8. Special circumstances

8.1 ASTHMA-COPD overlap syndrome (ACOS)

8.1.1. Concept and definition

C Asthma and chronic obstructive pulmonary disease (COPD) are two different chronic respiratory diseases[1], although it is common to find the characteristics of both diseases in a single patient[2].

C Asthma and smoking[3,4], low pulmonary function in childhood[5], exposure to irritants[6] or environmental contamination[7] can contribute to the development of associated COPD in adulthood.

D 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 (clínical, biological or functional)[8].

Different definitions of ACOS have been proposed[9-16], 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].

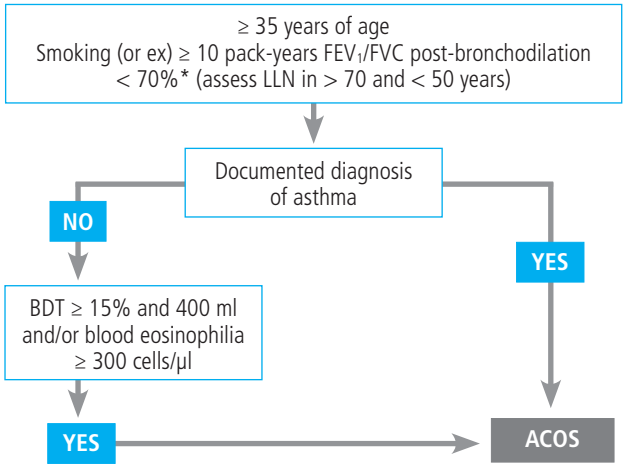
C The prevalence of ACOS varies according to the source considered and criteria used for definition[19-21], with estimates between 1.6% and 4.5% in the general population, and between 15% and 25% in patients with obstructive respiratory disease[11,22-36].

C 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].

C The mortality of chronic respiratory disease is higher in patients with ACOS or COPD than in those without chronic airway obstruction[44-46].

8.1.2. Diagnostic confirmation

D 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 ß2-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 patients meets criteria for COPD (> 35 years, smoker > 10 pack-years, post-bronchodilation forced expiratory volumen in one second/forced vital capacity [FEV_1/FVC] < 70% [assessing the lower limit of normal, particularly at extreme ages])[13,48]. D
- 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 (FEV_1 post-bronchodilation ≥ 15% y 400 ml) or blood eosinophilia (≥ 300 eosinophils/µl), confirms the diagnosis of ACOS.

8.1.3. Treatment

C D 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 D ACOS according to its treatable features[52,53] that should be agreed upon.

Therapeutic recommendations in patients with ACOS

A – If the diagnostic evaluation only confirms asthma, it will be treated according to GEMA guidelines[47], 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 guidelines[48], avoiding monotherapy with IGC.

D – If the evaluation confirms ACOS: start with a combination of IGC at low or moderated doses according to symptoms[54], associated with LABA[55-59].

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 omalizumab[62-67] or anti-leukin-5 (anti-IL-5) (benralizumab[68,69] or mepolizumab[67,70,71]) in ACOS remains unclear[72].

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 women[73]. Up to 18% of asthmatic pregnant women present worsening of her asthma during gestation, increasing to 50% in case of severe asthma[73-75]. 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 disease[76].

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 diabetes[77]. Prevention of exacerbation is essential for reducing the risk of complications[78].

B Poor adherence to treatment and upper respiratory tract infections are the most common trigger factors for exacerbations[73].

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].

A The appropriate use of IGC, LABA, montelukast and theophylline is not associated with an increase of fetal abnormalities[82].

B IGC prevent asthma exacerbations during pregnancy[83].

A 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 teratogeneis (3.8%) as compared with the general population (3.5%)[86].

C 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 gastroschisis[87], the use of these compounds is permitted[88].

B Oral glucocorticoids (OGC) cause teratogenic effects, and their use should be restricted to asthma exacerbations and severe asthma[89].

C 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].

C The same algorithms for the treatment of exacerbations in non-pregnant women with asthma should be followed, ensuring in addition an adequate fetal oxygenation (SaO_2 > 95%) and monitoring[73,76].

B 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 telehealth[92-95].

C

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 6 adults with asthma[98,99].

8.3.1. Types of occupational asthma

C – Immunological OA: induced by sensitization to specific agents which are present in the workplace, through a mechanism associated with a specific immunological response[96]. 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].

C – Non-immunological: induced by irritants in the absence of sensitization[102]. 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 levels[104].

8.3.2 Risk factors

C

– 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 agents[107].
– Rhrinitis: 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 mechanism[109].

8.3.3 Diagnosis

C

The diagnosis of asthma and its relationship with the patient's workplace should be confirmed[102]. 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 test[116].

8.3.4. Treatment

B

Patients with OA caused by sensitizing agents should be removed from the source of exposure[112]. 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 exposure[96].

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 exercise[117].

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 hyperventilation[122].

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 stress[123], 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 onset[126].

A Self-reported symptoms are unreliable for diagnosis. The diagnostic test is the finding of a FEV_1 decrease over 10% measured 30 minutes after cessation of exercise and compared with the previous FEV_1 values[127].

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 fibrosis[128].

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 exercise[118] 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 exacerbations[131].

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 obstruction[132].

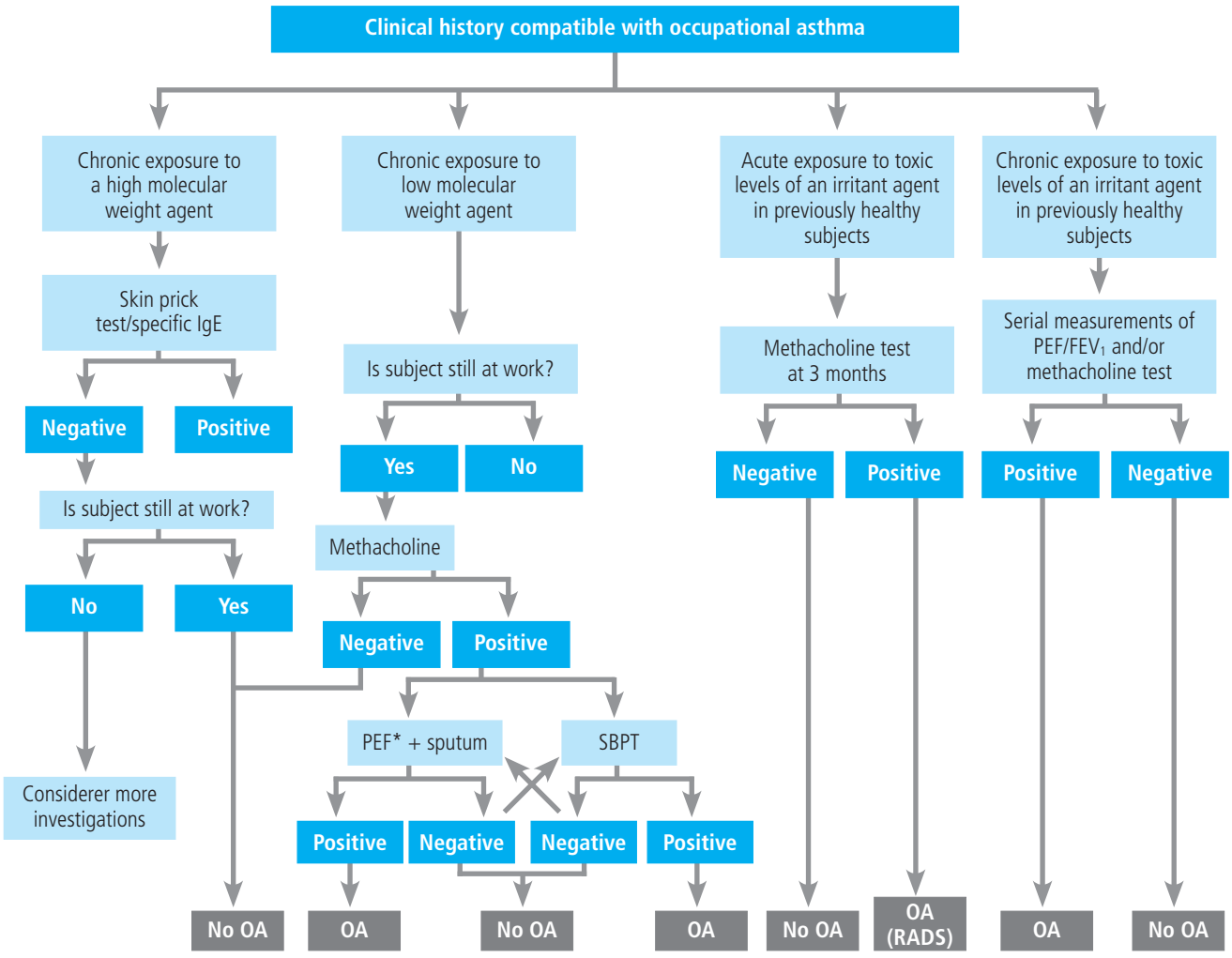
A Increasingly intense warm-up exercise before starting any sports activity may attenuate the intensity of bronchoconstriction[133,134].

C Reduction of dietary sodium intake and supplementation with ascorbic acid or fish oil may diminish the severity of exacerbations[135].

8.5. Aspirin-exacerbated respiratory disease (AERD)

C AERD or respiratoey 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 NSAIDs[115]. 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 astma and is higher than 20% in patients with severe asthma[137]. In patients with concomitant asthma, chronic rhinosinusitis (CRS) and nasal polyposis (NP), the prevalence reaches 40%[158]. 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-E2[139]. 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.

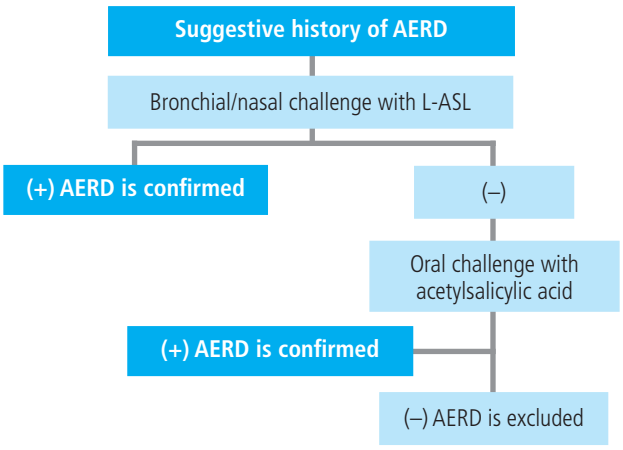
mast cells (in which the enzyme is overexpressed), basophils and abundant platelets Blockage of COX-1 by NSAID contributes to formation and release of T lymphocytes, and to the release of preformed mediators (PGD_2, histamine and tryptase[140]. Mucous secretion, vascular permeability and bronchoconstriction are rapidly increased. IL-C2 cells of innate immune response are also involved producing type T2 cytokines[141].

8.5.1. Diagnosis

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 symptoms[142]. 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 prediction[143]. 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 AERD[144-146].

8.5.2. Treatment

The medical-surgical treatment of underlying diseases should be considered[147]. Improvement in patients with moderate or severe asthma after adding LTRAs to the standard treatment[148] or after endoscopic sinus surgery has been reported[149]. 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 symptoms[58].

B Omalizumab significant reduces the use of rescue medication in patients with severe allergic asthma and AERD[150] and urinary concentration of leukotriene E_4[151]. Also, some patients treated with omalizumab may finally tolerate NSAIDs, although this possibility should always by assessed by means of controlled exposure tests[152]. Biologic drugs targeting eosinophilic inflammation (mepolizumab[153], reslizumab[154] and benralizumab[155], as well as dupilumab[156]) in patients with asthma and T2 high endotype, may be potentially beneficial in patients with AERD.

C COX-1 inhibitors should be avoided[157] (Table 8.3). Selective COX-2 inhibitors (celecoxib, etoricoxib, perecoxib)[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 tolerability[142].

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 considered[161]. It has been shown that ASA desensitization can improve nasal symptoms, asthma control, and quality of life in patients with AERD[162,163]. Moerover, these effects are maintained over time despite C requiring lower doses of ASA[164], although the procedure is not free from adverse effects[165]. The maintenance dose should not be withdrawn, as the therapeutic effect is lost and adverse reactions reappear when taking NSAID[166]. 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 ASA[167]. B C

Both challenge and desensitization tests are not routine techniques and should be performed by qualified personnel and with the adequate equipment to control reactions[147]. C

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 diffoculty 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 dysphonia[168]. C

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. C

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 asthma[169]. C

Clinical suspicion is essential for the diagnosis of ILO. There are questionnaires that can help to distinguish between asthma and ILO[170]. Flattening of the inspiratory portion of the flow-volume loop is of little value in the diagnosis of ILO[171], 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 methacholine[172]. C

The use of dynamic computerized tomography (CT) to demonstrate paradoxical laryngeal closure during attacks has been recently proposed[169]. C

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 ventilation[173]. B

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. B

Table 8.3. Classification of some NSAIDs based on their capacity of inhibition of cyclooxygenase isoforms[158]

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) – Highly selective	 Meloxicam, nabumetone 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)	Hydroxichloroquine	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	↑ [fluticanose 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 severeity 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 logophoniatric rehabilitation, infiltration of thyroarytenoid muscles with botulinum toxin may be used[174].

C In selected cases of supraglottic ILO, transoral laser surgical techniques have been used successfully[175].

C There is no solid evidence for the indication of tracheostomy in these patients; however, single case reports have been published[176].

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 globe[177].

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 patients[187].

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 indidualize 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 establish 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 tha 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 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 patiens 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 con asma 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), formerely known as vocal cord dysfunction, should be established after clinical suspcion and confirmation by laryngeal videoendoscopy.	R1
8.23.	Treatment of the acute phase of ILO should include respiratory logophoniatric reeducation (laryngeal muscle relaxation) techniques.	R2
8.24.	In the treatment of the acute phase of ILO, sedatives may be useful, whereas type A bolutinum toxin or surgery are reserved for refractory cases.	R2

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