9. Special circumstances

9.1 Asthma and pregnancy

B Asthma is the most common respiratory disease in pregnancy and affects 4-7% of pregnant women. Up to 20 % of asthmatic pregnant women experience exacerbations and 6% requires hospital admission for a severe acute episode[604]. These percentages are higher in patients with persistent asthma, in whom up to 50% may suffer from an asthma attack[605]. This might be due to mechanical and hormonal changes, and to the reluctance on the part of women and clinicians to use medications in pregnancy[606].

9.1.1 Effects of asthma on pregnancy

B Most women with asthma have normal pregnancies and the risk of complications is low in those with well controlled asthma.

Although there is a low risk, pregnant women with asthma have a higher risk of maternal and placental complications. In the baby, poor asthma control is associated with prematurity, low birth weight and increased perinatal mortality, whereas in the mother there is an increased risk of pre-eclampsia[607].

If asthma is well controlled, this increase in the risk of maternal or fetal complications is almost negligible[608].

9.1.2 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[609].

B The appropriate use of inhaled glucocorticoids, β_2-agonist, montelukast and theophylline is not associated with an increase of fetal abnormalities[610].

A Inhaled glucocorticoids prevent asthma exacerbations during pregnancy[608,611,612].

C Budesonide is a safe drug in pregnancy[613]. A study performed in 2014 newborns whose mothers had been treated with inhaled budesonide during pregnancy did not revealed an increased incidence of teratogenicity (3.8%) in comparison with the general population (3.5%)[614].

A Although safety studies of β_2-agonist during pregnancy are not totally conclusive, there is no solid evidence against their use[615].

C Oral glucocorticoids cause teratogenic effects, although the risk-benefit should be assessed on a case by case basis, because in some cases their administration cannot be discontinued[616].

B During pregnancy, asthma control may be improved and exacerbations prevented by using algorithms that include measurement of fraction of exhaled nitric oxide (FE_{NO}) and symptoms to adjust therapy[617].

The needs for asthma medication in women should be periodically evaluated based on criteria for disease control[618].

9.2 Work-related asthma

Work-related asthma (WRA) is asthma whose symptoms and/or changes in pulmonary function tests and/or bronchial inflammation are related to exposure to the workplace. It includes occupational asthma (OA) and work-exacerbated asthma (WEA)618 (figure 9.1).

9.2.1 Occupational asthma (OA)

C OA is asthma induced by work exposure and caused by agents (table 9.1) exclusively found in the workplace. It is the most common occupational respiratory disease and the risk attributable to work-place exposure is 10 to 25%, equivalent to an incidence of 250 a 300 cases per million per year[619].

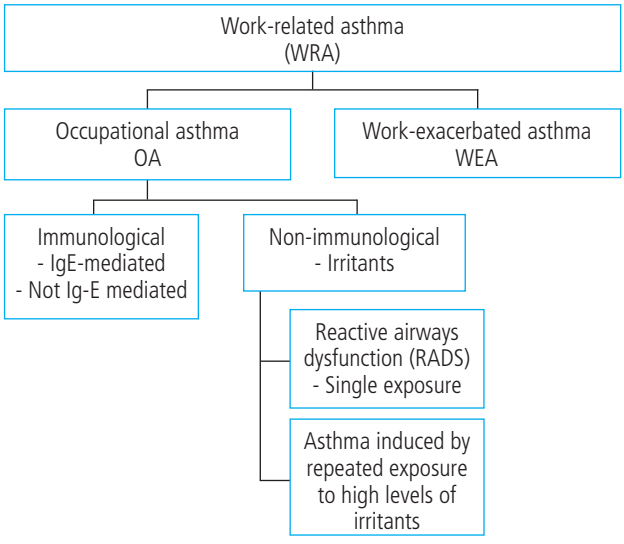


Figure 9.1. Classification of work-related asthma[618]

Table 9.1. Causative agents of occupational asthma[620,626]

Class	Agents	Jobs/tasks/cctivities involving 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	Health care 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	Platinum refinery, polishers, grinding, tanners
Biocides	Glutaraldehyde and chlorhexidine	Sanitary ware
Woods	Red cedar and tropical wood	Carpentry, electronic welding
Antibiotics	Penicillin, spiramycin, tetracycline	Pharmaceutical industry
Irritants		
Bleach/hydrogen chloride	Chlorine, ammonia, ClH	Cleaning
Smokes	Smokes	Firefighters
Gases	NO2, SO2, ozone	Metallurgy, agriculture
Other	Resin, acetic acid, caustic soda	Sanitary ware, chemical industry

9.2.1.1 Types of occupational asthma

C

1) ***Immunological OA:*** induced by sensitization to specific agents in the workplace through a mechanism associated with a specific immunological response[620]. The most common agents are those with a high molecular weight (HMW) (proteins or glycopeptides, > 10 kDa), which lead to a specific production of IgE and a typical allergic response. Low molecular weight (LMW) agents are chemical products that induce asthma through an unclear mechanism, although sensitization is likely to be involved.

D

2) ***Non-immunological OA:*** induced by irritants in the absence of sensitization[618]. The reactive airways dysfunction syndrome (RADS)[621] is the most representative form of this type of asthma. The initial Brooks' criteria were later modified[622] and the term irritant-induced asthma is currently used, which includes cases of asthma occurring after one or more exposures to high levels of irritants.

9.2.1.2 Risk factors

C

1) Exposure levels: the higher the level, the greater the risk of developing asthma caused by both HMW or LMW agents[623] and irritants[624].
2) Atopy: particularly in those exposed to HMW agents[625].
3) Rhinitis: often accompanying or preceding asthma produced by HMW agents[626].
4) Tobacco: an association may exist with the development of asthma caused by HMW and LMW agents, which act through an IgE-mediated mechanism[627].

C

9.2.1.3 Diagnosis

C

The diagnosis of asthma and its relationship with the patient's workplace should be confirmed[618]. Diagnostic tests are shown in table 9.2 and the diagnostic algorithm is summarized in figure 9.2.

9.2.1.4 Treatment

B

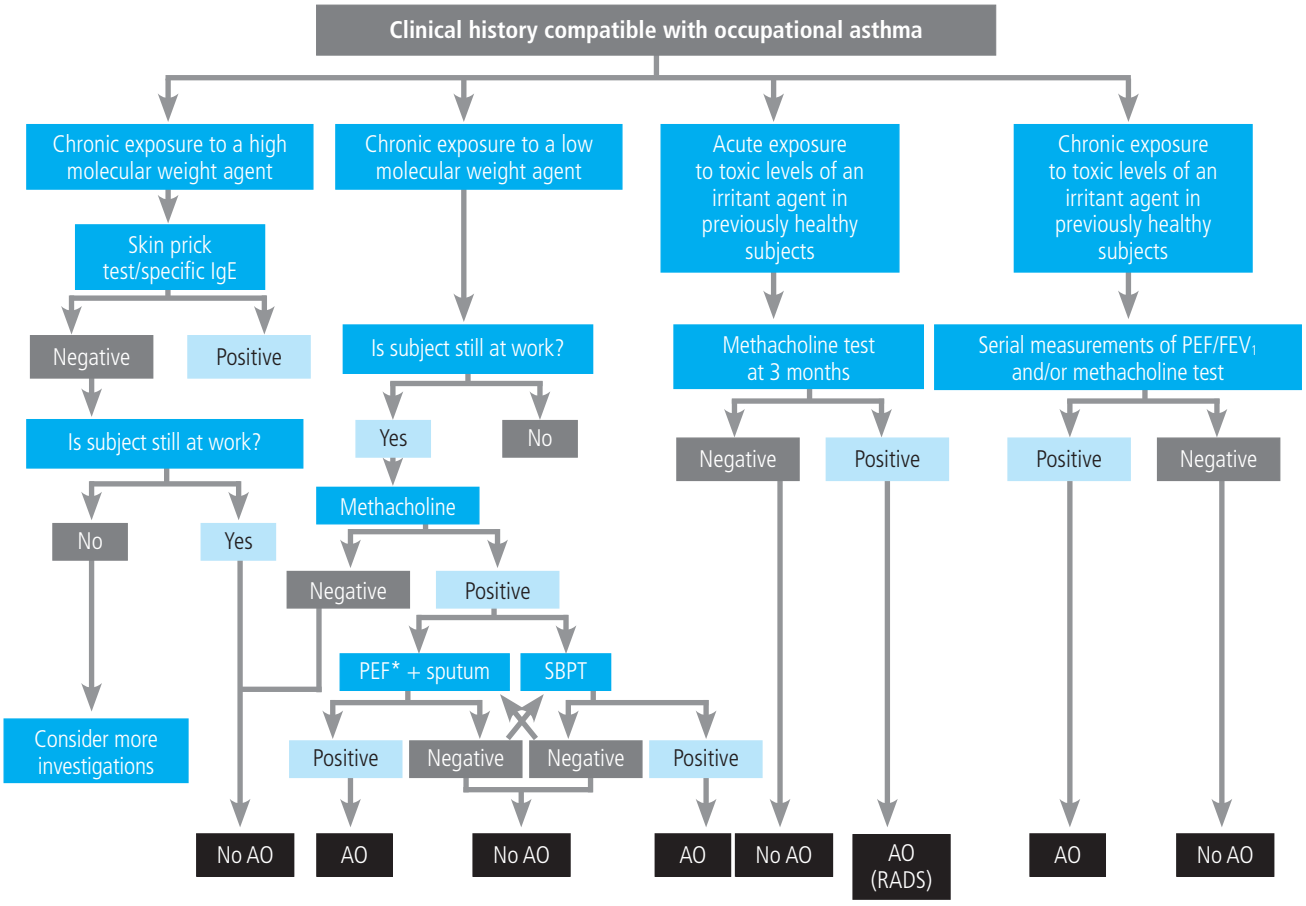
Patients with OA caused by sensitizing agents should be removed from the source of exposure[632]. Workers with irritant-induced asthma may continue to work provided they are transferred to lower exposure areas together with the implementation of industrial hygiene measures to reduce exposure.

C

In approximately 70% of patients, asthma symptoms and BHR persist for several years after being removed from the area of exposure[624].

Table 9.2. Diagnostic tests in occupational asthma

Diagnostic tests	Diagnostic value
Clinical and work history	- Essential, but with a low positive predictive value[628].
Allergic tests	- IgE sensitization → Prick test identifies the allergen. - Positivity only indicates that sensitization exists[625].
PEF monitoring: working versus non-working periods	- Sensitivity: 81-87%. - Specificity: 74-89%[629].
Non-specific bronchial hyperresponsiveness (NSBHR): working- versus nonworking-periods	- Associated with PEF monitoring. - Added value, but with no increase in sensitivity or specificity[630].
Induced sputum	- Eosinophilic patterns in most cases (> 3%). - It improves sensitivity of specific bronchoprovocation test[618].
Fractional exhaled nitric oxide (FENO)	- Information added to the specific bronchoprovocation test if induced sputum is not available[618].
Specific bronchoprovocation test (SBPT)	- Inhalation of the suspected agent at increasing doses. - Serial monitoring of FEV_1. - It is the most reliable and the reference test to confirm OA[631].



OA: occupational asthma; RADS: reactive airways dysfunction syndrome; SBPT: specific bronchial provocation test; PEF: peak expiratory flow.
*Measurements performed after 15 days of working time and 15 days off-work; sputum: assessment of change in the number of eosinophils.

Figure 9.2. Diagnostic algorithm of occupational asthma

9.2.2 Work-exacerbated asthma (WEA)

C It is defined as preexistent or concomitant asthma aggravated by work conditions[630]. These conditions may include chemical irritants, dust, passive smoking and common allergens, as well as stress, temperature (cold or heat) and physical exercise.

C The prevalence of WEA is 21.5% and is associated with more days with symptoms and increased use of health care resources than work-related asthma. Diagnosis of WEA requires that a relationship with the workplace be established and, particularly, to exclude the diagnosis of OA. Treatment consists in optimizing medication and/or reducing exposure at the workplace[633].

9.3 Exercise-induced asthma

C Exercised-induced asthma is a narrowing of the lower airways that is triggered by strenuous exercise[634].

Exercise-induced asthma is caused by the increased osmolarity at the airway surface due to cooling and dehydration following hyperventilation[635].

B It is associated with the release of mediators, such as prostaglandins, T lymphocytes and histamine. Exercise-induced asthma may be a reflection of a genetic predisposition and interaction with environmental pollutants, as well as of the resulting oxidative stress[636].

C The prevalence varies according to age (greater in young subjects), sex (more common in women), area of residence (higher prevalence in urban areas) and race (more prevalent in Afro-Americans)[637].

B Symptoms (cough and dyspnea with wheezing) usually occur during or following exercise, with a 2-3 hour-refractory period after their onset[638].

A Self-defined symptoms are an unreliable diagnostic tool. 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 value[82].

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, obesity, anatomical defects, diaphragmatic paralysis, pulmonary fibrosis and restrictive pulmonary diseases[639].

A The disease is more common in severely ill or poorly controlled asthma patients[640]. Its association with gastroesophageal reflux is not well established.

Occasional use of short-acting β_2-agonist (SABA) approximately 10 minutes before exercise is the treatment of choice. However, when used regularly, these agents gradually lose efficacy[641,642].

A ICG should be used with β_2-agonist when a continuous treatment is needed, since this combination reduces both the frequency and intensity of asthma attacks[643].

A LTRAs may be used either sporadically or continuously. They do not induce tolerance, although these agents are less effective for prevention and are not used to reverse an established obstruction[644].

A Increasingly intense warm-up exercise before starting any sports activity may attenuate the intensity of bronhcoconstriction[645,646].

C Reduction of dietary sodium intake and supplementation with ascorbic acid or fish oil may lessen the severity of attacks[647].

9.4 Aspirin-exacerbated respiratory disease (AERD)

C Formerly known as intolerance to acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs), it is currently called AERD, since it refers to acute reactions of the upper and lower airways after ingestion of acetylsalicylic acid or other cyclooxygenase-1 (COX-1) inhibiting NSAIDs[648,649]. These reactions occur in 20-40% of adults suffering from asthma and/or rhinosinusitis with sinonasal polyposis[552,650,651]. Asthma is usually severe[652].

C Reactions caused by NSAIDs occur between 30 minutes and 3 hours after their oral administration and are characterized by an acute worsening of asthma and nasal congestion, occasionally accompanied by other symptoms requiring urgent treatment. Many of these reactions are serious, albeit rarely fatal. Avoidance of NSAIDs does not resolve asthma or polyposis[638,649].

C The pathogenesis of AERD is not thoroughly characterized. There is intense eosinophilic inflammation and overproduction of local IL-5, as well as LTC_4, LTD_4 and LTE_4[653], and overexpression of their receptors[654,655]. In many cases, an overexpression of LTC4 synthetase in eosinophils and mast cells is observed[656]. This may be partially explained by genetic polymorphism of the LTC_4 synthetase gene, which is present in 70 % of patients with AERE[657].

9.4.1 Diagnosis

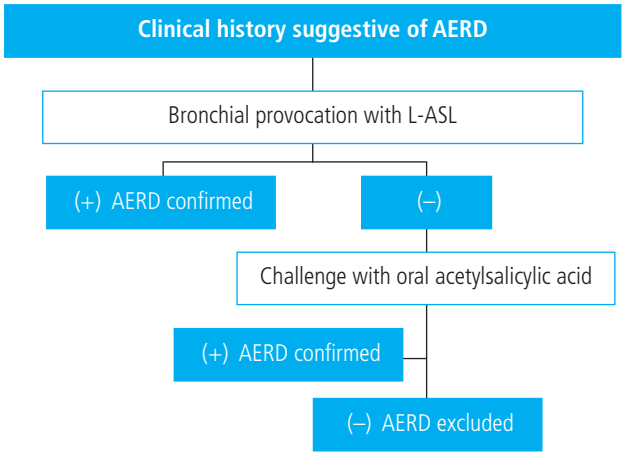
AERD should be suspected in any asthmatic patient with chronic rhinosinusitis and nasal polyposis, and confirmed through a detailed clinical history showing a relationship between ingestion of a NSAID and exacerbations. In case of doubt, and in the absence of in vitro tests, the diagnosis of AERD should be confirmed by using controlled exposure techniques with an NSAID[552], preferably acetylsalicylic acid. 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[237,655,658-660] (figure 9.3).

9.4.2 Treatment

C AERD treatment should include, on the one hand, the medical-surgical treatment of background diseases (asthma, nasal polyposis)[661] and, on the other, avoidance COX-1-inhibitor NSAIDs[652] (table 9.3), and in selected cases, desensitization to acetylsalicylic acid[663,664].

C Some studies have reported improvement in patients with moderate or severe asthma after adding LTRAs to the standard treatment[665-667], as well as in patients with nasal symptoms even in the absence of asthma[471,666,668].

These patients can receive paracetamol (acetaminophen), although the 650 mg dose should not be exceeded in order to avoid potential adverse reactions[669,670].



L-ASL: lysine acetylsalicylate.

Figure 9.3. Diagnostic algorithm of aspirin-exacerbated respiratory disease (AERD) with asthma symptoms[655]

C If a higher analgesic potency is required, tramadol, opiates and COX-2 selective NSAIDs (celecoxib, etoricoxib) may be used[671-673]. The tolerability of selective COX-2 inhibitors should be previously confirmed.

C Patients with AERD and severe uncontrolled asthma, particularly those with recurrent nasal polyposis after several polypectomies (despite receiving appropriate maintenance therapy), may benefit from acetylsalicylic acid desensitization[659,664,674-676]. Thereafter, a continuous treatment with acetylsalicylic acid (325 mg twice daily) is indicated[665]. Treatment with aspirin should not be discontinued given that adverse reaction will reappeared after a further oral intake[677]. Throughout this treatment period the patient will be able to tolerate any other NSAID different from acetylsalicylic acid[677].

C Since neither provocation tests nor desensitization procedures are routine techniques they should be performed by qualified personnel provided with the proper equipment to control reactions[652,677,678].

Table 9.3. Classification of some NSAIDs according to their ability to inhibit cyclooxygenase isoforms[662]

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

9.5 Vocal cord dysfunction (VCD)

C Vocal cord dysfunction is one of the most common term to designate a syndrome characterized by paroxystic episodes of dyspnea and respiratory sounds (wheezing/ stridor) resulting from the extrathoracic airway obstruction caused by the paradoxical adduction (on inspiration) of the vocal cords, in the absence of neurological diseases (dystonias, multiple sclerosis, autonomic dysfunction)[679].

C VCD is a common cause of misdiagnosis of asthma exacerbation unresponsive to treatment, since it is more prevalent in asthmatic patients[680].

C It is twice as common in women as in men, and has been related to psychiatric disorders (anxiety, personality disorders), physical exercise and laryngeal hypersensitivity to irritants (gastroesophageal reflux, post-nasal drip due to rhinitis or rhinosinusitis, smoke, and chemical substances)[681].

D A definitive diagnosis can be made by observing the paradoxical movement of the vocal cords (rhinofibrolaryngoscopy)[681]. This movement can be elicited by exercise, irritant inhalation (methacholine or histamine) or maneuvers such as panting, coughing or sniffing[680].

D Post-challenge spirometry may show (less often in asymptomatic patients) a flattened inspiratory loop and an increased forced expiratory flow/forced inspiratory flow ratio at 50% of vital capacity[682], although there is evidence both in favor of and against the diagnostic value of this test[683].

B The Pittsburgh Index is currently being developed and validated as a sensitive and specific tool that could help to distinguish VCD from asthma[684].

C In the acute phase of VCD, the patient should be calmed down (benzodiazepines may be used once respiratory insufficiency has been ruled out) and instructed to perform certain maneuvers, such as panting or pursed-lip breathing. Other useful measures include using a facial mask with continuous positive airway pressure (CPAP) or inhaling a mixture of helium and oxygen (Heliox). In order to prevent and avoid VCD episodes, techniques such as logophoniatric rehabilitation, psychotherapy, inhaled anticholinergic agents, and intralaryngeal injection of botulinum toxin or lidocaine have been proposed[685].

9.6 Criteria for specialist referral

The management of asthma patients requires a close coordination between primary care and specialized medical professionals. A significant proportion of patients can be managed in primary care settings, provided adequate levels of knowledge and resources are available for their evaluation and follow-up.

D Patients included in any of the following three groups should be referred for specialist assessment[5,6]:

- D ***Diagnostic problems:*** asthma diagnosis could not be objectively established using basic diagnostic testing; adequate resources for assessing triggers and pulmonary function are not available; assessment of the intensity of bronchial inflammation; evaluation of a potential allergic component; suspected pseudo-asthma; suspected undiagnosed aggravating disease; suspected OA.

D

With respect to childhood asthma, the younger the child, the greater the likelihood of misdiagnosis. Therefore, an infant with persistent moderate wheezing failing to respond to standard treatment should be evaluated by a specialist.

D

- ***Therapeutic problems:*** poor symptom control; frequent exacerbations; increased future risk; administration of special treatments (allergen immunotherapy, omalizumab, thermoplasty, prolonged treatment with macrolides, etc.); serious side effects of treatment; severe rhinosinusitis and nasal polyposis. Children with moderate or severe asthma who remain uncontrolled on appropriate medication despite a correct inhalation technique and a good adherence to treatment are also candidates for specialist referral.
- ***Special forms:*** Asthma-COPD overlap syndrome; serious uncontrolled asthma after using high doses of conventional multidrug treatment; allergic bronchopulmonary aspergillosis; poorly controlled asthma in pregnancy; history of life-threatening asthma; exacerbation caused by NSAID (AERD); corticosteroid-dependent and corticosteroid-resistant asthma; anaphylaxis; food allergy.

D

RECOMMENDATIONS

9.1.	Standard medication (β_2-adrenergic agonists and inhaled glucocorticoids) is recommended for the maintenance treatment of asthma in pregnant women.	R1
9.2.	In order to reduce the risk of maternofetal complications, pregnant women with asthma should control their asthma properly in order to avoid severe exacerbations as much as possible.	R2
9.3.	Work-related asthma should be ruled out in patients with adult-onset asthma or deterioration of previous asthma.	R2
9.4.	Occupational asthma should be confirmed using objective tests and in case of allergic etiopathogenesis, by means of immunological tests.	R2
9.5.	The reference test for the diagnosis occupational asthma is the specific bronchoprovocation (challenge) test.	R2
9.6.	For the treatment of immunological occupational asthma, removal of exposure to the causative agent is recommended.	R2
9.7.	The management of work-exacerbated asthma is based on the improvement of workplace hygienic conditions, and the optimization of asthma treatment.	R2
9.8.	Warm-up exercises before starting any sports activity are recommended, as they may reduce the intensity of bronchoconstriction.	R1
9.9.	Occasional use of SABA agonists is recommended as the most effective short-term control measure.	R1
9.10.	As IGCs decrease both the rate and severity of exacerbations, their use is recommendable for patients needing a regular use of β_2-adrenergic agonists.	R1
9.11.	LTRAs may be used either occasionally or continuously, although they are less effective for prevention and are not used to reverse an ongoing obstruction.	R1
9.12.	In patients affected by asthma and chronic rhinosinusitis with nasal polyps, it is advisable to exclude acetylsalicylic acid-exacerbated respiratory disease, particularly in case of severe asthma.	R2
9.13.	Patients with aspirin acid-exacerbated respiratory disease should avoid receiving NSAIDs or COX-1 inhibitors.	R2
9.14.	Paracetamol (acetaminophen), tramadol and opiates can be used for the analgesic or anti-inflammatory treatment of patients with acetylsalicylic acid-exacerbated respiratory disease. Cautious use of selective- (meloxicam) and specific- (celecoxib, etoricoxib) COX-2 inhibitors is also possible, provided their tolerability is confirmed.	R2
9.15.	The addition of leukotriene receptor antagonists (LTRAs) in patients suffering from aspirin-exacerbated respiratory disease and moderate-severe asthma with nasal polyposis should be considered.	R2
9.16.	Desensitization with acetylsalicylic acid may be useful in selected cases.	R2
9.17.	Definitive diagnosis of vocal cord dysfunction is made by rhinofibrolaryngoscopy. However, alterations in the inspiratory loop on spirometry may suggest the diagnosis.	R2
9.18.	Logophoniatric rehabilitation, use of inhaled anticholinergic agents and intracordal injection of botulinum toxin or lidocaine may also be considered for treatment.	R2
9.19.	Referral for specialist evaluation should be considered in patients with suspected asthma but without an objective diagnosis of the disease; poor symptom control; frequent exacerbations; severe uncontrolled asthma and other special forms of asthma; or needing special therapies.	R2