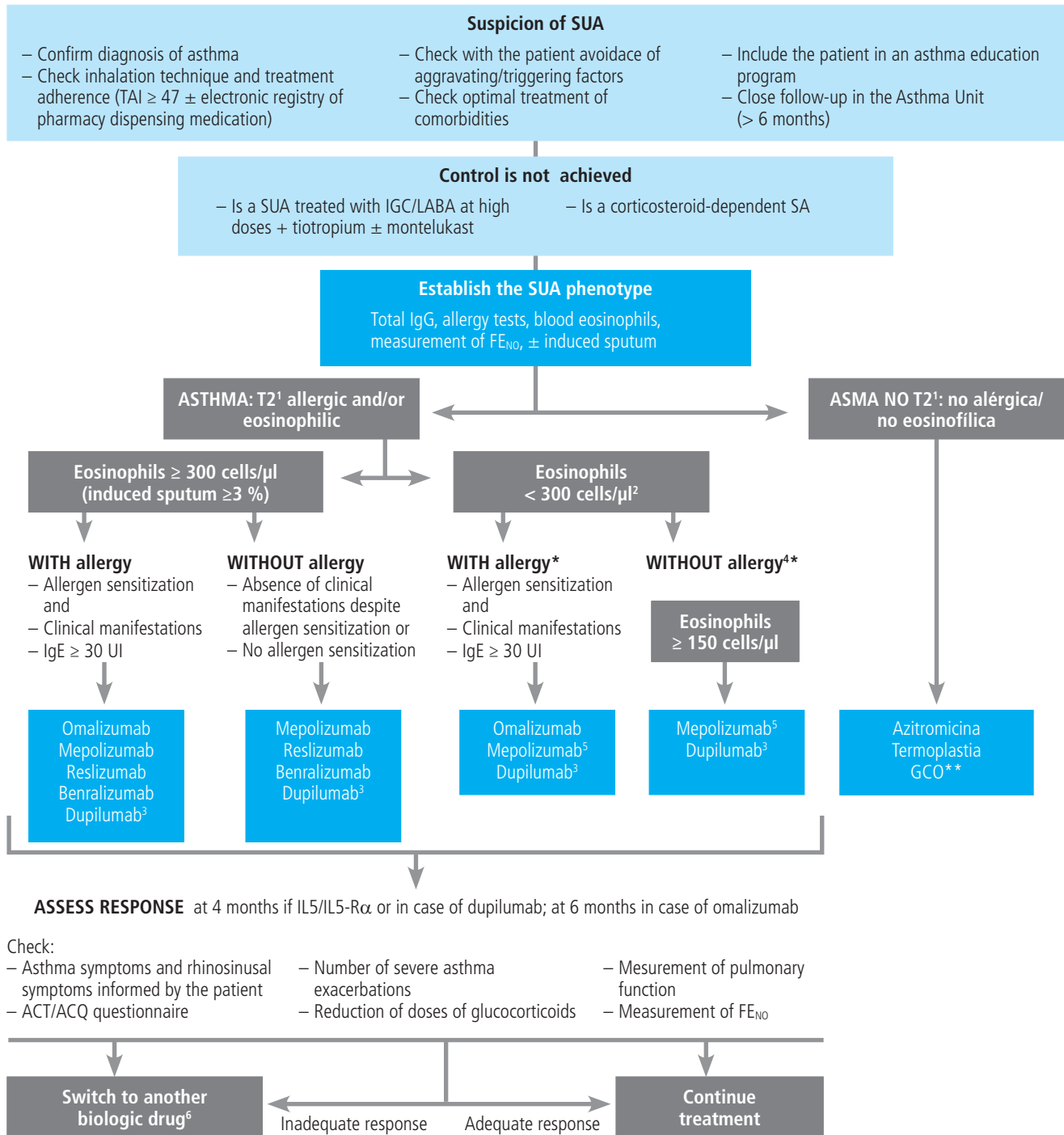
7.3.3 Non-T2 asthma

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}.

D

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.

D

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 glucocorticoids, 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}.

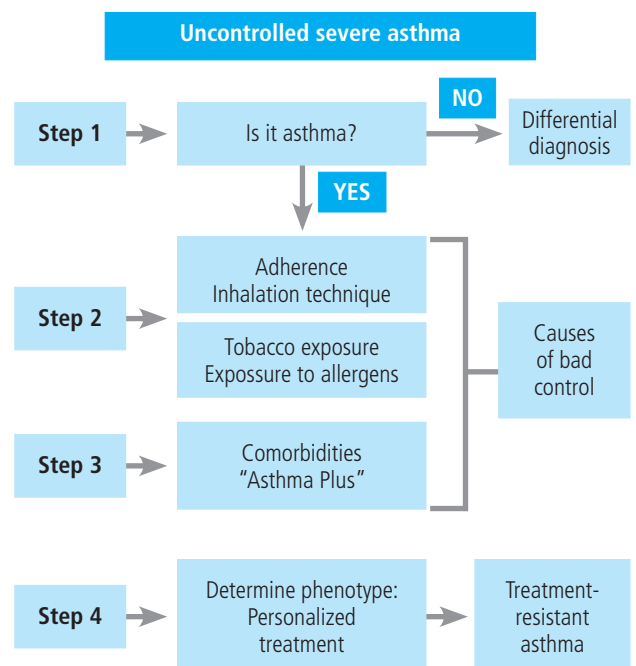


Figure 7.3. Uncontrolled severe asthma in children: stepwise assessment.

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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8. Special circumstances

8.1 ASTHMA-COPD overlap syndrome (ACOS)

8.1.1. Concept and definition

Asthma and chronic obstructive pulmonary disease (COPD) are two different chronic respiratory diseases¹, although it is common to find the characteristics of both diseases in a single patient².

Asthma and smoking^{3,4}, low pulmonary function in childhood⁵, exposure to irritants⁶ or environmental contamination⁷ can contribute to the development of associated COPD in adulthood.

The GesEPOC-GEMA consensus defines asthma-COPD overlap syndrome (ACOS) as the presence of persistent chronic airflow limitation (CAL) (crucial for diagnostic confirmation), in a current smoker or ex-smoker patient (main risk factor), who presents characteristics of asthma (clinical, biological or functional)⁸.

Different definitions of ACOS have been proposed⁹⁻¹⁶, the most recent of which are based on two types of patients:

- An asthma patient who smoke and develop chronic airway obstruction.
- Patients with COPD and eosinophilia^{8,15,17,18}.

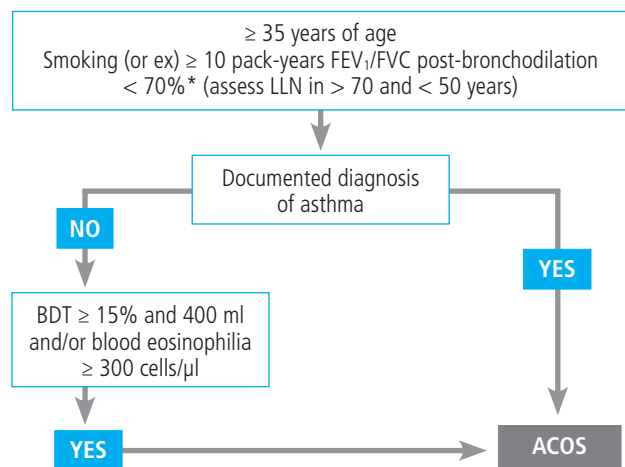
The prevalence of ACOS varies according to the source considered and criteria used for definition¹⁹⁻²¹, with estimates between 1.6% and 4.5% in the general population, and between 15% and 25% in patients with obstructive respiratory disease^{11,22-36}.

Patients with ACOS have more symptoms, poorer quality of life, higher risk of exacerbations, more accelerated loss of pulmonary function, higher incidence of comorbidities and greater consumption of healthcare resources^{9,10,31,37-41} as compared to patients with asthma or COPD, but a better survival when treated with inhaled glucocorticoids (IGC)^{11,23,42,43}.

The mortality of chronic respiratory disease is higher in patients with ACOS or COPD than in those without chronic airway obstruction⁴⁴⁻⁴⁶.

8.1.2. Diagnostic confirmation

The following sequential diagnostic evaluation is proposed (Figure 8.1)^{17,47}:



*Maintain on treatment with IGC/LABA (6 months). In some cases in addition after a course of oral steroids (15 days). ACOS: asthma-COPD overlap syndrome; IGC: inhaled glucocorticoids; LABA: long-acting β_2 -adrenergic agonist; BDT: bronchodilation test.
**LLN: lower limit of normal.

Figure 8.1. Diagnostic confirmation of asthma and COPD overlap syndrome (ACOS).

- To confirm that the patient meets criteria for COPD (> 35 years, smoker > 10 pack-years, post-bronchodilation forced expiratory volume in one second/forced vital capacity [FEV₁/FVC] < 70% [assessing the lower limit of normal, particularly at extreme ages])^{13,48}.
- If the patient also meets criteria for asthma^{13,49}, ACOS is confirmed.

If the patient does not meet complete criteria for asthma, the presence of a very positive bronchodilation test (FEV₁ post-bronchodilation \geq 15% y 400 ml) or blood eosinophilia (\geq 300 eosinophils/ μ l), confirms the diagnosis of ACOS.

8.1.3. Treatment

Although the initial treatment does not differ between patients with pure asthma and those with overlap syndrome, in patients with COPD, a diagnosis of ACOS predicts the response to IGC^{50,51}. There are proposals for the treatment of

C ACOS according to its treatable features^{52,53} that should be **D** agreed upon.

Therapeutic recommendations in patients with ACOS

- A** – If the diagnostic evaluation only confirms asthma, it will be treated according to GEMA guidelines⁴⁷, avoiding monotherapy with long-acting β_2 -adrenergic agonist (LABA).
- D** – If the diagnostic evaluation only confirms COPD, it will be treated according to GesEPOC guidelines⁴⁸, avoiding monotherapy with IGC.
- D** – If the evaluation confirms ACOS: start with a combination of IGC at low or moderated doses according to symptoms⁵⁴, associated with LABA⁵⁵⁻⁵⁹.
- D** – In case of persistence of exacerbations or relevant symptoms, it is recommended adding a long-acting muscarinic agonist (LAMA)^{60,61}.
- C** – Treatment of comorbidities.
- C** – Treatment with biologics: the role of omalizumab⁶²⁻⁶⁷ or anti-leukin-5 (anti-IL-5) (benralizumab^{68,69} or mepolizumab^{67,70,71}) in ACOS remains unclear⁷².
- C** – Other treatments (when necessary): smoking cessation, respiratory rehabilitation, oxygen therapy.
- C** – Patients should be referred to a specialized consultation in case of lack of response or partial response to the prescribed treatment.
- C** – Periodic follow-up assessments should be established.

8.2. Asthma and pregnancy

B Asthma is the most common respiratory disease in pregnancy and affects between 2% and 13% of all pregnant women⁷³. Up to 18% of asthmatic pregnant women present worsening of her asthma during gestation, increasing to 50% in case of severe asthma⁷³⁻⁷⁵. This may be due to mechanical and hormonal changes, the reluctance on the part of pregnant women to use medications and the degree of previous control of the disease⁷⁶.

8.2.1. Effects of asthma on pregnancy

B Although the risk is low, pregnant women with asthma may present maternal and fetal complications. In the neonate, poor asthma control is associated with prematurity, low birthweight and increased perinatal mortality, whereas in the mother there is an increased risk of pre-eclampsia, placenta previa and gestational diabetes⁷⁷. Prevention of exacerbation is essential for reducing the risk of complications⁷⁸.

B Poor adherence to treatment and upper respiratory tract infections are the most common trigger factors for exacerbations⁷³.

B Women with other comorbidities, such as rhinitis, obesity, sudden increase of body weight during the first trimester of gestation and smoking habit have a poorer control of asthma during pregnancy^{80,81}.

8.2.2. Treatment of asthma in pregnancy

A Virtually all drugs used in the treatment of asthma cross the placental barrier; however, the advantage of treating asthma

during pregnancy outweighs the potential shortcomings of the use of medication^{73,76,81}.

The appropriate use of IGC, LABA, montelukast and theophylline is not associated with an increase of fetal abnormalities⁸².

IGC prevent asthma exacerbations during pregnancy⁸³.

Budesonide and other IGC are safe drugs^{84,85}. A study carried out in 2014 in neonates born from mothers treated with inhaled budesonide during pregnancy showed a higher rate of teratogenesis (3.8%) as compared with the general population (3.5%)⁸⁶.

Although safety studies of β_2 -agonists during pregnancy are not totally conclusive, and a recent study revealed a slightly higher risk for the incidence of cleft palate and gastroschisis⁸⁷, the use of these compounds is permitted⁸⁸.

Oral glucocorticoids (OGC) cause teratogenic effects, and their use should be restricted to asthma exacerbations and severe asthma⁸⁹.

Omalizumab has not shown a higher association with congenital abnormalities, prematurity or low birthweight, but is not recommended starting its administration during pregnancy because of the risk of anaphylaxis^{90,91}.

The same algorithms for the treatment of exacerbations in non-pregnant women with asthma should be followed, ensuring in addition an adequate fetal oxygenation ($\text{SaO}_2 > 95\%$) and monitoring^{73,76}.

Control of asthma and prevention of exacerbation can be improved during pregnancy using measurement of FE_{NO} , questionnaires such as the Pregnancy Asthma Control Test (p-CAT) or the Asthma Control Questionnaire (ACQ) or telehealth⁹²⁻⁹⁵.

8.3. Occupational asthma

C Occupational asthma (OA) is asthma induced by work exposure and caused by agents exclusively found in the workplace (Table 8.1). It is the most common occupational respiratory disease and the risk attributable to workplace exposure is 10% to 25%; it has been estimated that this etiology is present in one out of 6 adults with asthma^{98,99}.

8.3.1. Types of occupational asthma

– Immunological OA: induced by sensitization to specific agents which are present in the workplace, through a mechanism associated with a specific immunological response⁹⁶. High molecular weight (HMW) agents (proteins or glycopeptides > 10 kDa) causing production of specific IgE and the typical allergic response are the most common. Low weight molecular (LMW) agents are chemical products causing asthma through an unclear mechanisms suggesting sensitization. OA induced by high molecular weight compounds is associated with rhinitis and conjunctivitis and characterized by an earlier reaction, whereas OA induced by low molecular weight agents presents higher bronchial hyperreactivity and more severe clinical manifestations^{100,101}.

– Non-immunological: induced by irritants in the absence of sensitization¹⁰². The reactive airways dysfunction

Table 8.1. Causative agents of occupational asthma^{96,97}

Class	Agent	Jobs/activities at risk of exposure
High molecular weight		
Animals	Mites, rats, crustaceans, mammal dander, etc.	Laboratory workers, farmers, veterinarians, seafood processors
Cereals and flours	Cereal powders, wheat, barley, oats, corn	Bakery, baker's shop, pastry-making, beer industry
Enzymes	Amylase, alcalase	Pharmaceutical companies, baker's shops
Latex	Latex	Healthcare personnel
Low molecular weight		
Diisocyanates	Toluene diisocyanate (TDI), methylene diisocyanate (MDI) and hexamethylene diisocyanate (HDI)	Polyurethane foams, varnish, plastics, insulators, gun spray painting
Acid anhydrides	Phthalic acid, trimellitic acid, maleic anhydride, trimellitic anhydride	Resins and plastics, chemical and adhesive industries
Metals	Nickel, platinum, cobalt, chrome, stainless steel salts Glutaraldehyde and chlorhexidine Red cedar and tropical wood	Platinum refinery, polishers, grinding, tanners Sanitary ware Carpentry, electronic welding
Biocides	Penicillin, spiramycin, tetracycline	Pharmaceutical industry
Woods	Nickel, platinum, cobalt, chrome, stainless steel salts	Platinum refinery, polishers, grinding, tanners
Antibiotics	Glutaraldehyde and chlorhexidine	Sanitary ware
Irritants		
Bleach/hydrogen chloride	Chlorine, ammonia, ClH	Cleaning
Smokes	Smokes	Firefighters
Gases	NO ₂ , SO ₂ , ozone	Metallurgy, agriculture
Other	Resin, acetic acid, caustic soda	Sanitary ware, chemical industry

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.

C syndrome (RADS)¹⁰³ is the most representative form of this type of asthma. The term irritant-induced asthma is currently used, which includes cases of asthma occurring after one or more exposures to high concentration levels¹⁰⁴.

8.3.2 Risk factors

- Exposure levels: the higher the level, the greater the risk of developing asthma caused by both HMW or LMW agents^{105,106}.
- Atopy: particularly in those exposed to HMW agents¹⁰⁷.
- Rhinitis: often accompanying or preceding asthma produced by HMW^{97,108}.
- Tobacco: an association may exist with the development of asthma caused by HMW and LMW agents, which act through an IgE-mediated mechanism¹⁰⁹.

8.3.3 Diagnosis

C The diagnosis of asthma and its relationship with the patient's workplace should be confirmed¹⁰². Diagnostic

tests are shown in Table 8.2 and the diagnostic algorithm is summarized in Figure 8.2. Methacholine challenge test has a high negative predictive value for the diagnosis of OA due to its high sensitivity (87-95%), in particular, if the patient has been recently exposed, but the specificity is low (36-40%)^{114,115}.

C Bronchial provocation test by the specific agent is the most accepted diagnostic confirmation test¹¹⁶.

8.3.4. Treatment

B Patients with OA caused by sensitizing agents should be removed from the source of exposure¹¹². Workers with irritant-induced asthma may continue to work provided they are transferred to lower exposure areas together with the implementation of industrial hygienic measures to reduce exposure.

B In approximately 70% of patients, asthma symptoms and BHR persist for several years after being removed from the site of exposure⁹⁶.

Table 8.2. Diagnostic tests in occupational asthma

Diagnostic tests	Diagnostic value
Clinical and work history	Essential but low positive predictive diagnostic value ¹¹⁰
Immunological tests	– IgE sensitization → Intraepidermal test/prick test identify the allergen – Positivity only indicates that sensitization exists ⁹⁷
PEF monitoring: working vs. non-working period	– Sensitivity: 81-87% – Specificity: 74-89% ¹¹¹
Non-specific bronchial provocation test: working vs. non-working period	– Associated to PEF monitoring – Added value, but with no increase of sensitivity or specificity ¹¹²
Induced sputum	– Eosinophilic pattern in most cases (> 3%) – Improves sensitivity of specific bronchoprovocation test ¹⁰²
Fractional exhaled nitric oxide fraction (FE _{No})	– Information added to the specific bronchoprovocation test if induced sputum is not available
Specific bronchial provocation	– Inhalation of the suspected agent at increasing doses – Serial FEV ₁ monitoring – Is the most reliable and the reference test to confirm OA ¹¹³

8.4. Physical exercise-induced asthma

C Exercised-induced asthma is defined as a narrowing of the lower airways that is triggered by strenuous physical exercise¹¹⁷.

C Exercise-induced bronchoconstriction is more frequent among patients diagnosed with asthma, but may be also present in non-asthmatic subjects^{118,119}.

A Exercise-induced asthma is more common in patients with poorly controlled asthma^{120,121}.

C Exercise-induced asthma is caused by the increased osmolarity at the airway surface due to cooling and dehydration following hyperventilation¹²².

B It is associated with the release of mediators, such as prostaglandins, leukotrienes and histamine. Exercise-induced asthma may be the expression of a genetic predisposition and interaction with environmental pollutants, as well as of the resulting oxidative stress¹²³, among other factors.

C The prevalence is higher in athletes, children and adolescents, females, urban environments, and among Afro-Americans and Asiatics^{124,125}.

B Symptoms (cough and dyspnea with wheezing) usually occur during or following exercise, with a 2-3 hour-refractory period after their onset¹²⁶.

A Self-reported symptoms are unreliable for diagnosis. The diagnostic test is the finding of a FEV₁ decrease over 10% measured 30 minutes after cessation of exercise and compared with the previous FEV₁ values¹²⁷.

B Differential diagnosis with laryngeal and glottic disorders should be made as well as with other conditions associated with exercise-induced breathlessness, such as COPD, restrictive pulmonary diseases, obesity, anatomical defects, diaphragmatic paralysis or pulmonary fibrosis¹²⁸.

A It is necessary to evaluate the degree of control of asthma and to consider the possibility of increasing a therapeutic step.

A Occasional use of short-acting β_2 -agonists (SABA) approximately 10 minutes before exercise¹¹⁸ is the treatment of

choice. However, when used regularly, these agents gradually lose effectiveness^{129,130}.

A IGC should be added when a continuous treatment with SABA is needed, since this combination reduces both the frequency and intensity of exacerbations¹³¹.

A LTRA is a therapeutic option as they have a similar efficacy to LABA for preventing exercise-induced bronchial obstruction but are not effective to reverse an established obstruction¹³².

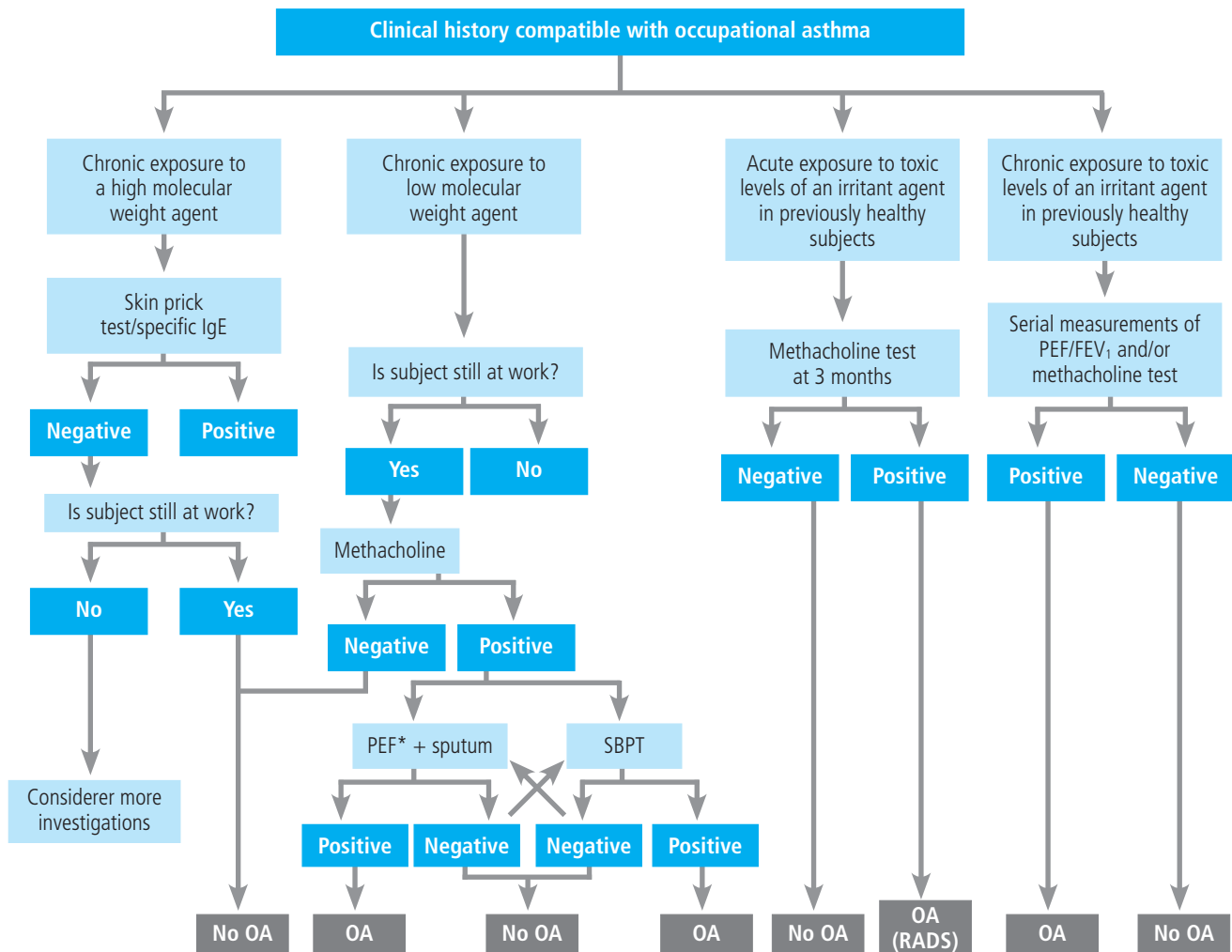
A Increasingly intense warm-up exercise before starting any sports activity may attenuate the intensity of bronchoconstriction^{133,134}.

C Reduction of dietary sodium intake and supplementation with ascorbic acid or fish oil may diminish the severity of exacerbations¹³⁵.

8.5. Aspirin-exacerbated respiratory disease (AERD)

C AERD or respiratory disease exacerbated by non-steroidal anti-inflammatory drugs (NSAIDs) refers to acute development of nasal and/or bronchial respiratory symptoms of any intensity between 30 minutes and 3 hours after the administration of acetylsalicylic acid (ASA) or other cyclooxygenase-1 (COX-1) inhibiting NSAIDs¹¹⁵. It can be associated with cutaneous symptoms and hypotension, although this occurs rarely. The prevalence of AERD in the general population is of 0.3-2.5% but increases to 9% in subjects with asthma and is higher than 20% in patients with severe asthma¹³⁷. In patients with concomitant asthma, chronic rhinosinusitis (CRS) and nasal polyposis (NP), the prevalence reaches 40%¹³⁸. Avoidance of NSAID does not resolve asthma or NP.

C There is a mechanism of non-IgE-mediated hypersensitivity with dysregulation of the arachidonic acid pathway by 5-LT-C4-synthase followed by overproduction of cysteinyl-leukotrienes (LT-C4, LT-D4, LT-E4) and a reduction of PG-E2¹³⁹. There is inflammation of the mucosa with activated eosinophils and



OA: occupational asthma; RADS: reactive airway dysfunction syndrome; SBPT: specific bronchial provocation test; PEF: peak expiratory flow. *Measurements performed after 15 days of a working period and 15 days of sick leave; sputum: analysis of the change in the number of eosinophils.

Figure 8.2. Diagnostic algorithm of occupational asthma.

C mast cells (in which the enzyme is overexpressed), basophils and abundant platelets. Blockage of COX-1 by NSAID contributes to formation and release of T lymphocytes, and to the release of preformed mediators (PGD₂, histamine and tryptase)¹⁴⁰. Mucous secretion, vascular permeability and bronchoconstriction are rapidly increased. IL-2 cells of innate immune response are also involved producing type 2 cytokines¹⁴¹.

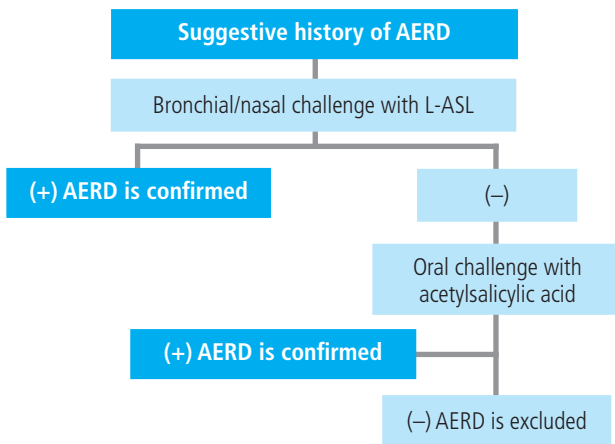
8.5.1. Diagnosis

C AERD should be suspected in any subject with asthma, with or without CRS and NP, and confirmed through a detailed clinical history showing a relationship between ingestion of a NSAID and the appearance of respiratory symptoms¹⁴². At the present time, sufficiently validated in vitro diagnostic tests are lacking. The use of E4 leukotriene concentration in urine

(uLTE4) together with clinical findings, slightly improves the diagnostic prediction¹⁴³. The diagnosis is confirmed by means of controlled exposure challenge with a NSAID, preferably ASA. The administration route may be oral, bronchial (inhaled) or nasal. These latter two routes are safer, although negative results do not exclude diagnosis; in this case, the result must be confirmed by using the oral route, which is the definitive diagnostic test to confirm or exclude AERD¹⁴⁴⁻¹⁴⁶.

8.5.2. Treatment

B The medical-surgical treatment of underlying diseases should be considered¹⁴⁷. Improvement in patients with moderate or severe asthma after adding LTRAs to the standard treatment¹⁴⁸ or after endoscopic sinus surgery has been reported¹⁴⁹. In addition, the administration of biologic drugs can be useful in the treatment of patients with AERD.



L-ASL: lysine-acetylsalicylate.

Figure 8.3. Diagnostic algorithm of aspirin-exacerbated respiratory disease (AERD) with asthma symptoms⁵⁸.

B Omalizumab significantly reduces the use of rescue medication in patients with severe allergic asthma and AERD¹⁵⁰ and urinary concentration of leukotriene E₄¹⁵¹. Also, some patients treated with omalizumab may finally tolerate NSAIDs, although this possibility should always be assessed by means of controlled exposure tests¹⁵². Biologic drugs targeting eosinophilic inflammation (mepolizumab¹⁵³, reslizumab¹⁵⁴ and benralizumab¹⁵⁵, as well as dupilumab¹⁵⁶) in patients with asthma and T2 high endotype, may be potentially beneficial in patients with AERD.

C COX-1 inhibitors should be avoided¹⁵⁷ (Table 8.3). Selective COX-2 inhibitors (celecoxib, etoricoxib, parecoxib)¹⁵⁹, or partially selective COX-2 inhibitors (nabumetone, meloxicam) are recommended, but in all cases after assessment of tolerability by oral controlled exposure testing. Doses of paracetamol higher than 500 mg should not be recommended without assessment of tolerability¹⁴².

B In selected cases (patients with uncontrolled severe asthma, recurrent nasal polyposis with several endoscopic sinus surgeries despite receiving appropriate maintenance treatment), ASA desensitization could be considered¹⁶¹. It has been shown that ASA desensitization can improve nasal symptoms, asthma control, and quality of life in patients with AERD^{162,163}. Moreover, these effects are maintained over time despite requiring lower doses of ASA¹⁶⁴, although the procedure is not free from adverse effects¹⁶⁵. The maintenance dose should not be withdrawn, as the therapeutic effect is lost and adverse reactions reappear when taking NSAID¹⁶⁶. However, the

cost-benefit of chronic treatment with high doses of NSAIDs should be evaluated. While this treatment is maintained, the patient can also tolerate other NSAIDs different from ASA¹⁶⁷.

Both challenge and desensitization tests are not routine techniques and should be performed by qualified personnel and with the adequate equipment to control reactions¹⁴⁷.

8.6. Inducible laryngeal obstruction

The ERS/ELS/ACCP working Group has defined inducible laryngeal obstruction (ILO), formerly known as vocal cord dysfunction, as a condition that causes sudden respiratory difficulty secondary to an obstruction of the airway at the level of the glottic or supraglottic larynx. These attacks are characterized by the presence of dyspnea, stridor of laryngeal origin and other symptoms such as cough, pharyngeal globe or dysphonia¹⁶⁸.

The term inducible refers to the mechanism by which the obstruction crisis is triggered, which can include physical exercise or the presence of external (odors, chemicals) or internal (gastroesophageal reflux) irritants.

Its presentation may suggest an asthma exacerbation episode, as well as other laryngeal diseases such as paralysis or dystonia. Its association with asthma is possible, which makes the diagnosis difficult. ILO is seen in about 25% of individuals with asthma, with a trend towards a higher frequency in severe asthma¹⁶⁹.

Clinical suspicion is essential for the diagnosis of ILO. There are questionnaires that can help to distinguish between asthma and ILO¹⁷⁰. Flattening of the inspiratory portion of the flow-volume loop is of little value in the diagnosis of ILO¹⁷¹, but may be suggestive. The confirmatory diagnosis is made by laryngeal videoendoscopy, which shows paradoxical adduction of the larynx during inspiration, or less frequently, during expiration. Usually requires a challenge test with exercise or inhalation of mannitol or methacholine¹⁷².

The use of dynamic computerized tomography (CT) to demonstrate paradoxical laryngeal closure during attacks has been recently proposed¹⁶⁹.

In the acute phase of ILO, respiratory techniques may be useful for controlling inspiratory flow. Mild sedatives (ketamine, benzodiazepines) have shown to be useful, as well as inhaling a mixture of helium and oxygen (Heliox) or non-invasive ventilation¹⁷³.

Long-term treatment aims to reduce the intensity and frequency of attacks. The first step includes logophoniatric rehabilitation focused on breathing techniques and relaxation of the laryngeal muscles.

Table 8.3. Classification of some NSAIDs based on their capacity of inhibition of cyclooxygenase isoforms¹⁵⁸

Potent COX-1 and COX-2 inhibitors	Acetylsalicylic acid, diclofenac, ibuprofen, metamizol
Weak COX-1 and COX-2 inhibitors	Paracetamol
COX-2 inhibitors	
– Partially selective (dose-dependent COX-1 inhibition)	Meloxicam, nabumetone
– Highly selective	Celecoxib, etoricoxib, parecoxib

Table 8.4. Possible pharmacological interactions between drugs used in the treatment of COVID-19 and medications for asthma (based on those proposed by the "Grupo Neumo SEFH 2020")¹⁹⁰

Group	Drug	Lopinavir/ritonavir (LPV/RTV)	Hydroxychloroquine	Azithromycin	Tocilizumab
Inhaled β ₂ -drenergic agonists	Formoterol	↑ QT ^{1,2,3} + ↑ [formoterol]	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↔
	Indacaterol	↑ QT ^{1,2,3} + ↑ [indacaterol]	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↔
	Olodaterol	↑ QT ^{1,2,3} + ↑ [olodaterol]	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↔
	Salbutamol	↑ QT ^{1,2}	↑ QT ^{1,2}	↑ QT ^{1,2}	↔
	Salmeterol	↑ QT ^{1,2,3} + ↑ [salmeterol]	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↔
	Terbutaline	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↔
	Vilanterol	↑ QT ^{1,2,3} + ↑ [vilanterol]	↑ QT ^{1,2,3}	↑ QT ^{1,2,3}	↔
Inhaled anticholinergics	Ipratropium	↔	↔	↔	↔
	Tiotropium	↑ [tiotropium]	↔	↔	↔
Inhaled glucocorticoids	Beclomethasone	↑ [beclomethasone] ⁴ + ↑ [LPV/RTV]	↑ AE ⁵	↔	↑ AE ⁵
	Budesonide	↑ [budesonide] + ↑ QT + ↓ [LPV/RTV]	↑ AE ⁵	↔	↑ AE ⁵
	Ciclesonide	↑ [ciclesonide]	↑ AE ⁵	↔	↑ AE ⁵
	Fluticasone	↑ [fluticasone propionate]	↑ AE ⁵	↔	↑ AE ⁵
	Mometasona	↑ [mometasona] + ↓ [LPV/RTV]	↑ AE ⁵	↔	↑ AE ⁵
Systemic glucocorticoids	Dexamethasone	↑ [dexamethasone] ⁶ + ↓ [LPV/RTV]	↑ AE ⁵	↔	↑ AE ⁵
	Hydrocortisone	↑ [hydrocortisone] ⁶	↑ AE ⁵	↔	↑ AE ⁵
	Methylprednisolone	↑ [methylprednisolone] ⁶ + ↓ [LPV/RTV]	↑ AE ⁵	↔	↑ AE ⁵
	Prednisone	↑ [prednisone] ⁶ + ↓ [LPV/RTV]	↑ AE ⁵	↔	↑ AE ⁵
Biologics	Benralizumab	↔	↑ AE ^{7,8}	↔	↑ AE ⁹
	Mepolizumab	↔	↑ AE ^{7,8}	↔	↑ AE ⁹
	Omalizumab	↔	↑ AE ^{7,8}	↔	↑ AE ⁹
	Reslizumab	↔	↑ AE ^{7,8}	↔	↑ AE ⁹
Other drugs	Montelukast	↑ [montelukast]	↔	↑ [montelukast]	↓ [montelukast]
	Theophylline	↑ vs. ↓ [theophylline]	↑ [theophylline]	↑ [theophylline]	↓ [theophylline]
	Azithromycin	↑ QT + ↑ [Azithromycin]	↑ QT	Not applicable	↓ [azithromycin]

↑ [x]: increases X drug concentration; ↓ [x]: decreases X drug concentration; ↔: no changes; ↑ AE: increase adverse effects, ↑ QT: QT prolongation.
 1. Variable severity according to the reference source. Possible greater severity of formoterol or salmeterol with LPV/RTV. 2. Precaution. Higher risk when higher dose of bronchodilator. 3. Assess preferential use of salbutamol in acute symptoms (probable less serious adverse effects and lower t1/2). 4. Beclomethasone has CYP3A4 hepatic metabolism. The administration of other inhaled glucocorticoids which are potent inhibitors of CYP3A4 increases significantly the exposure to the glucocorticoid agent. 5. Limited data. Potential increase of the risk or severity of adverse effects. 6. Precaution. Monitoring possible adverse effects. Risk of adrenal insufficiency on withdrawal. 7. Possible higher risk of adverse effects with hydroxychloroquine when using omalizumab. Due to the lack of data, this precaution is extended to the remaining biologics. 8. An in vitro study showed hydroxychloroquine may favor apoptosis of eosinophils. 9. Limited data. Potential increase of the risk or severity of adverse effects. Tocilizumab may have a higher risk or severity of adverse effects with any of the four biologics according to a consulted source.

NOTE: Remdesivir is not included in the list due to the lack of sufficient information.

Severity	Without relevant interaction	Mild	Moderate	Severe
Color code	Without relevant interaction	In general, no additional precaution is needed	Can require monitoring and assessing dose adjustment or withdrawal	Contraindicated or asses risk-benefit

B In refractory cases or in patients who are not candidates for logophoniatic rehabilitation, infiltration of thyroarytenoid muscles with botulinum toxin may be used¹⁷⁴.

C In selected cases of supraglottic ILO, transoral laser surgical techniques have been used successfully¹⁷⁵.

C There is no solid evidence for the indication of tracheostomy in these patients; however, single case reports have been published¹⁷⁶.

8.7. Asthma and the coronavirus disease 2019 (COVID-19)

A The new COVID-19 is caused by the virus SARS-CoV-2. This airborne infection has high transmissibility and within a few weeks from the outbreak in Wuhan (Hubei, central China) in December 19, it became a serious pandemic and rapidly spread throughout the globe¹⁷⁷.

C The disease has a broad clinical spectrum from mild forms with a few (or asymptomatic) manifestations, to influenza-like symptoms (fever, cough, myalgia, asthenia) and severe forms with bilateral pulmonary infiltrates and severe acute respiratory failure (5-20%) causing death (2.3-3.8%)¹⁷⁸⁻¹⁸³. The disease is less common in children, with usually milder clinical manifestations, although infants may be more vulnerable^{184,185}.

C The evidence available at the time of writing the present guideline (March 2020), based on case series studies from the epidemic in China, shows that suffering from asthma or allergy does not seem to be independently associated (in multivariate analyses after adjusting for confounding variables) to a higher probability of developing or dying from COVID-19^{183,186}.

C A study carried out in a reduced sample of cases showed that patients with allergic disorders infected by SARS-CoV-2 presented symptoms and a clinical course similar to those of non-allergic patients¹⁸⁷.

D Pulmonary function tests and induced sputum testing should be not be performed in order to prevent the spread of COVID-19 disease.

C In the treatment of patients with asthma infected by SARS-CoV-2, neither nebulizers to deliver aerosolized medications (but rather devices coupled to spacer or inhalation chambers) should be used, nor non-invasive single-arm ventilators without bacterial filter in the outlet port^{188,189}.

D There is no evidence of the deleterious effect of maintenance treatments for asthma, particularly IGC, on the prognosis of COVID-19. Therefore, patients should continue to take previously prescribed medications for their asthma. Systemic glucocorticoids should even be administered in case of exacerbations.

C However, although the information available is limited, there may be some pharmacological interactions between some drugs used for treating COVID-19 and medications for asthma (Table 8.4)^{190,191}. Very close clinical monitoring is recommended when administering these drugs and, in some cases, dose adjustments up or down may be considered (Table 8.4)¹⁹⁰.

D There is no evidence or clinical experience regarding safety of the use of biologics for the treatment of patients with uncontrolled severe asthma and SARS-CoV-2 infection. For this reason, and until having information available, it is recommended to individualize each case and to consider the convenience of spacing some doses based on the physician's clinical judgement.

RECOMMENDATIONS

- | | |
|--|----|
| 8.1. The diagnosis of ACOS will be established in patients with persistent chronic airflow limitation, current smokers or ex-smokers, with documented diagnosis of asthma, or in whom there is a very positive bronchodilation test or eosinophilia | R2 |
| 8.2. All patients with ACOS will be initially treated with a combination of IGC and LABA. | R2 |
| 8.3. In patients with ACOS treated with a combination of IGC and LABA who remain symptomatic or with exacerbations, a LAMA will be added. | R2 |
| 8.4. Drugs usually administered, LABA plus IGC, are recommended for the maintenance treatment of asthma in pregnant women. | R1 |
| 8.5. In the treatment of exacerbations in pregnant women the same algorithms than in non-pregnant women should be followed, ensuring adequate oxygenation (SaO ₂ > 95%) and monitoring of the fetus. | R1 |
| 8.6. In order to reduce the risk of maternal and fetal complications, pregnant women with asthma should be adequately controlled for preventing severe exacerbations. | R1 |
| 8.7. In adult-onset asthma or if there is a deterioration of previous asthma, it is recommended to exclude occupational asthma. | R2 |
| 8.8. The diagnosis of occupational asthma should be confirmed by objective tests, and in cases of allergic etiopathogenesis, by immunological tests. | R2 |
| 8.9. The specific challenge test is the reference diagnostic test for immunological occupational asthma. | R2 |
| 8.10. In the treatment of immunological occupational asthma, removal of exposure to the causative agent is recommended. | R2 |
| 8.11. In exercise-induced asthma, warm-up exercises before starting any sports activity are recommended. | R1 |
| 8.12. In exercise-induced asthma, SABA used occasionally are the most effective short-term treatment. | R1 |
| 8.13. In exercise-induced asthma, IGC reduce the frequency and intensity of symptoms, so that its use is advisable in patients usually treated with SABA: | R1 |
| 8.14. In exercise-induced asthma, LTRA is a therapeutic option less effective than IGC for preventing bronchoconstriction and is not useful to reverse an already established obstruction. | R1 |
| 8.15. It is recommended to evaluate the degree of control to determine the need for increasing a therapeutic step in known asthma patients with exercise-induced asthma. | R1 |
| 8.16. In patients with asthma and chronic rhinosinusitis with nasal polyps, it is advisable to exclude aspirin-exacerbated respiratory disease (AERD), particularly in case of severe asthma. | R1 |
| 8.17. Patients with AERD should avoid receiving treatment with any NSAID or COX-1 Inhibitors. | R1 |
| 8.18. In the analgesic or anti-inflammatory treatment of patients with AERD, an alternative medication of choice (opiates, systemic corticosteroids) should be used. After demonstrating their tolerability, paracetamol at doses lower than 500 mg and selective COX-2 inhibitors (celecoxib, etoricoxib, parecoxib) can be used. | R2 |
| 8.19. In patients with moderate or severe asthma and AERD, adding LTRA should be considered. | R2 |
| 8.20. Desensitization with acetylsalicylic acid may be useful in selected cases | R2 |
| 8.21. Biologic drugs can be used in patients with severe uncontrolled asthma and AERD, especially in the presence of concomitant nasal polyposis. | R2 |
| 8.22. The diagnosis of inducible laryngeal obstruction (ILO), formerly known as vocal cord dysfunction, should be established after clinical suspicion and confirmation by laryngeal videoendoscopy. | R1 |
| 8.23. Treatment of the acute phase of ILO should include respiratory logophoniatic reeducation (laryngeal muscle relaxation) techniques. | R2 |
| 8.24. In the treatment of the acute phase of ILO, sedatives may be useful, whereas type A botulinum toxin or surgery are reserved for refractory cases. | R2 |

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9. Organizational aspects. GEMA diffusion

9.1 Continuity of care

C Healthcare professionals should provide asthma patients with continuous care in order to ensure adequate prevention, diagnosis, control, treatment and follow-up¹, so that coherence of coordinated healthcare over time (continuity of care)² is perceived by the users.

C It is a priority to identify the current state of healthcare for patients with asthma³⁻⁸ to provide solutions in the three types of continuity of care: information (availability of data of previous episodes at different levels of care), relationship (between patients and providers) and management (coordination of actions)⁹.

D The multidisciplinary approach, the coordination between the levels of care, the patient's involvement and good management of social and healthcare resources are the essential elements to establish an integrated care network that provides quality care to patients with asthma¹⁰⁻¹². The involvement of nursing, as demonstrated by the Finish program, is essential to achieve good asthma control¹³. Also, the collaborative practice between physicians and community pharmacists has a positive impact on the patients' health, improving the knowledge they have of their disease, their quality of life, adherence to treatment and control of the disease¹⁴⁻¹⁶.

D Actions to be implemented for improving continuity of care in asthma are shown in Table 9.1.

D Referral to specialized care has shown to be effective for adequate management of patients with asthma in selected cases³⁴⁻³⁷.

Clinical practice guidelines should describe the criteria by which a patient with asthma should be referred to an asthma specialist, but an effective referral system requires good coordination between healthcare providers at the different levels of care³⁷.

D In Spain, the consensus document on referral criteria for asthma²¹, developed by professionals of Primary Care Medicine, Pneumology and Allergology, establishes the circuit to be followed by the primary care physician in the event of suspected asthma, in the evaluation of the control and follow-up of asthma patients, as well the referral of patients with asthma from primary care to specialized care in the following circumstances:

- To confirm the diagnosis of asthma when this is not possible with the resources available in the primary care setting.
- To study comorbidities when this cannot be completed in the primary care setting.
- Patients with severe asthma and uncontrolled asthma.
- Special circumstances (allergological study, occupational asthma, aspirin-exacerbated respiratory disease [AERD], exercise-induced asthma and asthma in pregnancy).
- To study other diseases for the differential diagnosis with asthma.

D For an adequate bidirectional communication between both levels of care and to improve continuity of care, the document proposes specific electronic referral templates and a minimum data set that should be included in specialized care reports of asthma patients²¹.

Table 9.1. Actions aimed to improve continuity of care in asthma

Healthcare professionals	Patients	Administration
GEMA implementation ^{7,37}	Education ^{18,19}	National Strategic Plan in Asthma (nonexistent)
Coordination between healthcare levels ^{20,21}	Adherence to treatment ^{22,23}	Integrated healthcare processes ²⁴
Consensuated criteria for asthma referral ²¹	Action plans ^{17,19}	Universal electronic medical history ²⁵
Asthma units ²⁶	Self-control ²⁷⁻²⁹	National registry of patients with severe asthma ^{30,31}
Importance of Nursing and Community Pharmacy ¹⁶ in the healthcare programs		Strategic plans adapted to local characteristics ¹⁰
Use of computerized tools for asthma control ^{32,33}		Provide necessary resources

9.2 Asthma unit

C

Prospective data from a UK registry showed that management of patients with difficult asthma in dedicated severe asthma centers resulted in improved health-related quality of life (HRQoL) and less use of healthcare resources³⁸. Some authors indicate that 1-day visit with extensive assessment in a severe asthma center is beneficial and sufficient for a large group of patients with uncontrolled asthma, reducing the need of high-cost special treatments³⁹.

C

En In 2015, the asthma area of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) addressed the task of establishing the necessary requirements for the provision of official accreditation standards of the different levels of care for asthma units already existing in hospitals of the Spanish National Healthcare System. Accreditation levels included basic units, specialized units, or specialized units of high complexity, with or without the distinctive of excellence, according to the fulfillment of a series of criteria⁴⁰. Also, recently the Spanish Society of Allergology and Clinical Immunology (SEAIC) has established criteria for accreditation of Severe Asthma Units (SAU) in the Allergology Services⁴¹.

C

These units coordinate the strategies aimed at improving the follow-up of patients with asthma, particularly those with severe asthma, interacting with other levels of care and with

all other specialists involved in care of asthma, as well as the use of complex diagnostic and therapeutic techniques that require rigorous knowledge and application. This strategy results in a personalized clinical approach that makes it possible to recognize individual needs and carry out special pharmacological or behavioral interventions (education, follow-up of adherence to treatment)⁴².

Given the complexity of asthma, different specialties (Otorrinolaryngology, Gastroenterology, Endocrinology, Psychology, Pharmacy, etc.) are involved to a greater or lesser extent in the care of asthma patients. It is indispensable to have available a specialized nurse who can perform all education tasks, including training and review of the inhalation technique, treatment adherence, self-management, written action plan and knowledge of the disease⁴³.

The distribution of tasks that should be assumed by the Asthma Unit is shown in Figure 9.1.

Development of an Asthma Unit in a healthcare areas is associated with important clinical benefits for the patient (increases considerably the percentage of patients with well-controlled asthma and reduces exacerbations substantially), with a highly favorable cost-effectiveness balance. In this respect, implementation of an Asthma Units is a beneficial option both from the perspective of efficiency for the healthcare system, and from the perspective of the patient, improving health outcomes and quality of care^{26,44}.

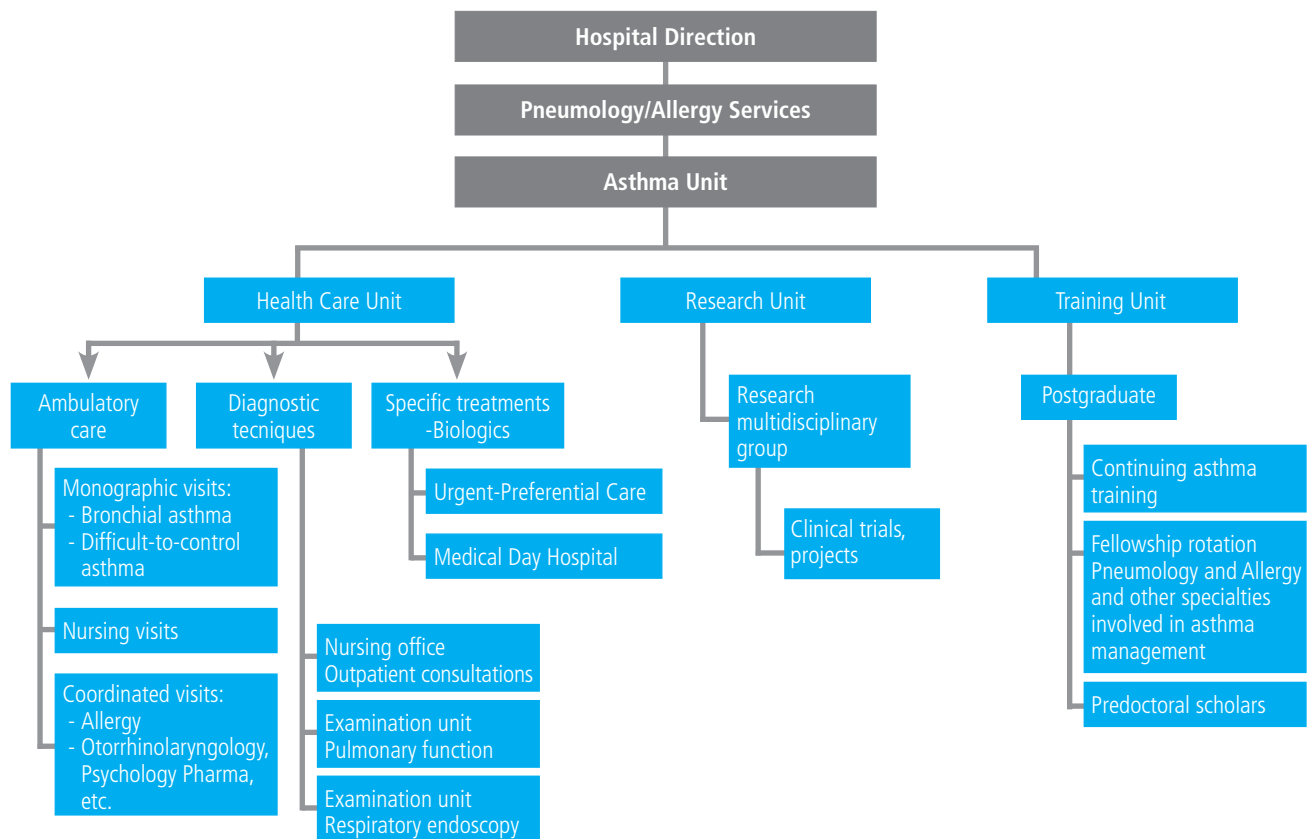


Figure 9.1. Working tasks and distribution of activities in a Specialized Asthma Unit in the hospital.

9.3 Implementation of GEMA

C For a clinical practice guideline (CPG) to be applied and adopted by healthcare professionals, three indispensable sequential key steps should be addressed: diffusion, implementation, and evaluation. The diffusion of a CPG (be means of medical and scientific publications, mailing, workshops, symposia and computer-based tools via Internet) will not be effective if is not accompanied by a proper implementation⁴⁵⁻⁴⁷.

C However, CPGs for asthma do not seem to meet this requirement. A study that aimed to evaluate the quality of these CPGs using the AGREE II instrument, found that none reached a score higher than 60% (minimum recommended level) in the evaluation of their respective implementation plans (domain 5: applicability or implementation)⁴⁸.

D For the correct application and implementation of a CPG, Graham proposes a series of structured and stepwise planning in order to transfer knowledge into action (*knowledge-to-*

action)⁴⁹. The diffusion and implementation plan of GEMA is based in part on such principles and includes the following 8 actions:

1. **Specific healthcare area.** For plan implementation a specific healthcare territorial area will be defined in order to assign a selected zone to a reference hospital and the various primary care teams assigned to the hospital.
2. **Analysis of needs and local deficiencies.** An audit will be performed in order to detect weak points and deficiencies in disease management within that territory.
3. **Executive Committee.** A multidisciplinary group of experts in asthma pertaining to the implementation area will be set up. The committee will comprise expert physicians (pneumologists, allergologists, primary care physicians and pediatricians) as well as influential representatives from the local nursing and pharmacy settings.
4. **Drawing up a functional document based on GEMA**⁵⁰. The Executive Committee will adapt evidences and

Table 9.2. Healthcare quality indicators for asthma proposed by the multidisciplinary expert group (Asmaforum II)

Grups of indicators	Indicator	Calculation
I. Diagnosis	1. Diagnostic confirmation by means of spirometry with bronchodilation test. Diagnostic confirmation of patients with asthma is established by spirometry and bronchodilation test as an objective measurement of functional involvement.	Number of patients with asthma undergoing spirometry x 100/ number of patients diagnosed with asthma.
	2. Sensitization study in allergic asthma. Patients with suspicion of allergic asthma should undergo a study of possible sensitization to different allergens.	Number of patients diagnosed with suggestive medical history of allergic asthma undergoing sensitization study to different allergens x 100/ number of patients diagnosed with asthma.
II. Non-pharmacological treatment	3. Smoking cessation. Smoking cessation is recommended in smokers with asthma.	Number of smoking patients with asthma and registered recommendation to quit smoking x 100/smoking patients with asthma.
	4. Education plan for patients with asthma. Patients with asthma should follow a basic education program (including knowledge of the disease and its treatment, written action plan and inhalation technique) as part of their management.	Number of patients with asthma with an asthma education program x 100/number of patients with asthma.
III. Pharmacological treatment	5. Treatment of choice in persistent asthma. The treatment of choice in persistent asthma includes the use of inhaled glucocorticoids (IGC) on a daily basis. In some cases, there may be justification for using leukotriene receptor antagonists as an alternative treatment.	Number of patients on control treatment due to persistent asthma receiving IGC x 100/number of patients on control treatment due to persistent asthma.
	6. Treatment of asthma in the pregnant woman. In the maintenance treatment of asthma in pregnancy, it is recommended to maintain usually administered medications (β_2 -adrenergic agonists and inhaled glucocorticoids).	Number of women with asthma who maintain their usual treatment (β_2 -adrenergic agonists and inhaled glucocorticosteroids) during pregnancy x 100/pregnant women with asthma on maintenance treatment.
IV. Follow-up	7. Periodic follow-up of patients. Need to establish a periodic follow-up of patients based on scheduled medical appointments, even in the absence of exacerbations.	Number of scheduled follow-up visits (non-unexpected) per patient per year x 100/number of patients with asthma on follow-up by year.
	8. Periodic registry of exacerbations. Specific assessment of exacerbations are periodically evaluated.	Number of patients with asthma in whom exacerbations have been evaluated and documented x 100/number of patients with asthma.

D

recommendations from GEMA^{5,0} to the local healthcare reality according to the resources assigned to the area, the type of professionals and their training level.

D

5. **Material resources.** A minimal amount of material resources should be available in the area in order to ensure the application of the guideline. Specific resources will include: spirometries (of good quality throughout the area) in all centers; electronic medical history (EMH) shared among healthcare levels; standardized asthma symptom questionnaires (ACT, ACQ); placebo-containing inhalation devices to be used in education programs to instruct patients in the inhalation technique; an accredited specialized hospital Asthma Unit, fitted with a complete technical equipment (bronchoprovocation tests, FE_{NO}, allergy skin tests, CT).

D

6. **Training plan.** An educational intervention on asthma will be performed among both medical and nursing professionals in the area.

D

7. **Professional motivation plan.** Administrative authorities will be engaged in promoting adherence of professionals involved in the “Implementation Plan” by setting up appropriate motivational interventions.

D

8. **Evaluation and follow-up plan.** To determine the impact of the “Implementation Plan” a set of indicators of health outcomes will be used in order to determine whether proposed objectives have been achieved, and to establish appropriate adjustments if objectives were not meet. Indicators of healthcare quality for asthma proposed by a multidisciplinary expert Group are shown in Table 9.2⁵⁰.

9.4 Telemedicine and asthma

Advances in knowledge and information technology make it possible to provide medical care for chronic conditions such as asthma. The terminology used to define healthcare based on the new technologies is continually evolving. It has been proposed to use the term *telehealthcare* as a general term, encompassing all the different forms of telemedicine-related healthcare. This term includes⁵¹:

- Tele-monitoring that involves storing and forwarding patients’ data.
- Tele-consultation is the use of technology allowing remote consultation between a patient and a clinician.
- Telemedicine that involved consultation among healthcare professionals.

Technology is based on 3 main strategies⁵²:

- Support for patients’ self-management through the use of automatic medication-taking reminders (tele-reminder) to improve adherence, educational games to improve knowledge or modify the attitude towards the disease, and tele-monitoring of clinical variables (PEF, use of medication, etc.).
- Remote consultation with a healthcare profesional.
- Computerized systems to aid decision-making for both physicians and patients.

The combined use of these strategies, which includes tele-case management or tele-consultation, improves the control of the disease and the quality of life of patients^{52,53}.

B

RECOMMENDATIONS

- 9.1. To achieve quality in continuing care of asthma, coordination of different healthcare levels, involvement of the patient and nursing as well as the rational use of resources is recommended. **R1**
- 9.2. It is suggested to promote the development of Asthma Units because they provide a better control of the disease, decreasing exacerbations and improving health-related quality of life of patients, with a favorable cost-effectiveness balance. **R2**
- 9.3. It is recommended to include a diffusion and implementation plan of this guideline to achieve the objectives of improving the level of training of healthcare professionals. **R2**
- 9.4. The GEMA implementation plan proposes: implementation of actions in a local specific health area; identification of local opinion leaders and engage them in this endeavor; adaptation of GEMA to the healthcare reality of the area; arrangement of an education plan for the professionals involved; and adjustment of actions according to whether objectives assessed by health outcomes have been attained. **R2**
- 9.5. The use of telemedicine or medical tele-assistance based on strategies of “tele-cases” or tele-consultation is proposed, given that it improves control of disease and quality of life of patients with asthma **R2**

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Tabla 3: Análisis combinado de la tasa de exacerbaciones clínicamente relevantes por recuento de eosinófilos en sangre al inicio del tratamiento en pacientes con asma eosinofílica refractaria grave.

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cél/μL		
n	123	66
Tasa de exacerbación por año	1,16	1,73
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,67 (0,46; 0,98)	---
150 a <300 cél/μL		
n	139	86
Tasa de exacerbación por año	1,01	1,41
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,72 (0,47; 1,10)	---
300 a <500 cél/μL		
n	109	76
Tasa de exacerbación por año	1,02	1,64
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,62 (0,41; 0,93)	---
≥500 cél/μL		
n	162	116
Tasa de exacerbación por año	0,67	2,49
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,27 (0,19; 0,37)	---

Estudio de reducción de corticoides orales MEA115575 (SIRIUS). El estudio MEA115575 evaluó el efecto de 100 mg de mepolizumab administrado por vía subcutánea en la reducción del tratamiento de mantenimiento con corticosteroides orales (OCS), manteniendo el control del asma en sujetos con asma eosinofílica refractaria grave. Los pacientes tenían un recuento de eosinófilos en sangre ≥ 150 cél/μL al inicio del estudio o un recuento de eosinófilos en sangre ≥ 300 cél/μL en los 12 meses anteriores a la visita basal. Durante el periodo de tratamiento, se administró a los pacientes mepolizumab o placebo una vez cada 4 semanas. Durante el estudio, los pacientes continuaron utilizando su tratamiento actual para el asma, con la excepción de la dosis de OCS, que se redujo cada 4 semanas durante la fase de reducción de dosis de OCS (semanas 4-20), siempre que se mantuviese el control del asma. En el estudio se reclutaron 135 pacientes. La media de edad fue de 50 años, el 55% eran mujeres, y el 48% había recibido tratamiento con corticosteroides orales durante al menos 5 años. La dosis media equivalente de prednisona al inicio del tratamiento fue de aproximadamente 13 mg al día. La variable principal fue el porcentaje de reducción en la dosis diaria de OCS (semanas 20-24), manteniendo el control del asma mediante la reducción de dosis por categorías definidas (ver Tabla 4). Las categorías predefinidas incluyeron rangos de porcentajes de reducción del 90-100%, hasta la no reducción de dosis de prednisona desde el final de la fase de optimización. La comparación entre mepolizumab y placebo fue estadísticamente significativa ($p=0,008$).

Tabla 4: Resultados de las variables primaria y secundarias en el estudio MEA115575.

	Población por intención de Tratar (ITT)	
	Mepolizumab 100 mg (Subcutáneo) N=69	Placebo N=66
Variable principal		
Porcentaje de reducción de OCS desde el inicio (semanas 20-24)		
90% - 100%	16 (23%)	7 (11%)
75% - <90%	12 (17%)	5 (8%)
50% - <75%	9 (13%)	10 (15%)
>0% - <50%	7 (10%)	7 (11%)
Sin reducción de OCS/falta de control del asma/ retirada del tratamiento	25 (36%)	37 (56%)
Odds ratio (IC 95%)	2,39 (1,25; 4,56)	
P-Valor	0,008	
Variables secundarias (semanas 20-24)		
Reducción en la dosis diaria de OCS hasta 0 mg/día	10 (14%)	5 (8%)
Odds ratio (IC 95%)	1,67 (0,49; 5,75)	
P-Valor	0,414	
Reducción en la dosis diaria de OCS hasta ≤ 5 mg/día	37 (54%)	21 (32%)
Odds ratio (IC 95%)	2,45 (1,12; 5,37)	
P-Valor	0,025	
Mediana % de reducción en la dosis diaria de OCS desde el inicio (IC 95%)	50,0 (20,0; 75,0)	0,0 (-20,0; 33,3)
Diferencia de la mediana (IC 95%)	-30,0 (-66,7; 0,0)	
P-Valor	0,007	

Estudios de extensión abiertos en asma eosinofílica refractaria grave MEA115666 (COLUMBA), MEA115661 (COSMOS) y 201312 (COSMEX). El perfil de eficacia a largo plazo de mepolizumab en pacientes con asma eosinofílica refractaria grave ($n = 998$) tratados durante una mediana de 2,8 años (rango de 4 semanas a 4,5 años) en los estudios de extensión abiertos MEA115666, MEA115661 y 201312 fue en general consistente con el de los 3 estudios controlados con placebo. **Población pediátrica.** *Asma eosinofílica refractaria grave.* En el estudio MEA115588 y en el estudio 200862 doble ciego controlado con placebo, participaron 34 adolescentes (de 12 a 17 años). De estos 34 sujetos: 12 recibieron placebo, 9 recibieron 75 mg de mepolizumab por vía intravenosa, y 13 recibieron 100 mg de mepolizumab por vía subcutánea. En un análisis combinado de estos estudios, se observó una reducción del 40% de las exacerbaciones clínicamente significativas en los adolescentes que recibieron tratamiento con mepolizumab comparado con placebo (razón de tasas 0,60; IC 95%: 0,17; 2,10). **5.2 Propiedades farmacocinéticas.** Tras la administración subcutánea a pacientes con asma, mepolizumab mostró una farmacocinética aproximadamente proporcional a la dosis, en el rango de dosis entre 12,5 mg y 250 mg. Tras una única administración subcutánea de 100 mg en sujetos sanos, la exposición sistémica a mepolizumab fue similar en ambas formulaciones. **Absorción.** Tras la administración subcutánea a sujetos sanos o a pacientes con asma, mepolizumab se absorbió lentamente, con una mediana de tiempo hasta alcanzar la concentración máxima en plasma (T_{max}) en un rango de entre 4 y 8 días. Tras una única administración subcutánea en el abdomen, el muslo o el brazo de sujetos sanos, la biodisponibilidad absoluta de mepolizumab fue del 64%, 71% y 75%, respectivamente. En pacientes con asma, la biodisponibilidad absoluta de mepolizumab administrado por vía subcutánea en el brazo varió desde el 74 hasta el 80%. Tras la administración subcutánea repetida cada 4 semanas, la acumulación es aproximadamente el doble que en el estado estacionario. **Distribución.** Tras la administración intravenosa de una sola dosis a pacientes con asma, el volumen medio de distribución de mepolizumab fue entre 55 y 85 mL/Kg. **Biotransformación.** Mepolizumab es un anticuerpo monoclonal humanizado IgG1 que se degrada por enzimas proteolíticas que se distribuyen ampliamente por el cuerpo y no se restringen sólo al tejido hepático. **Eliminación.** Tras la administración intravenosa de una sola dosis a pacientes con asma, el rango de la media del aclaramiento sistémico (CL) fue de 1,9 a 3,3 mL/día/Kg, con una semivida terminal media de aproximadamente 20 días. Tras la administración subcutánea de mepolizumab, el rango medio de semivida terminal ($t_{1/2}$) fue de entre 16 y 22 días. En el análisis farmacocinético poblacional, el aclaramiento sistémico de mepolizumab estimado fue de 3,1 mL/día/Kg. **Poblaciones especiales.** *Pacientes de edad avanzada (≥ 65 años de edad).* Los datos farmacocinéticos disponibles en pacientes de edad avanzada (≥ 65 años de edad) a lo largo de los estudios clínicos son limitados (N=90). Sin embargo, en el análisis farmacocinético poblacional, no hubo indicios de un efecto debido a la edad en la farmacocinética de mepolizumab en el rango de edad de 12-82 años. **Insuficiencia renal.** No se han realizado estudios formales para investigar el efecto de la insuficiencia renal en la farmacocinética de mepolizumab. De acuerdo al análisis farmacocinético poblacional, no se requiere ajuste de dosis en pacientes con valores de aclaramiento de creatinina entre 50-80 mL/min. Los datos disponibles de pacientes con valores de aclaramiento de creatinina < 50 mL/min son limitados. **Insuficiencia hepática.** No se han realizado estudios formales para investigar el efecto de la insuficiencia hepática en la farmacocinética de mepolizumab. Puesto que mepolizumab se degrada mediante enzimas proteolíticas ampliamente distribuidas, y no restringidas al tejido hepático, es poco probable que los cambios en la función hepática tengan algún efecto en la eliminación de mepolizumab. **Población Pediátrica.** Los datos farmacocinéticos disponibles en población pediátrica son limitados (59 sujetos con esofagitis eosinofílica, 55 sujetos con asma eosinofílica refractaria grave). La farmacocinética de mepolizumab intravenoso se evaluó mediante el análisis farmacocinético poblacional en un estudio pediátrico llevado a cabo con sujetos de edades comprendidas entre los 2-17 años de edad con esofagitis eosinofílica. La farmacocinética en población pediátrica fue ampliamente predecible de acuerdo a los datos en adultos, tras considerar el peso corporal. La farmacocinética de mepolizumab en adolescentes con asma eosinofílica refractaria grave se estudió en los estudios de fase 3, siendo consistente con la de los adultos (ver sección 4.2). Se investigó la farmacocinética pediátrica en un estudio abierto, no controlado de 12 semanas de duración, después de la administración por vía subcutánea en sujetos de 6 a 11 años con asma eosinofílica refractaria grave. Considerando el peso corporal y la biodisponibilidad, la farmacocinética pediátrica fue

ampliamente consistente con la de adultos y adolescentes. La biodisponibilidad subcutánea absoluta parece completa en comparación con la observada en adultos y adolescentes del 76%. La exposición después de la administración subcutánea de 40 mg (peso < 40 kg) o 100 mg (peso ≥ 40 kg) fue 1,32 y 1,97 veces la observada en adultos tratados con 100 mg. La investigación del régimen de dosificación subcutánea de 40 mg cada 4 semanas en niños de 6 a 11 años en un rango de peso amplio de 15-70 kg mediante un modelo farmacocinético y de simulación predijo que la exposición a este régimen de dosificación se mantendría en una media dentro del 38% de los adultos tratados con 100 mg. Este régimen de dosificación se considera aceptable debido al amplio índice terapéutico de mepolizumab. **5.3 Datos preclínicos sobre seguridad.** Puesto que mepolizumab es un anticuerpo monoclonal, no se han llevado a cabo estudios de genotoxicidad o carcinogenicidad. **Toxicología y/o farmacología en animales.** Los datos preclínicos de los estudios convencionales de seguridad farmacológica o de toxicidad a dosis repetidas en monos, no revelaron riesgos especiales para los seres humanos. La administración intravenosa y subcutánea en monos, se asoció a reducciones en el recuento de eosinófilos periféricos y pulmonares, sin hallazgos toxicológicos. Se piensa que los eosinófilos están asociados a respuestas del sistema inmune por infecciones parasitarias. Los estudios llevados a cabo en ratones tratados con anticuerpos anti-IL-5 o deficientes genéticamente en IL-5 o eosinófilos, no han mostrado disminución en la capacidad para eliminar infecciones parasitarias. Se desconoce la relevancia de estos hallazgos en humanos. **Fertilidad.** En un estudio de fertilidad y toxicidad general en la reproducción en ratones, realizado con un anticuerpo análogo inhibitorio de IL-5 en ratones, no se observó alteración en la fertilidad. Este estudio no incluyó partos o evaluación funcional de las camadas. **Embarazo.** Mepolizumab no tuvo efecto sobre el embarazo en monos o sobre el desarrollo embrionario/fetal y postnatal (incluida la función inmune) de sus crías. No se realizaron exámenes para determinar malformaciones internas o del esqueleto. Los datos obtenidos de monos cynomolgus demuestran que mepolizumab atraviesa la placenta. Durante varios meses después del parto, las concentraciones de mepolizumab fueron entre 1,2-2,4 veces mayores en niños que en las madres, y no afectaron el sistema inmune de los niños. **6. DATOS FARMACÉUTICOS. 6.1 Lista de excipientes.** Sacarosa. Fosfato de sodio dibásico heptahidratado. Ácido cítrico monohidratado. Polisorbato 80. Edetato disódico. Agua para preparaciones inyectables. **6.2 Incompatibilidades.** En ausencia de estudios de compatibilidad, este medicamento no debe mezclarse con otros medicamentos. **6.3 Período de validez.** 2 años. **6.4 Precauciones especiales de conservación.** Conservar en nevera (entre 2°C - 8°C). No congelar. Conservar en el embalaje original para protegerlo de la luz. Si es necesario, la pluma precargada y la jeringa precargada pueden ser retiradas de la nevera y conservadas en el envase sin abrir hasta un máximo de 7 días a temperatura ambiente (por debajo de 30°C) y protegidas de la luz. Se debe desechar el envase si se deja fuera de la nevera más de 7 días. La pluma precargada o la jeringa precargada se deben administrar en las siguientes 8 horas tras la apertura del envase. Se debe desechar el envase si no se administra en las siguientes 8 horas. **6.5 Naturaleza y contenido del envase.** Nucala 100 mg solución para inyección en pluma precargada. Solución de 1 mL en una jeringa de vidrio tipo 1 con una aguja fija (acero inoxidable) en una pluma precargada. Tamaños de envases: 1 pluma precargada. Envase múltiple conteniendo 3 plumas precargadas (3 envases de 1 pluma precargada). Puede que solamente estén comercializados algunos tamaños de envases. Nucala 100 mg solución para inyección en jeringa precargada. Solución de 1 mL en una jeringa de vidrio tipo 1 con una aguja fija (acero inoxidable) y un protector de aguja de seguridad pasiva. Tamaños de envases: 1 jeringa precargada. Envase múltiple conteniendo 3 jeringas precargadas (3 envases de 1 jeringa precargada). Puede que solamente estén comercializados algunos tamaños de envases. **6.6 Precauciones especiales de eliminación y otras manipulaciones.** Antes de la administración, la solución debe ser inspeccionada visualmente. El líquido debe ser de transparente a opalescente, de incoloro a amarillo pálido a marrón pálido. Si la solución está turbia, descolorida o contiene partículas, no se debe usar la solución. Después de retirar la pluma precargada o jeringa precargada de la nevera, deje que la pluma o jeringa alcance la temperatura ambiente durante al menos 30 minutos antes de inyectar Nucala. Al final del prospecto se proporcionan las instrucciones completas para la administración subcutánea de Nucala en una pluma precargada o jeringa precargada. **Eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/15/1043/003 1 pluma precargada; EU/1/15/1043/004 3 (3 x 1) plumas precargadas (envase múltiple); EU/1/15/1043/005 1 jeringa precargada; EU/1/15/1043/006 3 (3 x 1) jeringas precargadas (envase múltiple). **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 02 diciembre 2015. Fecha de la última renovación: 10 agosto 2020. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 08/2020. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos <http://www.ema.europa.eu>. **11. CONDICIONES DE PRESCRIPCIÓN Y DISPENSACIÓN.** Medicamento sujeto a prescripción médica. Diagnóstico hospitalario sin cupón precinto. Reembolsable por el Sistema Nacional de Salud. **12. PRESENTACIONES Y PRECIO.** Nucala 100 mg solución para inyección en pluma precargada. Nucala 100 mg solución para inyección en jeringa precargada. PVL: 1.086€; PVP 1.141,91 €; PVP IVA 1.187,59€. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos <http://www.ema.europa.eu>.

Tabla 3: Análisis combinado de la tasa de exacerbaciones clínicamente relevantes por recuento de eosinófilos en sangre al inicio del tratamiento en pacientes con asma eosinofílica refractaria grave

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cél/µL		
n	123	66
Tasa de exacerbación por año	1,16	1,73
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,67 (0,46; 0,98)	---
150 a <300 cél/µL		
n	139	86
Tasa de exacerbación por año	1,01	1,41
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,72 (0,47; 1,10)	---
300 a <500 cél/µL		
n	109	76
Tasa de exacerbación por año	1,02	1,64
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,62 (0,41; 0,93)	---
>500 cél/µL		
n	162	116
Tasa de exacerbación por año	0,67	2,49
Mepolizumab vs. placebo		
Razón de tasas (IC 95%)	0,27 (0,19; 0,37)	---

Estudio de reducción de corticoides orales MEA115575 (SRIUS). El estudio MEA115575 evaluó el efecto de 100 mg de mepolizumab administrado por vía subcutánea en la reducción del tratamiento de mantenimiento con corticosteroides orales (OCS), manteniendo el control del asma en sujetos con asma eosinofílica refractaria grave. Los pacientes tenían un recuento de eosinófilos en sangre ≥ 150 cél/µL al inicio del estudio o un recuento de eosinófilos en sangre ≥ 300 cél/µL en los 12 meses anteriores a la visita basal. Durante el periodo de tratamiento, se administró a los pacientes mepolizumab o placebo una vez cada 4 semanas. Durante el estudio, los pacientes continuaron utilizando su tratamiento actual para el asma, con la excepción de la dosis de OCS, que se redujo cada 4 semanas durante la fase de reducción de dosis de OCS (semanas 4-20), siempre que se mantuviese el control del asma. En el estudio se reclutaron 135 pacientes. La media de edad fue de 50 años, el 55% eran mujeres, y el 48% había recibido tratamiento con corticosteroides orales durante al menos 5 años. La dosis media equivalente de prednisona al inicio del tratamiento fue de aproximadamente 13 mg al día. La variable principal fue el porcentaje de reducción en la dosis diaria de OCS (semanas 20-24), manteniendo el control del asma mediante la reducción de dosis por categorías definidas (ver Tabla 4). Las categorías predefinidas incluyeron rangos de porcentajes de reducción del 90-100%, hasta la no reducción de dosis de prednisona desde el final de la fase de optimización. La comparación entre mepolizumab y placebo fue estadísticamente significativa ($p=0,008$).

Tabla 4: Resultados de las variables primaria y secundarias en el estudio MEA115575

Variable principal	Población por Intención de Tratar (ITT)	
	Mepolizumab 100 mg (Subcutáneo) N=69	Placebo N=66
Porcentaje de reducción de OCS desde el inicio (semanas 20-24)		
90% - 100%	16 (23%)	7 (11%)
75% - <90%	12 (17%)	5 (8%)
50% - <75%	9 (13%)	10 (15%)
>0% - <50%	7 (10%)	7 (11%)
• Sin reducción de OCS/falta de control del asma/ retirada del tratamiento	25 (36%)	37 (56%)
Odds ratio (IC 95%)	2,39 (1,25; 4,56)	
P-Valor	0,008	
Variables secundarias (semanas 20-24)		
Reducción en la dosis diaria de OCS hasta 0 mg/día	10 (14%)	5 (8%)
Odds ratio (IC 95%)	1,67 (0,49; 5,75)	
P-Valor	0,414	
Reducción en la dosis diaria de OCS hasta ≤ 5 mg/día	37 (54%)	21 (32%)
Odds ratio (IC 95%)	2,45 (1,12; 5,37)	
P-Valor	0,025	
Mediana % de reducción en la dosis diaria de OCS desde el inicio (IC 95%)	50,0 (20,0; 75,0)	0,0 (-20,0; 33,3)
Diferencia de la mediana (IC 95%)	-30,0 (-66,7; 0,0)	
P-Valor	0,007	

Estudios de extensión abiertos en asma eosinofílica refractaria grave MEA115666 (COLUMBA), MEA115661 (COSMOS) y 201312 (COSMEX). El perfil de eficacia a largo plazo de mepolizumab en pacientes con asma eosinofílica refractaria grave ($n = 998$) tratados durante una mediana de 2,8 años (rango de 4 semanas a 4,5 años) en los estudios de extensión abiertos MEA115666, MEA115661 y 201312 fue en general consistente con el de los 3 estudios controlados con placebo. **Población pediátrica.** Asma eosinofílica refractaria grave. En el estudio MEA115588 y en el estudio 200862 doble ciego controlado con placebo, participaron 34 adolescentes (de 12 a 17 años). De estos 34 sujetos: 12 recibieron placebo, 9 recibieron 75 mg de mepolizumab por vía intravenosa, y 13 recibieron 100 mg de mepolizumab por vía subcutánea. En un análisis combinado de estos estudios, se observó una reducción del 40% de las exacerbaciones clínicamente significativas en los adolescentes que recibieron tratamiento con mepolizumab comparado con placebo (razón de tasas 0,60; IC 95%: 0,17; 2,10). **5.2 Propiedades farmacocinéticas.** Tras la administración subcutánea a pacientes con asma, mepolizumab mostró una farmacocinética aproximadamente proporcional a la dosis, en el rango de dosis entre 12,5 mg y 250 mg. **Absorción.** Tras la administración subcutánea a sujetos sanos o a pacientes con asma, mepolizumab se absorbió lentamente, con una mediana de tiempo hasta alcanzar la concentración máxima en plasma (T_{max}) en un rango de entre 4 y 8 días. Tras una única administración subcutánea en el abdomen, el muslo o el brazo de sujetos sanos, la biodisponibilidad absoluta de mepolizumab fue del 64%, 71% y 75%, respectivamente. En pacientes con asma, la biodisponibilidad absoluta de mepolizumab administrado por vía subcutánea en el brazo varió desde el 74 hasta el 80%. Tras la administración subcutánea repetida cada 4 semanas, la acumulación es aproximadamente el doble que en el estado estacionario. **Distribución.** Tras la administración intravenosa de una sola dosis a pacientes con asma, el volumen medio de distribución de mepolizumab fue entre 55 y 85 mL/Kg. **Biotransformación.** Mepolizumab es un anticuerpo monoclonal humanizado IgG1 que se degrada por enzimas proteolíticas que se distribuyen ampliamente por el cuerpo y no se restringen sólo al tejido hepático. **Eliminación.** Tras la administración intravenosa de una sola dosis a pacientes con asma, el rango de la media del aclaramiento sistémico (CL) fue de 1,9 a 3,3 mL/día/Kg, con una semivida terminal media ($t_{1/2}$) de aproximadamente 20 días. Tras la administración subcutánea de mepolizumab, el rango medio de semivida terminal ($t_{1/2}$) fue de entre 16 y 22 días. En el análisis farmacocinético poblacional, el aclaramiento sistémico de mepolizumab estimado fue de 3,1 mL/día/Kg. **Poblaciones especiales.** *Pacientes de edad avanzada (≥ 65 años de edad).* Los datos farmacocinéticos disponibles en pacientes de edad avanzada (≥ 65 años de edad) a lo largo de los estudios clínicos son limitados ($N=90$). Sin embargo, en el análisis farmacocinético poblacional, no hubo indicios de un efecto debido a la edad en la farmacocinética de mepolizumab en el rango de edad de 12-82 años. *Insuficiencia renal.* No se han realizado estudios formales para investigar el efecto de la insuficiencia renal en la farmacocinética de mepolizumab. De acuerdo al análisis farmacocinético poblacional, no se requiere ajuste de dosis en pacientes con valores de aclaramiento de creatinina entre 50-80 mL/min. Los datos disponibles de pacientes con valores de aclaramiento de creatinina < 50 mL/min son limitados. *Insuficiencia hepática.* No se han realizado estudios formales para investigar el efecto de la insuficiencia hepática en la farmacocinética de mepolizumab. Puesto que mepolizumab se degrada mediante enzimas proteolíticas ampliamente distribuidas, y no restringidas al tejido hepático, es poco probable que los cambios en la función hepática tengan algún efecto en la eliminación de mepolizumab. **Población Pediátrica.** Los datos farmacocinéticos disponibles en población pediátrica son limitados (59 sujetos con esofagitis eosinofílica, 55 sujetos con asma eosinofílica refractaria grave). La farmacocinética de mepolizumab intravenoso se evaluó mediante el análisis farmacocinético poblacional en un estudio pediátrico llevado a cabo con sujetos de edades comprendidas entre los 2-17 años de edad con esofagitis eosinofílica. La farmacocinética en población pediátrica fue ampliamente predecible de acuerdo a los datos en adultos, tras considerar el peso corporal. La farmacocinética de mepolizumab en adolescentes con asma eosinofílica refractaria grave se estudió en los estudios de fase 3, siendo consistente con la de los adultos (ver sección 4.2). Se investigó la farmacocinética pediátrica en un estudio abierto, no controlado de 12 semanas de duración, después de la administración por vía subcutánea en sujetos de 6 a 11 años con asma eosinofílica refractaria grave. Considerando el peso corporal y la biodisponibilidad, la farmacocinética pediátrica fue ampliamente consistente con la de adultos y adolescentes. La biodisponibilidad subcutánea absoluta parece completa en comparación con la observada en adultos y adolescentes del 76%. La exposición después de la administración subcutánea de 40 mg (peso < 40 kg) o 100 mg (peso ≥ 40 kg) fue 1,32 y 1,97 veces la observada en adultos tratados con 100 mg. La investigación del régimen de dosificación subcutánea de 40 mg cada 4 semanas en niños de 6 a 11 años en un

rango de peso amplio de 15-70 kg mediante un modelo farmacocinético y de simulación predijo que la exposición a este régimen de dosificación se mantendría en una media dentro del 38% de los adultos tratados con 100 mg. Este régimen de dosificación se considera aceptable debido al amplio índice terapéutico de mepolizumab. **5.3 Datos preclínicos sobre seguridad.** Puesto que mepolizumab es un anticuerpo monoclonal, no se han llevado a cabo estudios de genotoxicidad o carcinogenicidad. **Toxicología y/o farmacología en animales.** Los datos preclínicos de los estudios convencionales de seguridad farmacológica o de toxicidad a dosis repetidas en monos, no revelaron riesgos especiales para los seres humanos. La administración intravenosa y subcutánea en monos, se asoció a reducciones en el recuento de eosinófilos periféricos y pulmonares, sin hallazgos toxicológicos. Se piensa que los eosinófilos están asociados a respuestas del sistema inmune por infecciones parasitarias. Los estudios llevados a cabo en ratones tratados con anticuerpos anti-IL-5 o deficientes genéticamente en IL-5 o eosinófilos, no han mostrado disminución en la capacidad para eliminar infecciones parasitarias. Se desconoce la relevancia de estos hallazgos en humanos. **Fertilidad.** En un estudio de fertilidad y toxicidad general en la reproducción en ratones, realizado con un anticuerpo análogo inhibidor de IL-5 en ratones, no se observó alteración en la fertilidad. Este estudio incluyó partos o evaluación funcional de las camadas. **Embarazo.** Mepolizumab no tuvo efecto sobre el embarazo en monos o sobre el desarrollo embrionario/fetal y postnatal (incluida la función inmune) de sus crías. No se realizaron exámenes para determinar malformaciones internas o del esqueleto. Los datos obtenidos de monos cynomolgus demuestran que mepolizumab atraviesa la placenta. Durante varios meses después del parto, las concentraciones de mepolizumab fueron entre 1,2-2,4 veces mayores en niños que en las madres, y no afectaron el sistema inmune de los niños.

6. DATOS FARMACÉUTICOS. 6.1 Lista de excipientes. Sacarosa. Fosfato de sodio dibásico heptahidratado. Polisorbato 80. **6.2 Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3 Periodo de validez.** 4 años. **Tras la reconstitución.** Se ha demostrado que la estabilidad química y física del medicamento reconstituido es de 8 horas cuando se almacena por debajo de 30°C. Desde un punto de vista microbiológico, y a menos que el método de reconstitución excluya el riesgo de contaminación microbiana, el medicamento se debe utilizar inmediatamente. Si no se utiliza inmediatamente, los tiempos y las condiciones de almacenamiento del producto reconstituido serán responsabilidad del usuario. **6.4 Precauciones especiales de conservación.** Conservar por debajo de 25°C. No congelar. Conservar el vial en el embalaje original para protegerlo de la luz. Para las condiciones de conservación tras la reconstitución del medicamento, ver sección 6.3 **6.5 Naturaleza y contenido del envase.** Vial de vidrio tipo I transparente, incoloro, de 10 mL, con tapón de goma de bromobutilo, una lámina de sellado de aluminio gris y una tapa de plástico que contiene 100 mg de polvo para solución inyectable. Tamaños de envases: 1 vial. Envase múltiple conteniendo 3 viales (3 envases de 1 vial). Puede que solamente estén comercializados algunos tamaños de envases. **6.6 Precauciones especiales de eliminación y otras manipulaciones.** La reconstitución se debe llevar a cabo bajo condiciones asépticas. **Instrucciones para la reconstitución de cada vial.** **1. Reconstituir el contenido del vial con 1,2 mL de agua estéril para preparaciones inyectables** utilizando, preferiblemente, una jeringa de 2 a 3 mL de capacidad y una aguja de calibre 21. La dirección del flujo del agua estéril debe ser vertical, para que caiga en el centro del liofilizado. Dejar que el vial repose a temperatura ambiente durante la reconstitución, girándolo suavemente mediante movimientos circulares durante 10 segundos, a intervalos de 15 segundos, hasta que el polvo se haya disuelto. **Nota: Durante el proceso, no se debe agitar la solución reconstituida, ya que esto podría ocasionar la formación de espuma o la precipitación. Normalmente, la reconstitución se completa dentro de los 5 minutos posteriores a la adición del agua estéril, pero podría requerirse más tiempo.** **2. Si** para la reconstitución de Nucala se utiliza un dispositivo de reconstitución mecánico (agitador orbital), la reconstitución puede llevarse a cabo mediante agitación orbital a 450 rpm durante no más de 10 minutos. Como alternativa, es aceptable que la agitación orbital se realice a 1000 rpm durante no más de 5 minutos. **3.** Tras la reconstitución, y antes de utilizar Nucala, se debe realizar una inspección visual para determinar la presencia de partículas y la transparencia. La solución debe ser de transparente a opalescente, y de incolora a amarillo o marrón pálido, libre de partículas visibles. Es de esperar y es aceptable que aparezcan pequeñas burbujas de aire. Si en la solución sigue habiendo partículas o si la solución es turbia o lechosa, no se debe usar. **4.** Si la solución reconstituida no se utiliza inmediatamente se debe: • Proteger de la luz solar. • Conservar por debajo de 30°C, no congelar. • Desecharse si no se ha utilizado en las 8 horas siguientes a la reconstitución. **Instrucciones de administración de una dosis de 100 mg.** **1.** Para la administración por vía subcutánea se utilizará preferiblemente una jeringa de polipropileno de 1 mL equipada con una aguja desechable de calibre 21 a calibre 27 x 0,5 pulgadas (13 mm). **2.** Antes de la administración, extraer 1 mL de la solución reconstituida de Nucala. No agitar la solución reconstituida durante este proceso, ya que esto podría ocasionar la formación de espuma o la precipitación. **3.** Administrar la inyección de 1 mL (equivalente a 100 mg de mepolizumab) por vía subcutánea en la parte superior del brazo, en el muslo o en el abdomen. **Instrucciones de administración de una dosis de 40 mg.** **1.** Para la administración por vía subcutánea se utilizará preferiblemente una jeringa de polipropileno de 1 mL equipada con una aguja desechable de calibre 21 a calibre 27 x 0,5 pulgadas (13 mm). **2.** Antes de la administración, extraer 0,4 mL de la solución reconstituida de Nucala. No agitar la solución reconstituida durante este proceso, ya que esto podría ocasionar la formación de espuma o la precipitación. Deseche la solución restante. **3.** Administrar la inyección de 0,4 mL (equivalente a 40 mg de mepolizumab) por vía subcutánea en la parte superior del brazo, en el muslo o en el abdomen. **Eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/15/1043/001; EU/1/15/1043/002. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 02 diciembre 2015. Fecha de la última renovación: 10 agosto 2020. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 08/2020. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos <http://www.ema.europa.eu>. **11. CONDICIONES DE PRESCRIPCIÓN Y DISPENSACIÓN.** Medicamento sujeto a prescripción médica. Diagnóstico hospitalario sin cupón pre-cinto. Reembolsable por el Sistema Nacional de Salud. **11. PRESENTACIONES Y PRECIO.** Nucala 100 mg polvo para solución inyectable. PVL: 1.086€; PVP: 1.141,91€; PVP IVA 1.187,59€. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos <http://www.ema.europa.eu>.

Nucala mejora el control de los pacientes con asma grave eosinofílica, recuperando el equilibrio.*1-6



NUCALA

mepolizumab



Polverio liofilizado*1
Pluma precargada*2

La libertad de elegir

Se trata de una paciente ficticia solo con fines ilustrativos.

*Nucala está indicado como tratamiento adicional en pacientes adultos, adolescentes y niños a partir de 6 años con asma eosinofílica refractaria grave.*1,2

La dosis recomendada de Nucala es 100 mg SC, una vez cada 4 semanas en adultos y adolescentes a partir de 12 años, disponible en pluma precargada, jeringa precargada o polvo liofilizado. La dosis autorizada en niños de 6 a 11 años es de 40 mg SC, una vez cada 4 semanas y se encuentra disponible en polvo liofilizado.*2

Referencias:

1. Ficha técnica Nucala polvo 08/2020, GSK
2. Ficha técnica Nucala líquido 08/2020, GSK
3. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017 May;5(5):390-400.
4. Taillé C, Chanez P, Devouassoux G, et al. Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme. *Eur Respir J.* 2020;55(6):1902345.
5. Harrison T, Canonica GW, Chupp G, et al. Real-world mepolizumab in the prospective severe asthma REALITI-A study: initial analysis. *Eur Respir J.* 2020 Oct 15;56(4):2000151
6. Hartl S, Breyer MK, Burghuber OC, et al. Blood eosinophil count in the general population: typical values and potential confounders. *Eur Respir J.* 2020 May 14;55(5):1901874

Para notificar una sospecha de reacción adversa contacte con GSK a través de <https://es.gsk.com/es-es/contacto/> o con el Sistema Español de Farmacovigilancia a través de www.notificaram.es



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