

# 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 days<sup>1-3</sup>.

**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 annually<sup>4</sup> (Table 6.1). Allergic rhinitis (AR) is the most prevalent of all chronic diseases, affecting 22-41% of the European population<sup>5</sup> and 12.6% of children aged 0-18 years<sup>6</sup>. 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 age<sup>7</sup>.

**C** In Spain, rhinitis is the most common reason for consultation in Allergology (62% in adults and 53.8% in children)<sup>8,9</sup>. 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)<sup>10</sup>.

**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€)<sup>11</sup>.

## 6.2 Diagnosis and classification

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 intensity<sup>1</sup>.

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 conditions<sup>12</sup> (Table 6.1).

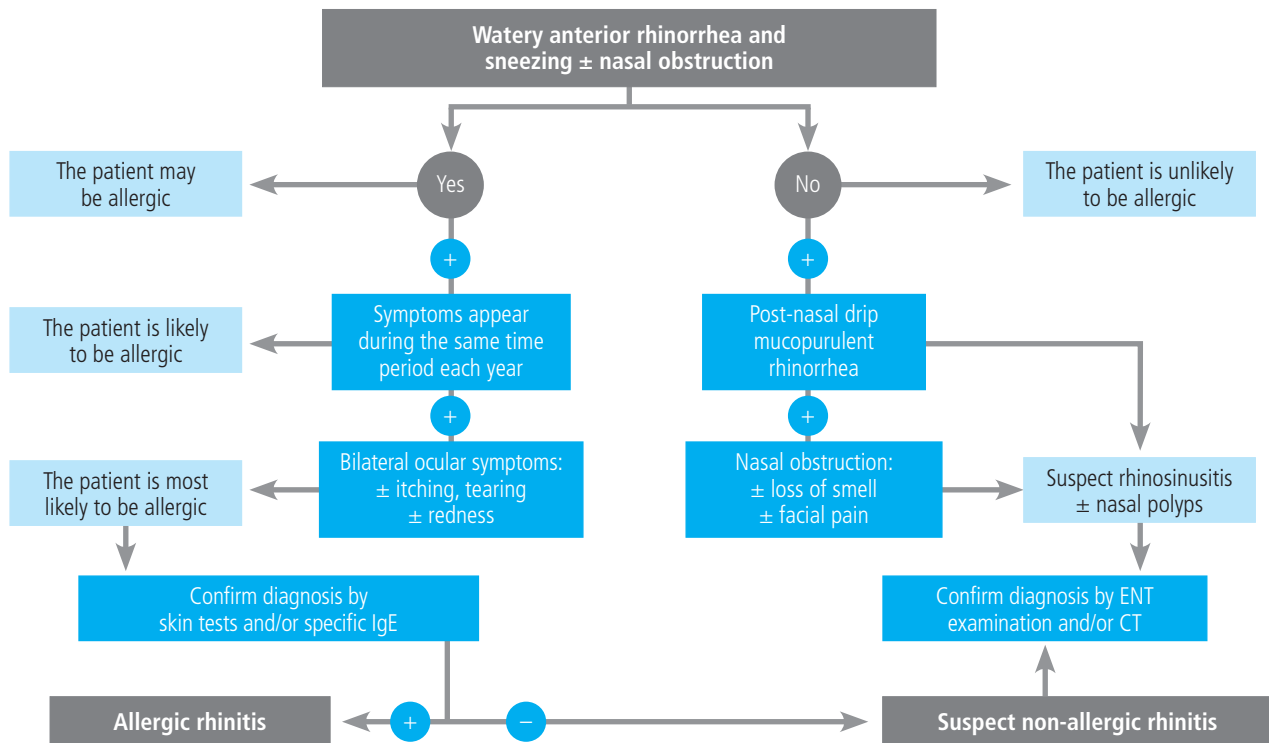
Family history of allergy, seasonal manifestation of symptoms, concomitant ocular and nasal symptoms and an association with exposure to aeroallergens are clinical data with a high predictive value for the diagnosis of suspected AR<sup>13</sup> (Figure 6.1).

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 allergens<sup>12</sup>. 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 diagnosis<sup>14</sup>.

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



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<sup>15,16</sup>.

**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 test<sup>17</sup>.

**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)<sup>18</sup>, assessment of nasal inflammation (nasal nitric oxide [nNO], nasal cytology, biopsy)<sup>19</sup> and assessment of olfactory function by dynamic olfactometry<sup>20</sup>.

**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 allergens<sup>21</sup>.

**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 patients<sup>22</sup>.

**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 treatment<sup>23-25</sup> (Table 6.2). A visual analogue scale can also be used to assess severity of AR<sup>26</sup>.

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)<sup>27</sup> or using a visual analogue scale (available as applications for mobile devices)<sup>28</sup>.

### 6.3 Rhinitis and asthma

Multiple epidemiological, pathophysiological and therapeutic studies have demonstrated the association between rhinitis and asthma<sup>1</sup>.

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<sup>29,30</sup>.

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<sup>23,31</sup>.

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 $\leq 4$ days a week or for $\leq 4$ 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)<sup>1</sup> according to (Valero 2007)<sup>25</sup>.

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<sup>32,36</sup>, higher number of sensitizations<sup>32,37,38</sup>, higher specific IgE levels<sup>39</sup> and in the presence of various associated allergic diseases (rhinitis, conjunctivitis, dermatitis)<sup>40,41</sup>.

**B** The prevalence of rhinitis in patients with asthma is high and much higher than in the general population<sup>42</sup>. In Spain, two studies showed a prevalence of rhinitis in patients diagnosed with asthma of 71% and 89.5%, respectively<sup>43</sup>. A parallel increase in the prevalence of asthma and rhinitis has been demonstrated<sup>44</sup>.

**B** Suffering from rhinitis aggravates asthma<sup>45</sup>, worsens asthma control<sup>46</sup> and asthma symptoms<sup>47</sup>, and increases the use of healthcare resources<sup>48,49</sup>.

**B** Inflammatory changes in the bronchial mucosa of non-asthmatic patients with AR have been observed<sup>50</sup>, as has been the case with nasal eosinophilic inflammation in asthma patients without nasal symptoms<sup>51</sup>.

**A** Treatment of AR with intranasal glucocorticoids may improve some aspects of asthma, such as pulmonary function<sup>52</sup>, symptom score, quality of life or the use of reliever or rescue medication<sup>53</sup>, the level of asthma control<sup>55</sup> and exacerbations in children<sup>34,54</sup>.

## 6.4 Treatment of allergic rhinitis

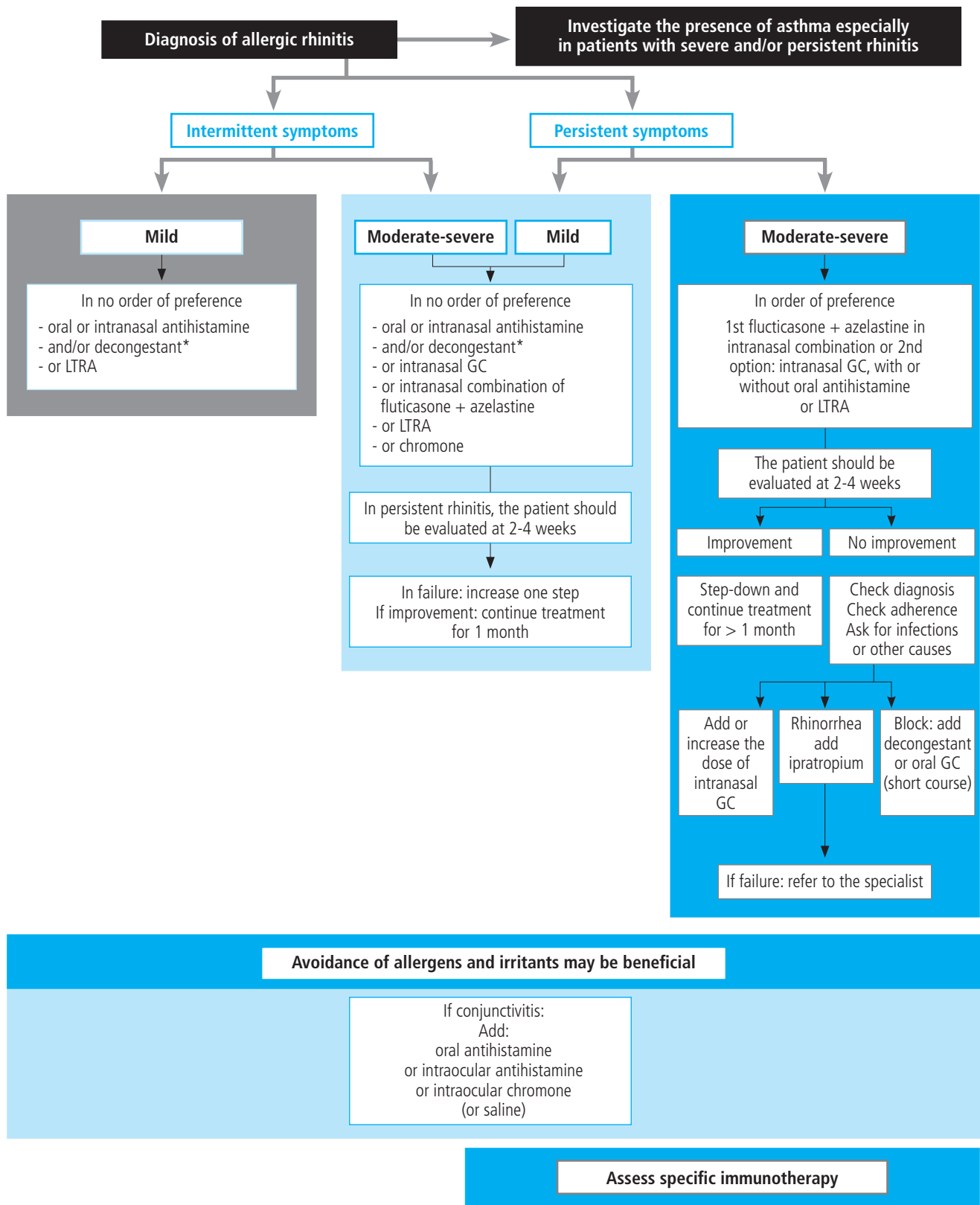
The treatment strategy of allergic rhinitis includes patient education, avoidance of allergens and contaminants, pharmacotherapy and allergen-specific immunotherapy. At the time of selecting the pharmacological treatment, efficacy, safety, cost-effectiveness relationship, patients' preferences, severity 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 ratio<sup>12</sup>.

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 taste<sup>12</sup>.

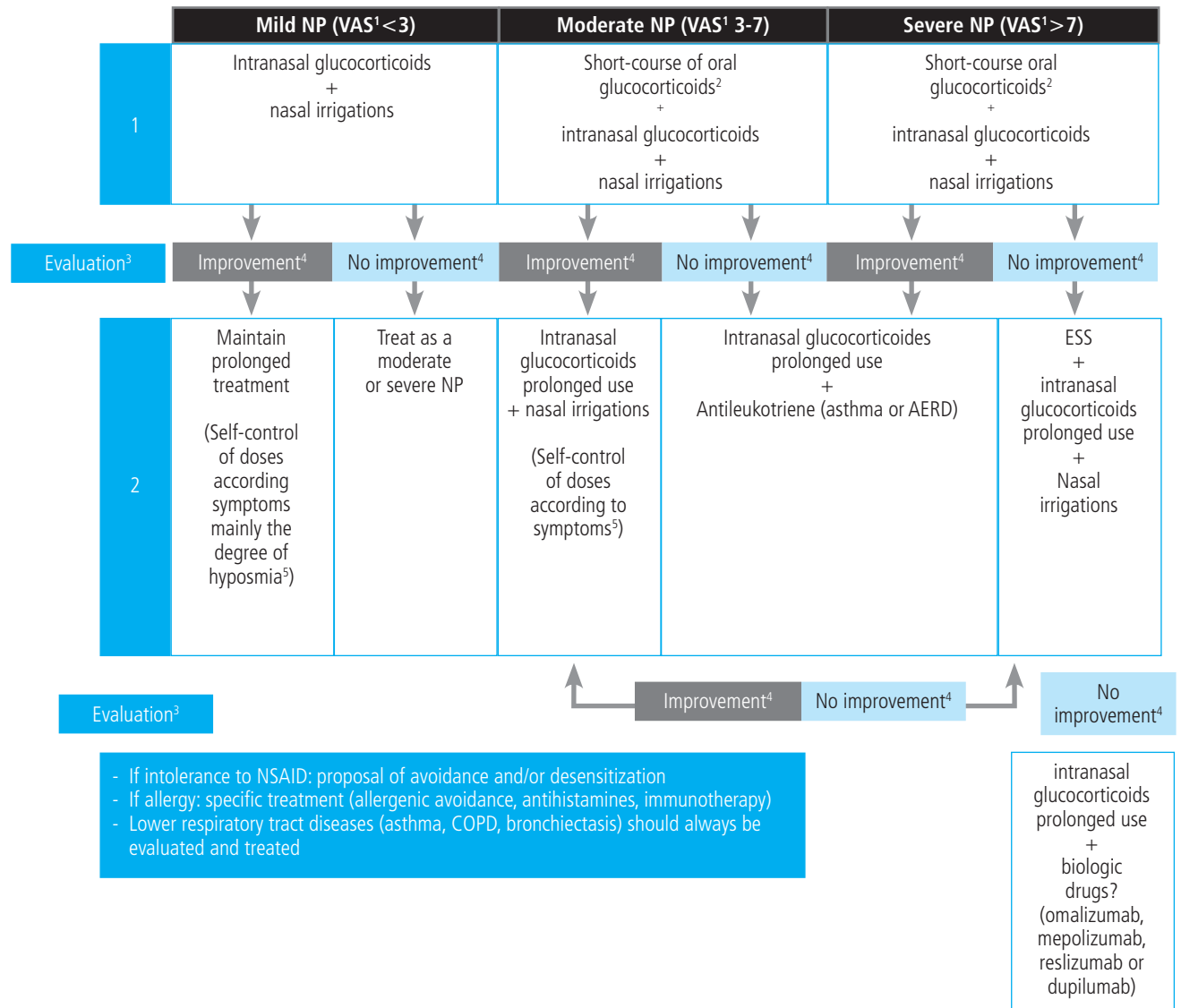
INGC (*budesonide, ciclesonide, fluticasone, mometasone and triamcinolone*) are very effective drugs for reducing nasal and ocular symptoms, even when administered intermittently, and are superior to oral antihistamines and *montelukast*. Their use may be associated with some minor adverse effects, such as epistaxis or headache, but a relevant effect neither on the hypothalamic-pituitary axis nor on the growth of children has been demonstrated<sup>12</sup>.

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<sup>1,52,53</sup>.



VAS: visual analogue scale; AERD: aspirin-exacerbated respiratory disease; ESS: endoscopic sinus surgery; COPD: chronic obstructive pulmonary disease; <sup>2</sup>short 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 monotherapy<sup>12</sup>.

**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 treatment<sup>12</sup>.

**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 medicamentosa<sup>12</sup>.

**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 status<sup>12</sup>.

**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 INGC<sup>12</sup>.

**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 rhinorrhea<sup>12</sup>.

**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 product<sup>12</sup>.

**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 rhinitis<sup>12</sup>.

**A** The combination of several avoidance measures of indoor allergens added to baseline pharmacological treatment is also effective<sup>12</sup>.

**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 drugs<sup>57-59</sup>.

## 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 weeks<sup>60</sup>. 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<sup>60,61</sup>.

**C** In Europe, the prevalence of CRS is 10.7%<sup>62</sup>.

**A** Patients with CRS have a 3.5-fold higher risk for asthma<sup>5</sup>. Aspirin-exacerbated respiratory disease (AERD) or NSAID-exacerbated respiratory disease associated with asthma, CRSwNP and NSAID intolerance is more severe and has a

poorer prognosis<sup>63</sup>. In patients with asthma, the prevalence of AERD is 7-15%, which increases with a greater severity of asthma<sup>64</sup>.

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-22<sup>60,65</sup>.

Imaging studies do not add value to endoscopic diagnosis<sup>66</sup> and should be reserved for surgical planning (computerized tomography), suspicion of complications or nasosinusual tumor (magnetic resonance)<sup>67</sup>.

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)<sup>68</sup>. A greater efficacy of one active principle compared to another has not been demonstrated, although high doses are more effective than low doses<sup>69-71</sup>.

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 polyps<sup>72</sup>.

Endoscopic sinus surgery should be indicated in patients in which medical treatment has been unsuccessful to achieve an adequate control of the disease<sup>73,74</sup>.

INGC should be used after surgery for the prevention of relapses and to improve outcome<sup>75</sup>. The need of revision surgery depends on the previous surgical procedures and postoperative medical treatment, being greater in AERD<sup>49,76</sup>.

An adequate medical/surgical control of CRS improves clinical and functional parameters of asthma<sup>77,78</sup>.

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

Up to 40% of patients have poor control of the disease<sup>81</sup>, evidencing the need to identify specific phenotypes that allow predicting therapeutic success<sup>61</sup>. Recent studies with different monoclonal antibodies, such as *omalizumab* (anti-IgE)<sup>82</sup>, *mepolizumab*<sup>83</sup>, *reslizumab* (anti-IL5)<sup>84</sup> and *dupilumab* (anti-IL4-receptor  $\alpha$ )<sup>85-87</sup> 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<sup>83,87</sup>. 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<sup>85,88</sup>. 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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