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SEAIC-SEORL Consensus Document on Nasal Polyposis
POLINA PROJECT

Official Organ of the Spanish Society
of Allergology and Clinical Immunology

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Official Organ of INTERASMA-
The International Association of Asthmology

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Contents

SEAIC-SEORL. Consensus Document on Nasal Polyposis

POLINA PROJECT

I. Introduction

Introduction

Nasal polyposis (NP) is a chronic inflammatory disease affecting the nasal mucosa and paranasal sinuses, and which leads to the formation of polyps. The most recent studies suggest NP to be a chronic rhinosinusitis subtype with differential characteristics that could advise a specific diagnostic and therapeutic approach to the disorder.

Although the precise prevalence of NP is not known, different epidemiological studies have suggested a figure of 2-4%. This indicates that the condition is an important health problem, with a high sociosanitary cost.

The management of NP involves the following specialties: Primary Care, Pediatrics, Pneumology, Allergology and Otorhinolaryngology (Ear, Nose and Throat, ENT). For this reason we consider a multidisciplinary approach to be essential for both diagnostic evaluation and treatment strategy of the disease.

Two years ago, on occasion of a joint meeting between ENT specialists and allergologists in Lisbon, Antonio Valero (Coordinator of the Rhinoconjunctivitis Committee of the Spanish Society of Allergology and Clinical Immunology (Sociedad Española de Alergología e Inmunología Clínica, SEAIC)) and Adolfo Sarandeses-García (President of the Rhinology and Allergy Commission of the Spanish Society of Otorhinolaryngology (Sociedad Española de Otorrinolaringología, SEORL)) proposed a group of experts in Rhinology from our respective Societies to create a Consensus Document and update on nasal polyposis. This SEAIC-SEORL Consensus Document on Nasal Polyposis has been called the "POLINA" Project.

Adolfo Sarandeses García

The work started by these two scientific societies is the best formula for improving the treatment of these patients and for drawing attention to the needs of a still little known illness. The document will help those professionals who care for patients with NP to offer help based on the best evidence possible.

Those who read this document will have the guarantee that it reflects the expertise of the best specialists, with a view to offering optimum evaluation, diagnosis and treatment, on the basis of current knowledge. The document contains no personalisms - only experience based on scientific evidence.

It has been particularly satisfying to see how colleagues and professionals from two different specialties have worked as a team with a common purpose, rather than as competitors. We feel that to address any given disease it is not enough to have the best specialist or the most advanced technology. In order to progress in our knowledge of the complexity of a disorder, we need multidisciplinary teams capable of working in harmony and with rigor, without losing respect for solid ethics in a highly technified world in which we sometimes forget that patients feel and suffer, even if their health problem does not represent a life-threatening condition.

It has been our firm intention, or at least our hope, to establish the POLINA Consensus Document as a useful tool for all physicians who deal with nasal polyposis – from primary to specialized care.

Before concluding, we would like to thank all those who have collaborated and contributed to this project with their work, implication, dedication and commitment to the final result. To all of them, our most sincere gratitude.

Antonio Luís Valero Santiago

II. Methodology for preparation of the POLINA document

1. Aims of the document

The POLINA Consensus Document aims to offer a structured and scientific update on nasal polyposis (NP), resulting from review of the available literature and consensus-based discussion by a group of experts in Rhinology from the Spanish Societies of Allergology and Otorhinolaryngology.

The basic aim of the document is to draw upon the best scientific evidence on each aspect of the disease (epidemiology, physiopathology, clinical manifestations, diagnosis and management) with a view to providing a reader-friendly guide to current knowledge, and to underscore those aspects where discussion or doubts still exist due to a lack of sufficient scientific evidence - with clear establishment of the need for research in such areas.

We have identified no similar documents or clinical guides specifically addressing NP in the current literature. The most recent studies suggest NP to be a chronic rhinosinusitis subtype with differential characteristics that could advise a specific diagnostic and therapeutic approach to the disorder.

The present document is addressed to those healthcare professionals dedicated to the management of patients with NP in both the primary and specialized healthcare settings, though a posterior objective will be to generate specific documents for each healthcare level, with a view to more specifically covering the needs in each case.

2. Sources of information and assessment of the quality of scientific evidence

The search for relevant scientific information is one of the most difficult challenges for clinicians and investigators alike. The strategy proposed for obtaining the scientific information upon which the POLINA document is based has been the following:

1. Identification of existing clinical guides with the purpose of avoiding unnecessary duplication of the search steps and the evaluation of the quality of scientific evidence.

2. Identification of systematic reviews addressing aspects related to the questions raised in each section of the document.

3. Identification of original works offering answers to the questions raised in each section.

All the scientific evidence gathered must have been evaluated from a critical perspective to ensure its maximum scientific quality and relevance to clinical practice and patients.

The fundamental objective of the POLINA Consensus Document is to draw conclusions with the maximum scientific rigor and to offer recommendations on the diagnosis and management of NP. In order to develop this objective, it is necessary to clearly and schematically grade both the scientific quality of the evidence supporting the affirmations made and the strength of the recommendations provided. There are a number of methods for doing this, though the currently most widely accepted options are the system proposed by the Centre for Evidence Based Medicine of the University of Oxford (CEBM, which can be consulted at http://www.cebm.net/index.aspx?o=1025) and the GRADE system, which is the option most recently proposed by an international group of experts in methodology, epidemiology and clinical medicine – many of them having been drawn from organizations which have proposed other systems. This system can be consulted at http://www.papps.org/upload/file/clasificacion_calidadevidencia_fuerza.pdf.

The proposal of the POLINA group is to classify the level of the quality of scientific evidence supporting the affirmations made by means of the following table obtained from the CEBM (Annex 1), since it is one of the most exhaustive options and also considers in detail the different types of studies made (etiology, diagnosis, treatment, prevention, adverse effects, prognosis, economical analyses and decision analyses). The recommendations made are classified using a scheme similar to that proposed by the GRADE, i.e., strong recommendation (grade 1) (level of quality of the scientific evidence supporting the recommendation = 1) or weak recommendation (grade 2) (quality level = 2, 3, 4 and 5). Each grade of recommendation would imply the following:

Grade of recommendation	Patients/caregivers	Clinicians	Managers/planners
1	The great majority of people would agree with the recommended action, and only a small part would not agree	Most patients should receive the recommended intervention	The recommendation can be adopted as healthcare policy in most situations
2	The majority of people would agree with the recommended action, but an important part would not agree	Recognition that different options are appropriate for different patients, and that the physician must help each patient reach the decision most consistent with his or her values and preferences	Important discussion is needed, with the participation of interest groups

III. List of acronyms

ASA: acetylsalicylic acid (aspirin)
QoL: quality of life
ESS: endoscopic sinus surgery
AERD: aspirin-exacerbated respiratory disease
VAS: visual analog scale
PNIF: peak nasal inspiratory flow
CF: cystic fibrosis
HLA: human leukocyte antigen – genetic region of the major histocompatibility complex (MHC)
L-ASA: lysine acetylsalicylic acid
NO: nitric oxide
nNO: nasal nitric oxide
NP: nasal polyps / nasal polyposis
AR: acoustic rhinometry
RNM: rhinomanometry
MRI: magnetic resonance imaging
CRS: chronic rhinosinusitis
CT: computed tomography

1. Epidemiology

1.1 Introduction

In addressing the epidemiology of nasal polyposis (NP), it is important to consider two aspects that cause the precise prevalence of this disorder to remain unclear. Firstly, the number of existing epidemiological studies is still insufficient. Secondly, the results of the studies that have been made differ considerably according to the study population selection criteria used and the diagnostic methods employed. The present review provides an update on the subject and analyzes the main factors implicated.

1.2 Studies on the prevalence of NP

In general terms, the different studies can be divided into two large groups. One group makes use of questionnaires while the other resorts to nasal endoscopy as the method for evidencing the presence of NP. According to the EP3OS guide [1], nasal endoscopy is a requirement for more precisely offering an estimate of the prevalence of NP, since those studies that make use of questionnaires could overestimate the prevalence of the disorder [1].

In this sense, the classical work of Larsen and Tos in cadavers revealed the differences in NP prevalence depending on the exploratory method used. In this context, the prevalence was reported to be 2% when using anterior rhinoscopy [2]. In contrast, when complete nasal-ethmoidal block resection was carried out, the prevalence was found to be 26% (5 out of 19 cadavers) [3]. Lastly, in a third study in which endoscopy was combined with endoscopic sinus surgery, the prevalence reached 32% [4]. It must be taken into account that the mean age of the patients included in these three autopsy-based studies was between 70-79 years.

The prevalences found in the medical literature vary between 0.2-5.6%, according to the consulted source [5-10], and logically depending on the diagnostic criterion used in each case. Table 1.1 shows the results obtained in different studies, and serves to illustrate their variability.

Table 1.1. Prevalence of NP

Author	Year	Prevalence	Method
Settipane [14]	1977	4.2%	Review of clinical histories
Portenko [7]	1989	1.3%-5.6%	Questionnaire
Ming YG [9]	1996	0.5%	Nasal endoscopy
Hedman [5]	1999	4.3%	Questionnaire
Johansson [8]	2003	2.7%	Nasal endoscopy
Klossek [6]	2005	2.1%	Questionnaire-specific algorithm

Questionnaire-based studies

In a study carried out in Finland, involving a mail-delivered questionnaire among adult subjects, Hedman et al. [5] documented a prevalence of 4.3% (95% CI: 2.8-5.8%). In turn, Klossek et al. [6], in France, administered a validated questionnaire / algorithm to 10,033 people, recording a prevalence of 2.1% (95% CI: 1.83-2.39%), and a clear increase in the prevalence of the disorder with advancing age. Portenko et al. [7], in 6748 candidates for specialization in ENT, administered a questionnaire on NP and recorded a prevalence of 1.3% (5.6% in the rural setting).

Nasal endoscopy-based studies

Studies of this kind have the advantage of allowing direct visualization of the polyps, thus affording more reliable data. Their main inconvenience is that they cannot be carried out in extensive population samples.

In a Swedish population study, Johansson et al. [8] reported a prevalence of 2.7%, with a 2.2-fold higher incidence in males than in females, and an increase in prevalence with advancing age – the figure reaching 5% among those over 60 years of age. In turn, in a national scale survey carried out in South Korea, Min et al. [9] recorded a prevalence of 0.5%.

In 211 adults with cystic fibrosis, Hadfield et al. used endoscopy to document a 37% prevalence of NP [10].

Incidence studies

Larsen and Tos [11] estimate an incidence of 0.86/1000 inhabitants/year in males and 0.39/1000 in females. On the other hand, Davidsson and Hellquist [12] estimated a gross incidence of 0.43/1000 in patients referred for polypectomy.

Drake-Lee (14) estimated that between 0.2-1% of the population will develop NP at some point in life.

Other studies

In turn, Settipane and Chafee [14], in a study carried out in 1977, found a 4.2% prevalence of NP in 5000 patients from hospitals and allergy clinics.

1.3 Influence of gender and age

In general terms, studies of NP have found the disorder to be more common in males. In the referred study of the incidence of symptomatic NP, Larsen and Tos [11] found NP to be practically twice as frequent in males versus females. In turn, Rugina et al. [15], in a study published in 2001, reported a male/female ratio of 1.69/1. This tendency was also observed by Johansson [8], with a ratio of 2.2/1. In a mail-delivered questionnaire-based study of 900 patients subjected to polypectomy, Collins et al. [16] recorded a 2/1 male/female ratio. In two of the published studies this tendency was not noted, however. In effect, Settipane [14] observed no gender differences, and Klossek [6] recorded a higher frequency of NP in women – though statistical significance was not reached.

Nasal polyposis fundamentally develops in middle age, with a peak incidence between the fourth and fifth decades of life [1]. The condition is very infrequent among the pediatric population. In this context, Settipane [14] estimated the prevalence among children to be 0.1%. It should be remembered that the diagnosis of NP in a child is suggestive of the existence of a more relevant disorder, such as cystic fibrosis.

In the different studies consulted for conduction of the present study, both the prevalence and incidence of NP were found to increase with age. Johansson [8] estimated a prevalence of 1% in individuals under 40 years of age, versus 5% in the case of those over age 60 years. Klossek [6] in turn reported a prevalence of 1.22% in the 18-24 years age range, and of 2.47% in those over 65 years of age. Similar data were also reported by Settipane [14], who found NP to be about four times more frequent in asthmatic individuals over 40 years of age.

Larsen and Tos [11], in their study of the incidence of symptomatic NP, also found the latter to increase with age. Thus, the incidence was seen to increase from 0.86 to 1.68 cases per 1000 inhabitants and year among males between 50-59 years of age, and from 0.39 to 0.82 cases per 1000 inhabitants among women over the same age interval.

1.4 Factors associated to nasal polyposis

A number of factors have been related to NP. These factors or associated conditions are: smoking, allergy, asthma, nonsteroidal antiinflammatory drug (NSAID) intolerance and genetic factors.

1.4.1. Smoking

In general, the different studies estimate that smoking is less common among patients with NP than in the general population. Rugina [15], in a prospective study carried out in France, observed a smoking prevalence of 15.5% in patients with NP, versus 35% in the general population. Likewise, Toledano et al. [17], in a Spanish population study published in 2008, reported a 25.5% prevalence of smokers among patients with NP, versus 38.9% in a control group of healthy individuals – though the differences were no statistically significant.

1.4.2. Allergy

The role of allergy as a potential cause of NP is subject to debate. Although many patients have positive skin tests or IgE determinations, the relationship between the two conditions has not been adequately clarified in the literature. Settipane [14] found the prevalence of polyposis in patients with allergic rhinitis to be low (1.5%). In contrast, other studies report a relationship with allergy. In an old study from 1933, Kern [18] recorded NP in 25.6% of patients with allergy, versus in 3.9% of the general population. Klossek [6] on the other hand recorded a higher frequency of allergic clinical manifestations in patients with NP than in the general population. Other authors have also published a higher incidence of food allergy in patients with polyposis [6,15], though these data have not been confirmed.

Regarding the relationship between positive skin tests and NP, abundant data can be found in the literature. Crampette et al. [19], in a multicenter study carried out in France, found 32.5% of the patients with NP to have positive skin tests or specific IgE determinations. Settipane [14] recorded a 55% positive skin test rate among 211 patients with NP. In turn, Klossek [6] observed positive tests in 26.1% of 212 patients. On the other hand, Bonfils et al. [20], in a work published in 2006 involving the presentation of the results of two studies – the first comprising 180 patients and the second 74 patients – reported NP with positive Phadiatop test results in 19.5% and 16.2% of the cases, respectively. Toledano et al. [17] observed allergic rhinitis in 47.9% of a total of 142 patients with NP, versus in 45.5% of the control group – the difference on comparing the two groups being statistically significant in this case. In a study published in 1983 involving 57 patients with NP subjected to allergic evaluations, Bunnang et al. [21] found 96.5% of the patients to be positive to at least one of the tests used.

In a study carried out in 25 consecutive patients with NP and 50 consecutive patients with allergic rhinitis, Van Lancker et al. [22] found 72% and 96% of the subjects, respectively, to show sensitization to perennial aeroallergens – the difference being statistically significant – while 84% and 86%, respectively, were sensitized to seasonal aeroallergens – the differences in this case being nonsignificant.

Muñoz del Castillo et al. [23], in a study carried out in Spain in 190 patients with NP and 190 healthy subjects, found skin testing with a battery of 18 aeroallergens to be positive in 63.2% of the patients with NP, of which over the half were sensitized to more than two aeroallergens, versus in only 31.1%

of the controls. In turn, Sin et al. [24] evaluated the existence of allergy using skin tests and specific IgE determination in a population of 95 patients with NP. According to the two tests, 45.2% of the sample was classified as allergic, though the skin tests proved positive in 66.3% of the patients.

On the other hand, Pastorello et al. [25], in a study of 90 patients subjected to polypectomy and the determination of IgE in serum and nasal secretions in response to a panel of aeroallergens, detected specific IgE in 38% of the sera and in 32% of the nasal secretions (with positivity exclusively in nasal secretions in 11%). Likewise, the total serum IgE levels were significantly higher than in a series of 50 controls.

Mention has also been made of the possibility that there may be local IgE production without detection in serum or through skin tests [26]. The authors of a metaanalysis comprising 9 studies in 287 patients subjected to specific IgE determination in serum and nasal mucosa found 19% of the patients to show positive nasal IgE but negative serum IgE; they therefore suggested that a percentage of patients with NP may present local allergy [27].

In 1979, Holopainen et al. [28] recorded positive skin tests in 42/109 patients with NP (38.5%), though only 23 of these cases were consistent with the clinical history.

Asero and Bottazzi [29], in performing skin tests with a broad battery of aeroallergens, recorded positive results in 63% of the patients. The authors compared the sensitizations with a personal historical series of patients with respiratory allergies and found a higher percentage sensitization to perennial aeroallergens, particularly Dermatophagoides and also Candida albicans.

Lastly, and as has been commented, NP has also been related to food allergy [30].

1.4.3. Asthma

The third associated factor mentioned is asthma. The relationship between NP and asthma can be assessed from two different perspectives: the percentage of patients with bronchial asthma who develop NP, and those patients diagnosed with NP who develop asthma at some point over time. A number of studies are described below that illustrate the relationship between these two clinical entities.

In a study published by Bonfils et al. [20] evaluating asthma and allergy in a group of 180 patients diagnosed with NP on the basis of the endoscopic and computed tomography (CT) findings, a 48.6% incidence of asthmatics and a 22.8% incidence of patients with bronchial hyperresponsiveness was observed among the individuals presenting positive skin tests, versus 28.3% and 20%, respectively, among those presenting negative skin tests.

In the mentioned study by Muñoz del Castillo et al. [23], the authors found 48.9% of the patients with NP to have asthma, versus only 2.6% of the controls.

In an analysis of the 38 patients of the epidemiological study carried out in Skövde and diagnosed with NP on the basis of the fibroscopy findings, Johansson et al. [31] found that one-third of the patients answered affirmatively when asked whether they had experienced asthma attacks or breathing difficulties accompanied by wheezing in the last year.

In the aforementioned study by Collins et al. [16], the authors reported a 36% incidence of asthma, which moreover proved significantly more frequent in females (46%) than in males (31%).

In a study involving 342 asthmatic patients, the investigators found 9% to have NP, and the presence of the latter was associated to increased severity of asthma [32].

In 1977 a retrospective study was made of 445 patients with NP, of which 21% were found to have asthma. Although NP was seen to be twice as common in males as in females, the latter had twice the probability of suffering asthma [33].

Bronchial hyperresponsiveness (BHR) has also been investigated in patients with NP. In a study involving 122 patients with NP and subjected to methacholine challenge testing, the investigators found 35% to have bronchial hyperresponsiveness [34].

1.4.4. NSAID intolerance

The relationship between NP and NSAIDs intolerance is well known in daily clinical practice. Likewise, the literature offers several studies in which this relationship is illustrated on a quantitative basis. Settipane [14] recorded a 14.2% incidence of patients with NP who showed NSAID intolerance. Somewhat higher figures have been reported by Crampette [19]: 31%, Klossek [6]: 20.3% and Toledano [17]: 26.7%.

On the other hand, Bonfils et al. [20], in a previously mentioned publication, recorded a lesser association between NP and NSAID intolerance: 8.5% in patients with positive skin tests, and 4.8% in those with negative skin tests.

1.4.5. Genetic-hereditary factors

Lastly, mention will be made of the relationship between NP and genetic-hereditary factors. As regards familial association, two studies have documented family history in patients with NP. Rugina et al. [15] found that 52.7% of a total of 224 patients with NP had family history of the disorder in the last three generations. In turn, Greisner et al. [35] recorded family antecedents in 14% of a series of 50 patients with NP. In contrast to the above, studies in homozygous twins made by Lockey [36] in 1973 failed to identify any major concordances.

In a study involving 99 members of a French family in which 19.7% of the members had NP, Delagrand et al. [37] identified a recessive autosomal hereditary pattern.

Table 1.2 shows the associations we have found in the literature between different HLA complex antigens and NP.

Table 1.2. Relationship between NP and HLA

Author	HLA	Risk
Luxemberg [39]	HLA-A74	Increased
Molnar Gabor [40]	HLA-DR7-DQB1*0202 HLA-DR7-DQA1*0201	2-3 times
Fajardo-Dolci [38]	HLA-DQB1*0202 HLA-DQA1*0201	5,5 times

Key points

- The precise prevalence of NP is not known. The figures found in the literature vary between 0.2-5.6%, and the diagnostic method used exerts an important influence.
- Questionnaire-based epidemiological studies report a prevalence of between 2.1-5.6%. Nasal endoscopy-based studies report a somewhat lower prevalence of between 0.5-2.7%. In both cases an increase with patient age has been observed.
- The incidence is somewhat higher in males and between the fourth and fifth decades of life.
- No relationship between NP and smoking has been demonstrated.
- The relationship between NP and allergy has not been clarified to date.
- Bronchial hyperresponsiveness and asthma are common (21-48%) in patients with NP. This association increases in patients with NSAID intolerance.
- The genetic-hereditary factors underlying NP remain to be clarified. The existing studies offer conflicting results.

2. Physiopathology

2.1. Concept of sinonasal polyposis

At present, nasal polyposis (NP) is regarded as a bilateral and idiopathic clinical form of chronic rhinosinusitis (CRS) (Figure 2.1), the latter comprising an heterogeneous group of disorders of different etiologies and involving different etiopathogenic mechanisms [41,42]. In some cases CRS and NP may represent different stages of one same disease process.

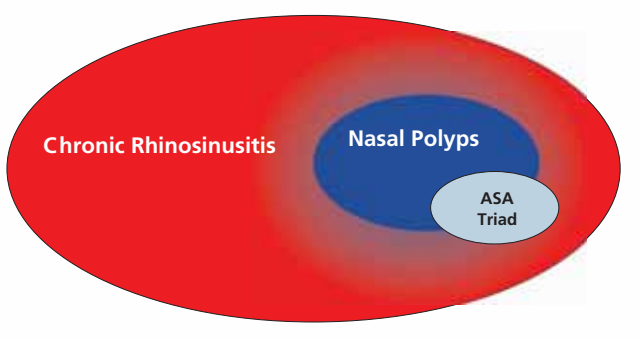


Figure 2.1. Nasal polyposis is a clinical subtype of chronic rhinosinusitis (ASA triad: asthma, chronic rhinosinusitis and NSAID intolerance).

Nasal polyposis is defined as a chronic inflammatory process of the nasal cavity and paranasal sinuses mucosal membranes. While the etiology remains uncertain, eosinophils appear to play an important role. Affected patients show bilateral benign edematous polyps extending from the paranasal (fundamentally ethmoidal) sinuses towards the nasal cavity [43]. Bacterial infection does not appear to be a significant factor in the etiology of NP. The role of allergy remains unclear [44, 45].

2.2 Histopathology

Histopathologically, polyps consist of a generally ciliary epithelium, though squamous epithelium is also observed, together with a thickened basal membrane and lax stromal component, with few vascular and glandular structures, and the absence of neurological elements and connective tissue. A typical finding is the presence of an intense inflammatory cell infiltrate within the stroma, with a predominance of eosinophils (Figure 2.2) – in contrast to other secondary polyps where neutrophils or other cells characteristic of the pathological process are seen to predominate.

Bilateral eosinophilic NP is often associated to non-allergic asthma and, in some patients, to NSAID intolerance, conforming what is known as the ASA triad, also known as Widal syndrome or Samter syndrome (NP, asthma and NSAID intolerance), or aspirin-exacerbated respiratory disease (AERD) – which is a more serious and recurrent clinical form of NP.

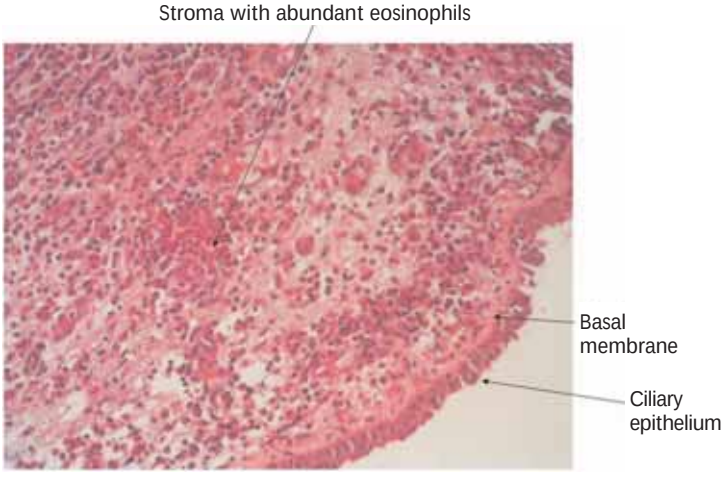


Figure 2.2. Etiopathogenesis of nasal polyposis.

2.3 Pathophysiological mechanisms

NP is an inflammatory disease of uncertain etiology and with a multifactorial physiopathology in which several factors can probably intervene in one same patient. In recent years there have been great advances in the study of the different physiopathological mechanisms implicated in the development and persistence of polypoid growth of the nasosinusal mucosa, some of which will be dealt with in this chapter (Table 2.1).

Table 2.1. Physiopathological mechanisms in NP

- Decrease in permeability of the osteomeatal complex
- Alterations in mucin production
- Inflammation and inflammatory mediators
- Altered tissue remodeling
- Nasal epithelial dysfunction
- Allergy
- Alterations in innate immunity
- IgE and *Staphylococcus aureus*
- Bacterial biofilms
- Fungi
- Eicosanoids
- Aspirin-exacerbated respiratory disease (AERD)
- Nitric oxide
- Genetic factors

2.3.1. Mucin expression pattern

Mucociliary clearance and permeability of the osteomeatal complex are the two main factors allowing physiological function of the paranasal sinuses. CRS and NP are characterized by mucosal hypersecretion and hyperviscosity that complicates mucociliary clearance, together with mucosal inflammation and histological changes that tend to become chronic. Mucins (MUC) are the principal component of mucus and are responsible for its viscoelastic properties. NP, CRS, cystic fibrosis and asthma all show different altered mucin expression patterns. The study of these altered patterns or profiles can help us establish a differential diagnosis. Thus, NP is characterized by an increased expression of MUC1, MUC2, MUC5A and MUC8, while CRS is characterized by an increase in the expression of MUC5B and MUC8 [46].

2.3.2. Inflammation and inflammatory mediators

The study of inflammatory mediators is essential for improving our knowledge of the physiopathological mechanisms of NP, with a view to differentiating among CRS with NP, cystic fibrosis with NP, and CRS without NP [47].

The main factor responsible for polyp formation in persistent eosinophilic inflammation of the nasosinusal mucosa. Another characteristic finding in NP is the presence of abundant activated memory T lymphocytes (CD3+CD45RO+) of mixed Th1/Th2 phenotype [48], with the production of IL-5 (Th2) and IFN-ß (Th1), and a reduction in the expression of FOXP3 (signal transmission factor related to the regulatory T cells) and TGF-ß1 (transforming growth factor-beta 1) – a cytokine produced by the regulatory T cells and implicated in bronchial remodeling. This results in a reduction in the activity of the regulatory T cells (Treg), and leads to an increase in the expression of T-bet (signal transmission factor related to Th1 responses) and GATA-3 (signal transmission factor related to Th2 responses). In contrast, CRS without NP is characterized by increased levels of TGF-ß1 and IFN-ß (a cytokine produced by the Th1 cells) [49].

Moreover, IL-5 is essential for the recruitment, activation and maturation of eosinophils, as well as for inhibition of their apoptosis [50]. Eotaxin and RANTES are also key elements for the recruitment and activation of eosinophils. The activated eosinophils in turn release proinflammatory, vasoactive and cytotoxic mediators such as eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN). The degree of eosinophilic inflammation is strongly correlated to the ECP and IL-5 levels. The clinical form of NP with the highest ECP levels is NP with non-allergic asthma and cross-intolerance of NSAIDs.

CRS with NP shows a Th2 inflammatory profile with increased concentrations of IL-5, eotaxin, ECP and IgE, while CRS without NP shows a Th1 inflammatory profile with increased levels of interferon-gamma (IFN-γ) and TGF-α [47]. The main differences in inflammatory mediators between CRS with and without NP are reported in Table 2.2.

In the near future it is very probable that subgroups can be differentiated within CRS with NP, such as the presentations associated to asthma or AERD [47].

Table 2.2. Inflammatory differences between CRS with and without NP

CRS without polyps	CRS with polyps
Nasal secretion: CD3, CD25, CD68, neutrophils	Nasal secretion: CD3, CD25, CD138, CD68 Neutrophils, eosinophils IL-5, eotaxin, ECP
IFN-γ ↑, TGF-ß ↑, IL-1 FOXP3, collagen ↑	TGF-γ ↓, IgE, MMP ↑, GATA -3 ↑, T-bet ↑, FOXP3↓
Mucosa: Neutrophils and fibroblasts	Mucosa Eosinophils, T cells and B cells

2.3.3. Tissue remodeling

One of the proposed etiopathogenic mechanisms is the existence of altered tissue remodeling, resulting in defective repair or fibrosis of the extracellular matrix (ECM). The cytokine TGF-α_1 is an important immune modulating and remodeling initiating factor that intervenes in the formation of the ECM, favoring the production and accumulation of extracellular proteins, and inhibiting the synthesis of proteinases such as matrix metalloproteinases (MMPs) that degrade ECM. TGF-α also has regulatory functions, suppressing T cell activation and B cell antibody synthesis.

Patients presenting CRS with NP show low mucosal TGF-α_1 concentrations, while subjects with CRS without NP have higher TGF-α_1 levels than the healthy controls (Table 2.2). This decrease in TGF-α leads to a reduction in T regulatory functions and to a decrease in the production of ECM components.

2.3.4. Nasal epithelial dysfunction

Recent studies suggest that CRS with and without NP may be the cause, at least in part, of alterations in nasal epithelial function as a mediator and regulator of the immune and inflammatory response. These studies have shown the epithelial cells to intervene in the regulation of dendritic cells and T and B cells, and to moreover serve as a barrier against external agents and to intervene in innate immunity [52].

2.3.5. Allergy

According to different studies, the incidence of atopy in patients with NP may range from 10-96.5% [21,23,33,53]. Although patients often show aeroallergen-positive prick-tests, the potential role of IgE-mediated hypersensitivity in the development of NP is the subject of debate. Some authors have suggested the existence of a local allergic response with the presence of specific IgE in the mucosa, but not in peripheral blood [54].

Although there is no proof of the existence of a clear causal relationship between allergy and NP, respiratory allergy (rhinitis and/or asthma) in these patients is a factor in many cases associated to serious forms of NP, and contributes to the worsening of patient quality of life. A correct diagnosis and treatment would thus be needed in order to improve the chances for successful management of NP [55].

2.3.6. Innate immunity

One of the most recently proposed physiopathological mechanisms is the existence of an innate immune defect that could favor microbial colonization and the development of an abnormal immune response [56]. The main components of innate immunity include: human antimicrobial peptides (AMPs), such as the defensins and cathelicidins; pathogen recognizing receptors such as the TOLL (toll-like receptors, TLR); and the alternative pathway of the complement system. Patients presenting CRS with NP exhibit a lesser expression of innate immunity genes (including TLR-9 and human beta-defensin-2) than patients with CRS without NP and healthy controls [56].

Knowledge of the defensive functions of the AMPs, which attack key structures of the microorganism that prove very difficult to replace, opens the door towards new treatments involving lesser development of resistances than when chemical antibiotics are used [57-59].

2.3.7. IgE and Staphylococcus aureus

Staphylococcus aureus frequently colonizes the nasal mucosa of the middle meatus in patients with NP, and may release superantigens that interfere with the activities of the local B and T cells [60]. The highest colonization rates are usually found in patients with NP and asthma or NP and NSAID intolerance [61]. A characteristic finding in NP is the local synthesis of multiclonal IgE and specific IgE against *Staphylococcus aureus* enterotoxins (sIgE-SAE) [54,62-65], which are related to the degree of eosinophilic inflammation [54].

The classical SAEs can act as conventional allergens and as superantigens, particularly toxic shock syndrome toxin (TSST)-1 and staphylococcal protein A (SPA). Superantigens are able to directly activate the T cells, binding to the variable beta-chain of the T cell receptor (TCR) – triggering a strong primary response, with the polyclonal activation of lymphocytes and hypergammaglobulinemia far greater than that produced by conventional antigens [66] (Figure 2.3).

Patients with NP who present sIgE-SAE suffer more serious forms of the disease, at both local and systemic level, with increased eosinophilic inflammation and a greater association to asthma and/or NSAID intolerance [54]. This is because the SAEs amplify eosinophilic inflammation in CRS with NP, and can reduce the therapeutic effect of corticosteroids, altering the sensitivity and expression of the glucocorticoid beta-receptors [67]. All this opens the door to new therapeutic approaches, still in the experimental stages, and fundamentally in relation to the serious forms of NP associated to bronchial asthma and in recurrent NP. Among these new treatment options, mention should be made of anti-IL-5 [68], anti-IgE, and antibiotic treatments. The latter have demonstrated their efficacy in severe atopic dermatitis with staphylococcal colonization [69].

2.3.8. Biofilms

Biofilms are complex organizations of bacteria that develop grouped in an exopolysaccharide matrix adhered to a live or inert surface. Biofilms isolate the bacteria from the surrounding medium, facilitate communication between bacteria, reduce accessibility on the part of the host immune system, and prevent phagocytosis. In addition, biofilm bacteria

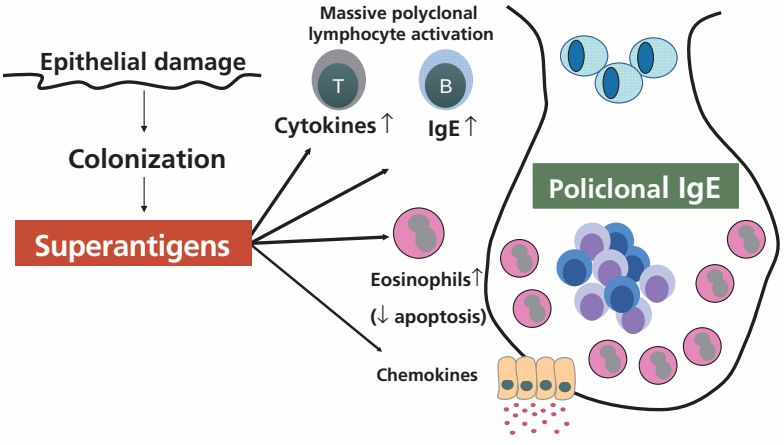


Figure 2.3. Role of the superantigens of *Staphylococcus aureus* in NP.

are extraordinarily resistant to antibiotic action, since such drugs can only penetrate the outermost layers of the film. Biofilms are implicated in many human infections, and there is growing evidence of their role in CRS [70].

Many common pathogenic bacteria colonize the damaged mucosal surface in CRS and NP, forming biofilms. These are not primary etiological factors in NP, though they do contribute

significantly by further incrementing the inflammatory component [71]. Clinically, cases of NP with biofilms are correlated to more serious forms of the disorder and to a poorer postoperative course [72].

2.3.9. Fungi

The role of fungal infection in NP is subject to controversy, since the demonstration of such a role proves difficult – mainly because of the ubiquity of the fungal spores. The purported influence of fungal species is based on the histological similarity between allergic bronchopulmonary aspergillosis and allergic fungal rhinosinusitis. Rhinosinusitis of the maxillary sinuses due to *Aspergillus* was described by Millar in 1981, and Katzenstein in 1983, who described the presence of groups of necrotic eosinophils, Charcot-Leyden crystals and noninvasive fungal hyphae in the sinusal mucin of patients with chronic sinusitis [73,74] – referring to this condition as allergic rhinosinusitis due to *Aspergillus*. Posteriorly, Robson proposed the term "allergic fungal sinusitis" [75].

According to these authors, the condition is mediated by IgE in response to different fungi present in the sinusal eosinophilic mucin. The theory is supported by the observation of specific IgE in cultures. At present, the most widely accepted hypothesis excludes the allergic factor and proposes the term "eosinophilic fungal sinusitis" [76,77], based on the fact that skin testing proves negative in many patients presenting CRS with fungi shown to be present in nasal mucus. In fact, the results of the quantification of antifungal specific IgE do not differ between patients with CRS and healthy individuals. Attempts have been made to explain this contradiction in terms of the importance of local IgE in the absence of systemic IgE [78].

2.3.10. Eicosanoids and aspirin-exacerbated respiratory disease (AERD)

One of the most serious, recurrent and treatment-resistant forms of NP is the condition recently referred to as aspirin-exacerbated respiratory disease (AERD), which combines CRS (with NP in 80-90% of the cases), NSAID cross-intolerance and asthma, and which was previously known as the ASA triad [79,80]. Patients with NP and NSAID intolerance show intense tissue eosinophil infiltration with very high levels of eosinophil cationic protein (ECP) [44,81] and cytokines related to eosinophil activation and survival (IL-5, GM-CSF, RANTES, eotaxin) [82-84]. Deficient local production of cyclooxygenase-2 (COX-2) and prostaglandin E_2 (PGE_2) appears to be the factor triggering the development of severe eosinophilic inflammation mainly in patients with NSAID intolerance [85-88].

The production of cysteinyl leukotrienes (cysLT) is correlated to the degree of tissue eosinophilia and the production of ECP, but not to NSAID intolerance [51]; some studies have reported no differences in the release of leukotriene C_4 (LTC_4) or in the production of either COX or lipoxygenases (LOs) between patients with and without NSAID cross-intolerance [88,89], while other studies have detected increments in 5-LO and LTC_4-synthase, cysLT and $cysLT_1$ receptors in the tissues of patients with NP and NSAID intolerance [90-93].

2.3.11. Nitric oxide

The epithelium of patients with NP shows an increased expression of inducible nitric oxide synthase (iNOS), particularly in subjects with asthma and AERD [94]. The role of nitric oxide in the development of NP and its possible diagnostic utility are currently being investigated [95].

2.3.12. Genetic factors

The alterations in eicosanoid metabolism found in patients with ASA triad appear to indicate that there may be a genetic basis in some cases of NP. Knowledge of the possible genetic origin of NP is still limited, though there is some evidence that certain cases may have a genetic origin [42]. In effect, family history is present in some patients (see the chapter on epidemiology). In addition, genetic studies have revealed correlations between certain HLA alleles and NP. In this context, in patients with HLA-DR7-DQA1*0201 and HLA-DR7-DQB1*0202, the incidence of NP is three times greater than in the general population [40]. Also of note is the existence of a racial factor, since the intense tissue eosinophilia of NP is typical of Caucasians, while in China NP is not eosinophilic [96].

Studies made with microarrays, which monitor the simultaneous expression of thousands of genes, have revealed altered genetic expressions of many cell processes in patients with NP. The genes identified as potentially pathogenic can be classified into four groups on the basis of their biological roles: a) genes implicated in growth and development; b) genes encoding for cytokines; c) genes with immune functions; and d) genes with other unknown functions [97]. In the future these alterations probably will prove fundamental for the new management strategies in patients with NP.

2.4. Secondary nasal polyps. Nasal polyps in cystic fibrosis

Different multisystemic diseases and some nasosinusal disorders can express as NP. The study of the inflammatory infiltrate of the polyp is essential for establishing a differential diagnosis and for clarifying the underlying pathogenesis [98] (Table 2.3).

With the exception of antrochoanal or Killian's polyp, which is an idiopathic unilateral form of polyp but with a neutrophilic inflammatory infiltrate, unilateral polyps are secondary lesions and constitute satellite conditions to other nasal pathologies – the clinically most relevant cases being those associated to benign and malignant nasosinusal tumors.

Bilateral non-eosinophilic polyps can manifest in the following conditions:

A. Cystic fibrosis (CF): The differential diagnosis is considered in cases with NP in childhood. Twenty percent of all patients with CF develop NP, though in these subjects the lesions are different from those of patients who only present NP. In effect, in CF the polyps show a predominantly neutrophilic

Table 2.3. Differential diagnosis of NP according to the predominant inflammatory infiltrate

Eosinophil	Neutrophil	Others
Allergic rhinitis	Bacteria	Viruses
Fungal allergic sinusitis	PCD	Granulomatous diseases (Wegener, TBC, sarcoidosis)
Eosinophilic CRS	Cystic fibrosis	Vasculitis (lupus, Churg-Strauss)
Non-allergic rhinitis	Foreign body	Pemphigoid
Nasal polyposis		
ASA triad		

Abbreviations: CRS, chronic rhinosinusitis; PCD, primary ciliary dyskinesia.

infiltration, with an increase in interleukin expression: IL-8 and particularly IL-9, which appears to be responsible for the over-production of mucus. Clinically, mucopyocele and pseudomucocele of the maxillary sinus are common.

B. Primary ciliary dyskinesia: In this disorder the polyps are secondary to chronic infection, with a predominance of neutrophils, in patients with bronchiectasis, male sterility and (in 50% of the cases) situs inversus.

C. Inflammatory granulomatous diseases: Wegener's syndrome, sarcoidosis, Churg-Strauss syndrome. These lesions manifest as crusted and destructive rhinosinusitis. The inflammatory infiltrate differs in each etiological context, though the clinical course and complementary tests will establish the diagnosis.

D. Infectious granulomatous diseases: Fungal or mycobacterial infections, rhinoscleroma. The diagnosis in this case is established by the clinical picture and the histopathological findings.

E. Neoplastic granulomatous diseases: Nasal T-NK lymphoma. Progression of the disease and the biopsy findings are key elements in the differential diagnosis.

Key points

- NP is a bilateral, idiopathic and eosinophilic clinical form of CRS.
- Histopathologically, NP is characterized by a generally ciliary epithelium, a thickened basal membrane and lax stromal component, with few vascular and glandular structures, and the absence of neurological elements and connective tissue.
- The presence of an intense inflammatory infiltrate in the stromal component, with a predominance of eosinophils, is a characteristic finding.
- Eosinophilic NP is often associated to non-allergic asthma and NSAID intolerance.
- Infection is not a primary etiological factor in NP. However, in the form of biofilms, infection does significantly contribute to increase inflammation and the severity of the process.
- Different multisystemic diseases and some nasosinusal disorders can express as NP.
- Studies made with microarrays, which monitor the simultaneous expression of thousands of genes, have revealed altered genetic expressions of many cell processes in patients with NP.
- NP is an inflammatory disorder of unknown etiology and with a multifactorial physiopathology.
- Studies of the altered mucin patterns and inflammatory mediators allows us to differentiate among CRS, NP and CF.
- Although there is no evidence of a relationship between allergy and NP, atopy is sometimes associated to severe forms of NP.
- The existence of an innate immune defect that could favor microbial colonization and the development of an abnormal immune response has been described in NP. Such knowledge has paved the way towards the investigation of new antimicrobial treatments.
- One of the most important physiopathological mechanisms involves the production of polyclonal IgE antibodies against enterotoxins of *Staphylococcus aureus*, associated to the more severe forms of NP.

3. Clinical aspects and quality of life considerations

3.1 Clinical manifestations

The clinical history is essential, since the main symptom described by the patient will help define the problem, assess its severity and impact upon quality of life (QoL), as well as contribute to establish the best possible treatment and patient response to therapy, and to identify associated disorders. Of these manifestations, the most important are asthma and NSAID intolerance, as discussed in more detail in chapters 2 and 5. Episodes of acute rhinosinusitis, otitis media and adenoid hypertrophy may also be associated.

3.2 Evaluation of symptoms

In the last decade attention has been focused not only on the clinical manifestations but also on the effects upon patient quality of life [99, 100].

The symptoms are evaluated based on two characteristics: their intensity and duration. QoL studies have shown symptoms duration to have a greater impact than symptoms intensity. Intensity in turn can be evaluated using semiquantitative scales that assign more or less arbitrary values to each symptom (rhinorrhea, sneezing, nasal obstruction or plugging), or to all the symptoms globally (e.g., 0: no symptoms, 1: mild symptoms, 2: moderate symptoms that do not interfere with daily life or leisure activities, and 3: intense symptoms that affect daily life activities and/or sleep).

A visual analog scale (VAS) can also be used. With scales of this kind, the patient rates his or her discomfort globally or in reference to each individual symptom, based on a line measuring from 0 to 10 cm, where 0 = no discomfort and 10 = worst discomfort imaginable. Based on the scores obtained, the disorder can be classified as mild (VAS 0-3), moderate (VAS > 3-7) or severe (VAS > 7-10) [1].

Attempts have been made to evaluate the relevance of the symptoms of CRS/NP with a view to differentiating between different degrees of the disease, assessing the validity of the scores in one same patient (intra-individual and longitudinal) and between patients (inter-individual and cross-sectional). Recently, the development of quality of life questionnaires has provided more specific and valid instruments. Such tools can be used to assess either general health [101] or the specific impact of a given disease [102].

3.3 Nasal obstruction

Nasal obstruction is a subjective sensation dependent not only on the size of the nasal passages but also on the nasal epithelial perception of cold when the air flows during inspiration. It is therefore a subjective parameter inherent to each individual patient. On interpreting patient nasal obstruction/congestion, the condition can be found to range from genuine mechanical airflow obstruction to fullness sensation in the middle region of the face. Congestion sensation is not always correlated to the different objective measures at our disposal (acoustic rhinoscopy (AR), magnetic resonance imaging (MRI), peak nasal inspiratory flow (PNIF)). The use of a visual analog scale (VAS) is useful for determining changes in one same individual over short periods of time, for example. Evaluation is moreover made of the response to vasoconstrictor use, or of the variations resulting from nasal provocations. Nasal obstruction in CRS with NP characteristically varies little or remains constant, and in some cases a valve sensation is experienced, since the polyp can move during inspiration and expiration.

In general, the subjective sensation of nasal obstruction and the MRI and PNIF findings show good correlation according to different studies involving healthy subjects and patients with structural alterations, nasal hyperresponsiveness and infectious rhinitis [103]. No such correlation has been found in other studies, however [104, 105] (see chapter 4, section 4.2.2).

3.4 Rhinorrhea

Rhinorrhea or runny nose in CRS with NP may be of variable consistency and color, in contrast to allergic rhinitis, where the secretions tend to be watery. Attempts have been made to objectively measure the amount secreted, using paper discs. These discs are weighed before use and are then counted and again weighed after use. There are no data correlating these measurements to subjective rhinorrhea perception.

3.5 Loss of smell

Nasal polyposis is associated to fluctuations in smell sensation that may be due to mucus obstruction of the olfactory

mucosa (loss of conduction) and/or inflammatory alterations of the latter secondary to NP or its treatment (e.g., repeated surgical procedures). The subjective scoring of smell is often used for evaluation purposes.

A number of tests are available for the study of smell (olfactometry). All of them determine whether a given smell is identified, and also the perception threshold. The subject is asked not only to indicate whether he or she detects the smell, but also which of two or more stimuli appears most intense. Such "forced" responses have been shown to afford lower detection thresholds, and are more reproducible.

A number of commercial kits can be used that determine the threshold using concentrations of a substance that are duplicated, and odorless substances or blanks (Smell Threshold test®). Other tests are designed to allow patients to identify a series of smells at concentrations that are above the detection threshold. Of these, the most popular is the UPSIT or 40 Odor University of Pennsylvania Smell Identification Test. The patient perforates a microcapsule with a given odor, and is instructed to identify it from among four different possibilities. The UPSIT can measure each nostril individually, and offers very good reproducibility [106]. In Spain the Barcelona Smell Test-24 (BAST-24) has been validated, consisting of 24 odors, with scores for detection, identification and olfactory-forced selection [107].

It has been seen that the subjective scores are significantly correlated to the objective olfactory threshold and to the results of the qualitative tests made in normal subjects and in individuals with rhinosinusitis and other disorders [107-109].

3.6 Facial pain pressure

In patients with suspected acute maxillary rhinosinusitis, facial or dental pain has been found to be indicative of the possible presence of fluid – this correlation having been validated by means of maxillary sinus aspiration tests [110] or paranasal sinus X-rays [111]. In patients with presumed acute or chronic infection, the location of the facial pain has been shown to be weakly correlated to the pathological computed tomography (CT) findings of the affected paranasal sinus [112].

3.7 Severity assessment

The evaluation of severity can be made based on an individualized or global symptoms score of the disease. Both approaches are commonly used, though according to an old validation study on the severity of rhinitis, the scores that indicate the course of each of the symptoms should not be combined in the form of a global index; rather, use should be made of the global evaluation of the disease of the patient [113]. Quality of life studies have yielded validated questionnaires that measure the impact of the global symptoms of CRS upon daily life [114]. There are no specific questionnaires for evaluating QoL in patients with NP; rather, specific questionnaires for CRS are used. Two types of health-related quality of life (HRQoL) questionnaires are available: specific questionnaires and generic questionnaires.

3.8 Specific quality of life questionnaires

These are instruments that evaluate quality of life in relation to a concrete disease. Several questionnaires are presently available for application to CRS (as has been mentioned, there are no specific QoL questionnaires for NP):

1. Rhinosinusitis Disability Index (RSDI). This instrument comprises 30 items addressing the nasal and sinus symptoms and their impact in terms of the limitation of daily life activities. Robinson et al. have shown that patients with CRS and asthma, with or without NSAID intolerance, experience an improvement in QoL after endoscopic sinus surgery (ESS) [115].

2.Rhinosinusitis outcome measure (RSOM-31). This instrument comprises 31 items grouped into 7 domains that assess symptoms severity and their importance for the patient. It consists of a magnitude scale and an importance scale. Ebbens et al. studied the effect of treatment of CRS (with and without polyps) with intranasal amphotericin B versus placebo. The authors found QoL as evidenced by the RSOM-31 to be similar in the two groups, with no differences after treatment [116].

3. Sinonasal Outcome Test 20 (SNOT-20). The SNOT-20 is a modification of the RSOM comprising 20 items addressing nasosinusal symptoms and general health. The SNOT-20 comprises two summaries: a) a total summarizing score of the 20 items, and b) an importance scale that includes those items identified as being important. The disadvantage of this questionnaire is that it does not evaluate nasal obstruction or loss of smell. In a randomized study, Ragab et al. [117] compared medical treatment (erythromycin for 10 weeks) versus surgery in patients with CRS. The authors concluded that both treatments improve patient QoL as assessed with the SNOT-20. Validation has been made of the SNOT-22, which is the SNOT-20 with two additional items for evaluating nasal obstruction and smell [118].

4. Sinonasal Outcome Test 16 (SNOT-16). This instrument consists of 16 items that evaluate symptoms severity and the emotional and social consequences of chronic rhinosinusitis. Briggs et al. [119] studied the effects of smoking on the results of nasal endoscopic surgery, and found QoL as assessed with the SNOT-16 to be poorer among the smokers.

5. Chronic Sinusitis Survey (CSS). This instrument consists of 6 items divided into two sections: A) Symptoms section, encompassing pain or facial pressure, nasal congestion or nasal breathing difficulty, and rhinorrhea; B) Medication section, encompassing oral treatment with antibiotics or intranasal treatment. Gliklich and Metson investigated QoL among patients before surgery, showing the CSS to be valid and reliable in assessing QoL in patients with CRS [120].

6. RhinoQoL. This is a specific instrument that addresses the frequency of symptoms, discomfort and impact scales in the form of a 17-item questionnaire. Atlas et al. [121] studied patients with CRS after surgery, and found internal consistency to be high on the symptoms impact scale. The frequency of symptoms, and particularly the discomfort scales showed poorer internal consistency. The RhinoQoL showed excellent sensitivity to change.

3.9 Generic quality of life questionnaires

Generic quality of life questionnaires are useful as health profiles, are relatively short, and offer established reliability and validity guarantees. The advantage of such generic instruments is the possibility of comparing NP with different chronic illnesses. Their main disadvantage is that they may contain components that are not relevant to NP, or which may not be sensitive to change. Such instruments have frequently been used for the evaluation of QoL in NP.

1. Short Form-36 Health Survey (SF-36). The SF-36 is regarded as the most widely used generic questionnaire in NP. Based on 36 components, this instrument aims to measure 8 generic health concepts. The 8 domains generate two summarizing measures:

• Physical health summarizing component: this comprises the components Physical function, Physical role, Bodily pain and General health.

• Mental health summarizing component: this comprises the components Vitality, Social function, Emotional role and Mental health.

Radenne et al. [122] demonstrated a significant reduction in all the SF-36 dimensions on comparing patients with NP versus a control group. In another study of 130 patients with NP, the authors found QoL among the subjects with severe NP to be poorer than in the Spanish general population for all the domains of the SF-36 except Physical function. Patients with NP and asthma have poorer QoL than the patients without asthma, and NSAID intolerance also exerts a negative effect upon QoL [123]. Alobid et al. showed the presence of atopy in these patients to worsen QoL [123]. Treatment with short course oral corticosteroids followed by intranasal corticosteroids improved the quality of life of the patients with NP, reaching the mean levels recorded for the Spanish general population. Both medical treatment with corticosteroids (oral and intranasal) and endoscopic sinus surgery (ESS) improved QoL [99].

Key points

- The evaluation of symptoms (intensity and duration) is essential for assessing severity, the impact upon QoL, and for defining the best possible treatment.
- Quality of life studies have yielded validated questionnaires that measure the impact of the global symptoms of CRS upon daily life.
- There are no specific QoL questionnaires for NP. Instead, CRS questionnaires are used.
- Generic questionnaires are useful as health profiles, are relatively short, and offer established reliability and validity guarantees. The advantage of such generic instruments is the possibility of comparing NP with different chronic illnesses.

4. Examination and diagnosis

Nasal polyposis (NP) is a chronic inflammatory disease affecting the nasal mucosa and paranasal sinuses, and which leads to the formation of bilateral polyps of edematous and/or fibrous appearance. The clinical exploration and diagnostic tests should evidence these two basic aspects of the disease (chronic inflammation and polyps), establishing an evaluation of the severity of the condition, its course and prognosis. These aspects in turn serve to define the most appropriate approach to treatment.

4.1. Examination

4.1.1. Clinical diagnosis of NP

A clinical definition of CRS has been established, based on the presence of main symptoms (nasal obstruction, altered smell, anterior and/or posterior rhinorrhea, and pain or facial pressure) and secondary symptoms (sore throat, dysphonia, cough, malaise, fever, dental pain, halitosis or pain/discomfort in the ears) [124]. The EP3OS 2007 consensus document, warranted by the European Academy of Allergy and Clinical Immunology (EAACI) [125], proposes a clinical definition of CRS (including NP) as inflammation of the nose and paranasal sinuses characterized by the presence of two or more symptoms, one of which must be nasal blockage/obstruction/congestion or rhinorrhea (anterior/posterior/posterior nasal dribbling):

- with or without facial pressure/pain
- with or without loss of smell or diminished smell, together with
- nasal endoscopic signs of:
  - nasal polyps and/or
  - mucopurulent rhinorrhea mainly in the middle meatus region and/or mucosal edema / obstruction mainly in the middle meatus region, and/or:
- CT changes (mucosal changes affecting the osteomeatal complex and/or paranasal sinuses).

Exclusively basing the diagnosis on the presence of symptoms has been shown to be imprecise, since it yields a false diagnosis of CRS in a large percentage of patients with these symptoms (false-positive cases) [126, 127].

Adding endoscopic evaluation, visualizing the polyps within the nasal passages, improves specificity and the positive and negative predictive values, and increased the chances for correct diagnosis four-fold [128].

The most frequent symptoms in patients with NP have been shown to be nasal obstruction, smell alterations, rhinorrhea (anterior or posterior) and facial pressure or pain, in this order [129], though only smell alterations have been significantly correlated to a precise diagnosis of CRS [130]. It also has been shown that the degree of smell disturbance is well correlated to the severity of CRS as assessed by CT or nasal endoscopy, though not to QoL as determined by specific instruments [131].

A study analyzing nasal mucosal biopsies has revealed a correlation between smell alteration and the degree of inflammation of the nasal mucosa, though no correlation has been shown between the degree of inflammation and QoL [132].

4.1.2. Examination of the nasal passages

Anterior rhinoscopic exploration of the nasal passages may be useful for visualizing NP (employing a nasal speculum and light source), though nasal endoscopy is the most effective technique for correct visualization of the entire nasal passages – since anterior rhinoscopy is only able to visualize approximately the anterior third of the passages. In performing nasal endoscopy, use can be made of a rigid endoscope or a flexible fibroscope, though the imaging quality of the latter is not as good. Exploration of the nasal passages should include the morphological features, visualizing the turbinates, septum and choanae. The meatuses are particularly important, especially the middle meatus.

A number of semiquantitative systems have been developed to explore the nasal passages, assigning scores to the clinical findings of NP, edema, rhinorrhea and ulcerations or crusts (for postoperative exploration), though they have not been adequately validated [125].

The size and extent of NP has been shown to be an important prognostic factor in reference to the degree of recurrence of the disease [133]; evaluation of this aspect therefore appears important in establishing the clinical diagnosis of NP. Several NP size and extent grading scales have been proposed and evaluated for reproducibility and inter-individual variability [134]. The grading system proposed by Lildholdt [135] has been recommended as one of the best methods for evaluating

the evolution of the size of the nasal polyps (Table 4.1). In patients subjected to ESS due to CRS, nasal endoscopy was not seen to correlate well to the symptoms scores [136].

Table 4.1. Nasal endoscopic evaluation of NP according to Lildholt et al. [135]

Grade 0	No polyps
Grade 1	Small polyps not extending beyond the middle turbinate
Grade 2	Polyps between the cranial and caudal margins of the lower turbinate
Grade 3	Polyps extending beyond the lower margin of the lower turbinate

4.1.3. Assessment of the clinical severity of NP

The evaluation of the severity of a disease has two fundamental aims: to establish a prognosis and to implement an adequate management strategy.

The EP^{3}OS 2007 consensus document [125] proposed three grades of severity: mild, moderate and severe, according to subjective patient evaluation based on a VAS, in response to the question: "How would you describe the discomfort caused by your rhinosinusitis symptoms?" (scores of 0-3 being considered mild, > 3-7 moderate, and > 7 severe). The use of the VAS has been validated in the evaluation of the severity of CRS [137].

Other proposals for the evaluation of clinical severity have not been sufficiently validated, though they have been used in clinical research (subjective rating from 0-100 according to Lund [138] and a symptoms score).

Evaluation of the severity or degree of involvement of NP can also be made using generic or specific QoL questionnaires. A systematic review analyzing specific instruments for evaluating QoL in patients with CRS found that of the examined tools, the RSOM-31 and RHINOQoL met the validation requirements and obtained the highest methodological quality scores, and were thus the instruments preferred by the authors [139]. A detailed review of the different QoL questionnaires in CRS and NP has been published by Alobid et al. [118].

No specific method has been designed or validated for assessing clinical severity in NP. A survey conducted in the United Kingdom with 1459 patients showed subjective self-assessed health using a specific questionnaire (SNOT-22) to be poorer in patients with CRS without NP than in those with NP – and this was found to be the case both before and after surgery. However, the disease recurrence rate and the need for reinterventions were greater among the patients with NP [140]. This may indicate that the symptoms alone are not sufficient in evaluating the severity of NP, and that endoscopic evaluation offers important prognostic utility that should be taken into account.

The clinical severity of NP could be evaluated including subjective patient assessment based on the VAS and combining the clinical evaluation as established from nasal endoscopy with a validated scale such as that developed by Lildholdt, assigning a numerical value to the combination. Use could be made of the mean value of severity self-assessment derived from the VAS (scoring from 0-10) and the value of multiplying by three the nasal endoscopy score according to Lildholdt (scored from 0-9). Empirical cutoff points could be established for severity (until validation is made), similar to those proposed in the EP^{3}OS 2007 consensus document (mild 0-3, moderate 4-7 and severe 7-9.5). This proposed combination scale for assessing severity and its empirically defined cutoff points require due validation.

4.2. Diagnosis

Complementary diagnostic tests aim to consolidate the diagnosis, evaluate the extent of the disease and complete assessment of the severity of the condition.

4.2.1. Imaging

Plain X-rays: A plain X-ray study of the paranasal sinuses has been shown to be of little help in diagnosing CRS [141].

Computed tomography (CT): CT is the imaging technique recommended by most clinical guides on the management of CRS. The sensitivity and specificity of CT has been evaluated using the scoring system of Lund-Mackay [138] (Table 4.2), concluding that this technique offers good sensitivity with specificity superior to that of the rest of the explorations in diagnosing CRS, taking biopsy as the gold standard [142].

At CT, patients with NP yield significantly higher scores (according to the Lund-Mackay system) than patients with CRS but without NP [143]. However, the specificity of CT does not appear to suffice to differentiate CRS with NP from those cases without NP - nasal endoscopy in this sense probably being better for detecting nasal polyps [144]. It is important to mention that CT yields pathological findings in a large proportion of the healthy population [145].

CT evaluated using the Lund-Mackay system shows low correlation to the VAS scores for CRS symptoms, moderate correlation to the endoscopy findings, and no correlation to QoL as assessed by means of specific questionnaires [146].

It has been found that CT-based staging of CRS is of no utility as a factor of good or poor prognosis in relation to the clinical course of the disease following endoscopic sinus

Table 4.2. Lund and Mackay scale for the computed tomographic (CT) scoring of NP [138]

Affected sinus	Left	Right
Maxillary*	0-1-2	0-1-2
Anterior ethmoidal*	0-1-2	0-1-2
Posterior ethmoidal*	0-1-2	0-1-2
Sphenoidal*	0-1-2	0-1-2
Frontal*	0-1-2	0-1-2
Osteomeatal complex**	0 or 2	0 or 2
Total	0 to 12	0 to 12

*No occupation=0; partial occupation=1; full occupation=2
**free=0: occupied=2

surgery (ESS) [147]. These data imply that the usefulness of CT as an etiological diagnostic tool and for the evaluation of disease severity is limited, though there is no doubt regarding its utility in assessing the preoperative extent of the disease and for the follow-up of patients subjected to surgery [148].

The Lund-Mackay scoring system for CT evaluation of the nasal passages and paranasal sinuses has been validated [149] and adopted as standard by the American Academy of Otorhinolaryngology – Head and Neck Surgery.

Magnetic resonance imaging (MRI): MRI exploration of the sinuses has not been regarded as a first choice in the diagnosis of CRS, though recent studies have shown good correlation to CT [150], with the advantages of involving no patient irradiation and of being very useful in the differential diagnosis of tumors of the nasal passages and paranasal sinuses [151]. For this reason MRI could be regarded as a first choice technique for the initial evaluation of NP, though prospective studies are needed to determine its diagnostic yield and efficiency [152] (Figure 4.1).

4.2.2. Nasal function

The functions of the nasal passages include the conditioning of inspired air and smell. Both functions have been shown to be altered in NP. Altered nasal flow (nasal obstruction being the most frequent complaint of patients with NP) causes a decrease in nasal breathing, preventing the latter from performing its functions [129, 153]. Smell is affected in a very large percentage of patients with NP, and such alteration often occurs in the very early stages, even before evidence is obtained from the imaging tests [154].

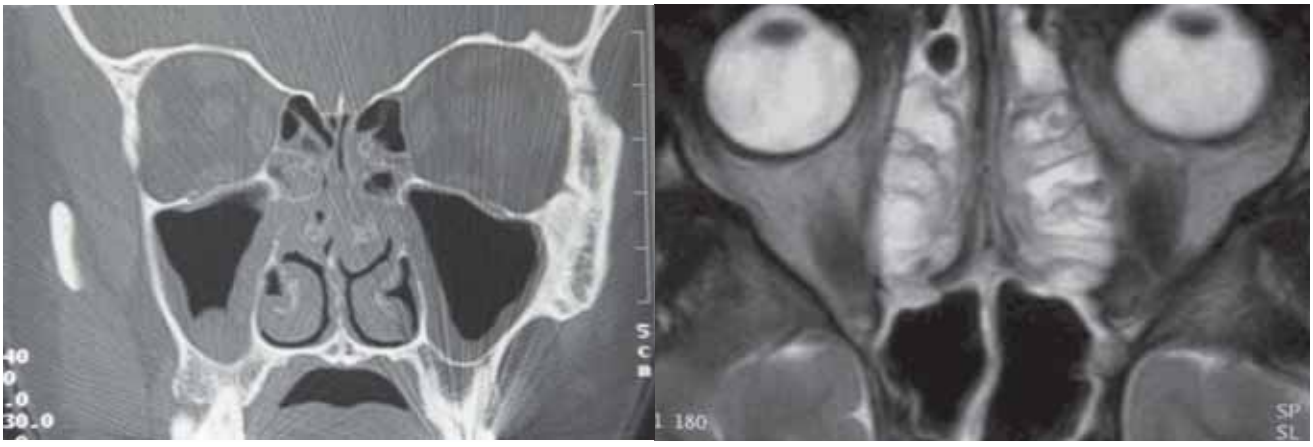
Tests for evaluating nasal obstruction: Nasal obstruction is a frequent symptom of NP; as a result, its evaluation is of interest particularly for determining the impact of the disease upon the patient and the response to treatment, though it is not so relevant to the diagnosis of the disorder.

Nasal obstruction can be subjectively evaluated by the patient using a symptoms score and a VAS [155]. It has been shown that nasal obstruction rated by means of a VAS is very significantly associated to measures of volume and areas of the nasal cavity (compared with acoustic rhinometry) and to nasal airflow (compared with peak nasal inspiratory flow [PNIF] measuring devices) [156]. The VAS is recommended as a useful method for evaluating the presence (weak recommendation) and severity (strong recommendation) of nasal obstruction, as well as for follow-up and the assessment of treatment response (strong recommendation) [157].

The objective evaluation of nasal obstruction may be important for demonstrating the existence of nasal respiratory failure, and for appraising the effects of treatment. Different methods are available for assessing nasal obstruction, such as techniques that measure nasal permeability (e.g., active anterior rhinomanometry [RNM and PNIF), and tests that measure nasal geometry (e.g., acoustic rhinometry).

Rhinomanometry (RNM) measures the relationship between pressure and airflow as the air flows through the nasal passages during breathing. RNM is regarded as the standard technique for evaluating nasal resistance and permeability. It is a very physiological procedure and requires only minimal collaboration on the part of the patient. The active anterior technique is the most commonly used modality in RNM. While a certain association has been shown between RNM and subjective nasal obstruction / congestion sensation, the degree of correlation is not good [158]. This may be explained by the fact that the nasal resistance values are dependent fundamentally upon the valvular area, while subjective nasal obstruction / congestion sensation could depend on other areas such as the ethmoidal region. The international standardization of RNM techniques has recently been revised [158]. RNM is firmly recommended for evaluating the presence and severity of nasal obstruction [157].

Peak nasal inspiratory flow (PNIF) in turn is a simple and low cost technique that has been adequately validated [159] and has been shown to be well correlated to nasal resistance as determined by RNM [158] and to subjective nasal obstruction



Coronal projection CT view | Magnetic resonance imaging view

Figure 4.1. CT and MRI images in NP.

sensation, though its variability is greater than in the case of RNM [160, 161]. PNIF is likewise firmly recommended for evaluating the presence and severity of nasal obstruction [157].

Acoustic rhinometry (AR) evaluates areas and volumes of the nasal cavity, based on principles similar to those of ultrasound. AR has been shown to offer good correlation to both CT and MRI – such correlation in turn increasing after decongestion with topical nasal vasoconstrictors [158]. This is a simple technique that does not require patient cooperation, and is very sensitive to change. As a result, it could be used for the objective quantification of the degree of nasal passage occupation before and after medical and/or surgical treatments. The results obtained with the nasal provocation or nasal vasoconstriction tests are comparable for AR, RNM and PNIF [158], though one study concluded that AR is more sensitive than RNM in detecting changes at nasal provocation testing [162]. Other studies have concluded that this does not happen in subjects with perennial rhinitis [163], or that PNIF may be more sensitive than AR [164]. AR has also been evaluated as a diagnostic technique in application to NP, being able to precisely measure the geometry of the nasal cavity in its anterior region [165]. It has demonstrated its reliability in evaluating the anterior portion of the nasal passages [166]. AR is recommended for evaluating the presence (strong recommendation) and severity (weak recommendation) of nasal obstruction [157]. RNM and PNIF in turn are better correlated to subjective nasal obstruction sensation than nasal cavity volume assessment with AR [103].

Olfactory tests: The subjective evaluation of smell is well correlated to changes in smell or olfactory threshold and qualitative tests in healthy individuals and in patients with rhinosinusitis and other disorders [167]. Smell alterations can be evaluated with a visual analog scale (VAS), since they are well correlated to the objective tests used to measure smell [168].

Many tests have been developed for evaluating smell alterations, though no standard test has been established to date. In Spain, a test (BAST-24) has been developed and validated, offering good precision in detecting smell alterations [107]. In an attempt to unify the smell tests, a multicultural instrument has been developed to assess olfactory capacity in the European population [169].

Objective tests for the evaluation of smell pose the usual complications of complexity and their time-consuming nature. Research is being carried out to develop simple and rapid techniques with a good cost / effectiveness performance and which maintain validity in detecting smell disorders. Recently a modification of the Connecticut olfactory test has been developed in Spain that complies with these requirements [170].

Objective tests are being developed, such as cortical evoked potentials involving stimulation with a odorous substance, functional MRI and functional positron emission tomography (PET) – though these methods lack an adequate cost / effectiveness ratio [171].

4.2.3. Histopathological diagnosis techniques

Nasal polyposis presents differential histological features with respect to the rest of CRS subtypes and tumors of the nasal passages. Eosinophil infiltration and tissue edema have been shown to be very constant findings in NP, and are correlated to the clinical stage of the disease [172]. An increased degree of eosinophil infiltration, thinning of the basal membrane and goblet cell hyperplasia are related to the more serious forms of the disorder, characterized by coexistence with asthma [173]. Intense eosinophilia together with asthma and NSAID intolerance imply a 4.5-fold greater recurrence risk after surgery [174].

It may be advisable to conduct a histopathological study of tissue samples through brushing, nasal lavage or biopsy, with the purpose of establishing a firm differential diagnosis and adequately evaluating the prognosis of the disease (Figure 4.2).

In relation to the differential diagnosis of tumors of the nasal cavity, the combination of an endoscopy-guided incisional biopsy and an imaging study has been shown to offer very high sensitivity and specificity, while the clinical symptoms alone have very little diagnostic value [175].

4.2.4. Laboratory tests

Although a differential and quite specific inflammatory mediator profile has been described for NP in the western population [47], we have identified no studies describing efficient laboratory test parameters for diagnosing the disease.

4.2.5. Sinonasal inflammation: nNO

Inflammation of the nasal mucosa and paranasal sinuses can be measured using devices that determine nasal nitric oxide (nNO). Recommendations have been published, based on studies that have validated different measurement methods [176].

Nasal nitric oxide has been shown to be decreased (paradoxical reduction) in patients with NP, in comparison with the situation seen in other nasal disorders, and this reduction is inversely correlated to polyp size [177] – though the maximum decrease in nNO is observed in patients with primary ciliary dyskinesia [178].

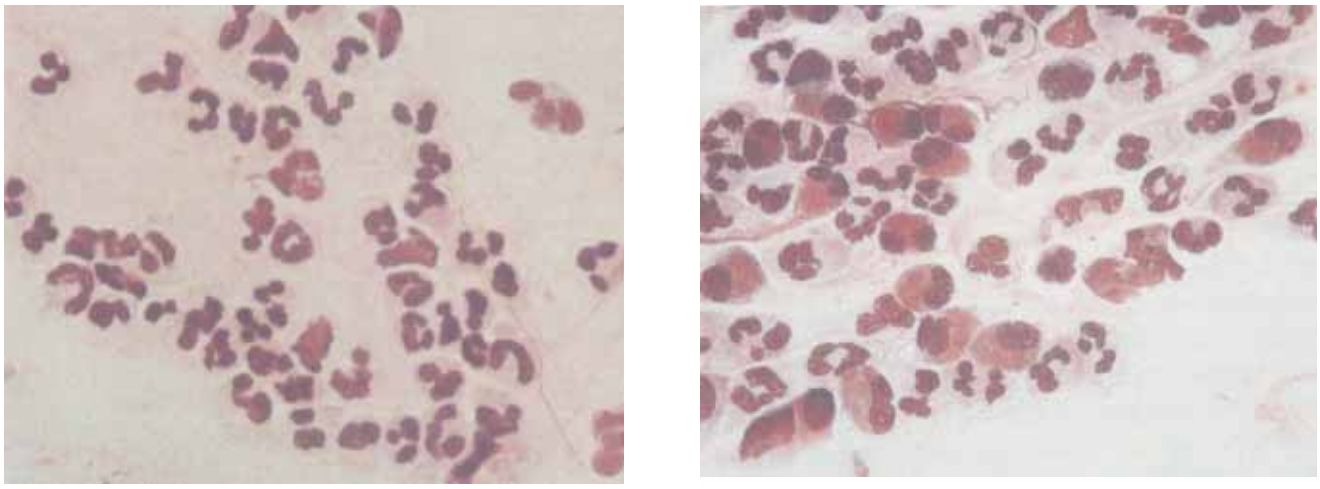
This reduction can be explained by obstruction of the osteomeatal complex caused by NP, blocking nitric oxide release from the paranasal sinuses towards the nasal cavity. An increase in nNO could be used as a marker of the efficacy of medical and/or surgical treatments [179].

A moderate (inverse) correlation has been reported between nNO determination and clinical severity, along with a good correlation to the endoscopic findings in patients with NP, and a good correlation between exhaled bronchial nitric oxide and expiratory flow limitation. Both nitric oxide parameters responded well to medical treatment during 11 months, an association being observed between spirometric improvement and the clinical severity and endoscopic parameters [180].

4.2.6. Complementary tests

Lung function and inflammation

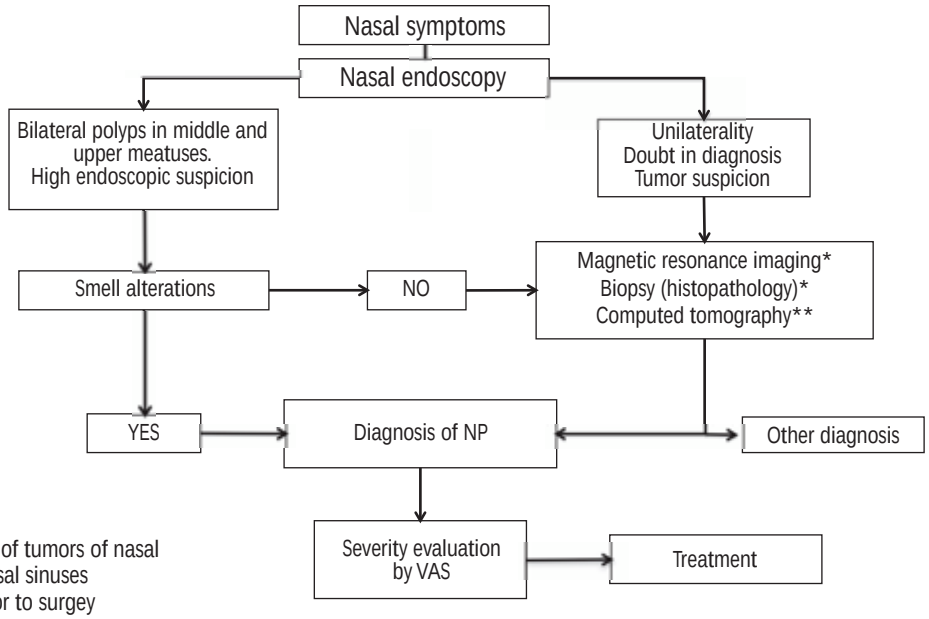
The prevalence of asthma in patients with NP is much higher than in the general population (see the chapter on epidemiology). A study conducted in Spain found 36% of the patients with NP to have asthma, versus only 15.4% of the volunteers without nasosinusal problems [129]. The severity of CRS is greater when NP and asthma coexist [181].



Antroanal polyp: neutrophilia

Nasosinusal polyposis: eosinophilia

Figure 4.2. Nasal cytology in NP and antrochoanal polyps.



* Differential diagnosis of tumors of nasal passages and paranasal sinuses
** Study of spread, prior to surgey

Figure 4.3. Diagnostic algorithm of NP

Spirometry-based evaluation of lung function is necessary in patients with NP, since it has been shown that those subjects who fail to respond to nasal topical corticosteroids develop scantly symptomatic and irreversible, progressive airway obstruction [182].

Lung inflammation can be measured by determining exhaled NO. Nasal polyposis has been shown to be an independent variable associated to exhaled NO elevation in patients with CRS, and the respiratory symptoms are associated to eosinophilic inflammation and exhaled NO elevation only in patients with NP – not in those with other types of CRS [183].

Allergy tests

The prevalence of allergic sensitization in patients with NP varies between 10-96.5%. Studies in Spain have reported prevalences of 63% [23] and 48% [129]. It is advisable to investigate the existence of allergic sensitization in patients with NP, based on skin tests or the determination of specific IgE following the international standards. The treatment of coexisting allergic rhinitis improves the symptoms of patients with NP [184, 185].

Table 4.3. Scientific quality levels for the diagnosis of NP

	Quality level
• Clinical diagnosis based on nasal endoscopy or CT is more precise than diagnosis based only on symptoms	1b
• Alteration in smell is the symptom best correlated to the diagnosis of NP and its severity	2b
• Visualization of bilateral edematous polyps via nasal endoscopy is the most precise complementary technique for the diagnosis of NP	2b
• VAS is useful for evaluating the clinical severity of NP	2b
• NP grading based on the Lidholt scale is useful for evaluating the clinical severity of the disease	2b
• RSOM-31 and RHINOqoL appear to be the best instruments for evaluating QoL in CRS	1a
• CT is poorly correlated to other NP evaluative parameters such as symptoms scores, VAS or QoL	2b
• MRI is a first choice test in the differential diagnosis of NP	4
• VAS, PNIF, rhinomanometry and acoustic rhinomanometry are precise methods for objectively assessing nasal obstruction	1b
• VAS more precisely assesses alterations in smell in patients with rhinosinusitis	2b
• Tests that precisely measure alterations in smell have been validated in the Spanish population	1b
• Cytology- or biopsy-based histophathological diagnosis improves the diagnostic precision and prognostic evaluation of NP compared with other diagnostic techniques	2b
• The determination of nNO is correlated to clinical severity and the endoscopic findings	2b
• Spirometry detects changes in lung function in patients with NP even when asymptomatic	2b
• Exhaled bronchial NO determination is independently associated to eosinophilic inflammation and respiratory synptoms only in patients with NP, and not in patients with other types of CRS	2b
• The tests for diagnosis NSAID intolerance have been standardized	1b
• Nasal endoscopy is well correlated to sinusal occupation as evidenced by CT	1b

Table 4.4. Recommendations and degree of recommendation in the diagnosis of NP

Recommendation	Grade of recommendation
• NP should be diagnosed by nasal endoscopy	1
• Alterations in smell, measured subjectively or assessed by VAS or olfactory testing, can be used as an NP-defining symptom, and for assessing the severity and prognosis of the disease	2
• The severity of NP can be evalated by means of a combined score of severity as determined by VAS and endoscopic grading using the Lildholt scale	2
• CT should be used for the study of disease spread and for the preoperative assessment of NP	2
• MRI can be used as the first choice imaging technique in the initial diagnosis of NP, particularly in establishing a differential diagnosis with other nasosinusal tumors	2
• A histopathological study is recommended in the differential diagnosis and prognostic evaluation of NP	2

Local specific polyclonal IgE production has been reported in a large proportion of patients with NP [186]. In this context, an evaluation is being made of the role of *Staphylococcus aureus* enterotoxins in the pathogenesis of the disease [187] (see chapter 2, section 2.3.7).

Diagnostic tests for NSAID intolerance

The prevalence of NP in patients with asthma and NSAID intolerance can reach 70% [14]. The concurrence of these three conditions gives rise to a particularly serious syndromic

condition, due to its scant response to treatment and high recurrence rate [188], known as the Samter, Widal or ASA triad.

An adequate diagnosis of NSAID intolerance allows the recommendation to avoid such drugs and the use of an alternative list of analgesic / antiinflammatory agents, and in some cases may serve as an indication for evaluating aspirin desensitization.

The diagnosis of NSAID intolerance is based on a clear clinical history of reactions to two or more NSAIDs from different chemical groups and/or an aspirin provocation test. There are different types of provocation tests: oral, bronchial and nasal. The provocation protocols are not without risks, and must be used by trained personnel. Oral testing is the most commonly used procedure, but also implies the greatest risk for patients. Bronchial testing is safer than oral testing.

Provocation testing via the nasal route is the safest and also the fastest option [189]. Nasal provocation is contraindicated in the case of massive NP or in the presence of serious anatomical alterations. During nasal provocation testing, nasal response must be monitored through the clinical manifestations and the objective measurement of nasal obstruction using AR, RNM and/or PNIF. Likewise, bronchial response must be assessed through forced spirometry (preferably) or peak bronchial expiratory flow. If nasal provocation proves negative, oral provocation should be carried out. The protocols for diagnosing NSAID intolerance have recently been reviewed in detail [190].

Figure 4.3 shows a clinical diagnostic algorithm for NP. Table 4.3 in turn shows the scientific quality levels for the diagnosis of NP, while Table 4.4 summarizes the recommendations regarding the diagnostic methods.

Key points

- In diagnosing NP it is essential to visualize the polyps occupying the middle and upper meatal regions of the nasal passages. Nasal endoscopy is the best diagnostic technique in NP.
- Total or partial loss of smell is the symptom best correlated to a precise diagnosis of NP and its severity.
- The defining symptoms of CRS (nasal obstruction, anterior or posterior rhinorrhea, total or partial loss of smell and facial pressure or pain), together with pathological CT findings of the nasal passages and paranasal sinuses, can help in diagnosing NP.
- MRI and biopsy are first-choice complementary tests when establishing a differential diagnosis with other tumors of the nasal passages and paranasal sinuses.
- Nasal obstruction tests (RNM, PNIF and AR) and the determination of nNO can serve as a complement to evaluation of the severity of NP and its response to treatment.
- The lower respiratory tract should be evaluated in all patients diagnosed with NP.
- The presence of allergy to aeroallergens or NSAID intolerance should be investigated in all patients diagnosed with NP.

5. Differential diagnosis and associated diseases

Nasal polyposis (NP) is a bilateral disease process originating in the ethmoidal mucosa that generally affects patients over 40 years of age [42]. Those disorders characterized by the development of bilateral polypoid formations will be analyzed in the section on associated diseases. The differential diagnosis is established with the unilateral NP presentations.

5.1 Differential diagnosis

When polypoid formations are present only in one nasal passage, the possibility of a neoplastic process always must be considered [191]. The differential diagnosis is established from the clinical and histological data. Imaging studies tend to be nonspecific, showing mucosal thickening in the early stages and bone destruction in the more advanced stages or more aggressive presentations. However, in the case of unilateral polyposis of upper nasosinusal origin or of a vascular appearance, the imaging studies should precede the obtainment of a biopsy. Table 5.1 shows the most characteristic presentations.

• ***Antrochoanal or Killian's polyp:*** This is a benign mass of gelatinous appearance and consistency originating in the mucosa of the maxillary sinus and growing from the maxillary ostium towards the nasal passage until the choana is occupied. These polyps are found particularly in younger individuals (mean age 27 years), and both sexes are affected equally. The initial symptom is unilateral nasal obstruction, and the diagnosis is based on nasal endoscopy and computed tomography (CT), which identifies the originating sinus, discards other neoplastic processes such as angiofibroma, and proves essential prior to surgery [192]. The treatment of choice is surgery using the nasosinusal endoscopic technique.

• ***Sphenochoanal and ethmoidochoanal polyps are less frequent than Killian's polyps.*** Sphenochoanal polyps are implanted in the wall of the sphenoidal sinus and migrate through the ostium towards the choana. Ethmoidochoanal polyps in turn occupy the choana and are implanted in the ethmoid sinus.

• ***Anatomical variants such as pneumatization of the middle turbinate or concha bullosa.*** The endoscopic image may be similar to that of an endonasal mass, though the bony consistency upon palpation of the lesion and the CT image confirm the diagnosis [193].

• ***Allergic fungal rhinosinusitis.*** This is a more serious variant of chronic rhinosinusitis (CRS), characterized by the production of eosinophilic mucin containing noninvasive mycotic hyphae. The patients who present this disorder are

Table 5.1. Differential diagnosis of unilateral and obstructive nasal polypoid neoformation, with its most characteristic clinical features

Antrochoanal polyp	• Young individual with soft gelatinous mass originating in maxillary sinus
Fungal allergic sinusitis	• Asthmatic with hyperintense maxillary image in CT scan without contrast
Rhabdomyosarcoma	• Child with ocular involvement
Nasoangiofibroma	• Adolescent male with nosebleed and multilobular vascular mass in cavum
Encephalocele	• Pulsatile mass in roof of nasal passage that increases in size with Valsalva maneuver and can show a fistular trajectory in sagittal MRI view
Inverted papilloma	• Mass of papillary, friable appearance in a male over 40 years of age
Esthesioneuroblastoma	• Polypoid mass in roof of nasal passage, with pain, anosmia, epistaxis and/or cervical adenopathies. MRI reveals cystic images at intracranial margin
Chordoma	• Septal mass with curvilinear and irregular calcifications on CT scan
Melanoma	• Polypoid mass with intense MRI signal in T1 sequencing without contrast, and showing very good gadolinium contrast uptake

characteristically young, immunocompetent, non-diabetic and have a history of allergy. The predominant manifestations are nasal obstruction and rhinorrhea, and uni- or bilateral polypoid formations are observed. A very characteristic finding in CT imaging without contrast is the presence of hyperdense material in the nasosinusal cavities. The condition could be regarded as a presentation mediated by IgE antibodies. Fungal allergic rhinosinusitis can be associated to asthma in 40% of patients [194] (see chapter 2, section 2.3.4).

• ***Chronic sinonasal infections.*** Tuberculosis can manifest with endonasal polypoid formations [195].

• ***Neoplastic processes in childhood:***

– *Rhabdomyosarcoma*. These tumors represent 75% of all pediatric head and neck sarcomas, and 70% are located in the orbital region. Treatment consists of radiotherapy and chemotherapy.

– *Nasoangiofibroma*. This is a benign lesion with a locally aggressive behavior exclusively found in boys or adolescent males. These tumors originate in the proximity of the sphenopalatine foramen and spread to the nasopharynx and rest of the nasal passage. The typical manifestations are nasal obstructions and epistaxis. The lesions are of hard consistency, with a smooth and multilobulated appearance and red/gray color, and bleed easily. The obtainment of a biopsy can cause bleeding that proves difficult to control. CT and magnetic resonance imaging (MRI) confirm the diagnosis and extent of the tumor [193].

– *Encephalocele / meningocele.* These lesions appear in the upper portion of the nose and increase in size with the Valsalva maneuver. They may be pulsatile in nature.

– *Dermoid cyst.* This is a benign and slow-growing tumor of ectodermal origin. It can appear along the margin of the nose, though it is more often found along the midline at any point between the glabella and the nasal columella. Dermoid cysts are usually located subcutaneously, though they are sometimes found in the nasal septum. MRI shows an adipose-type lesion in those cases where the dermoid content predominates, or a liquid-type appearance when the epidermoid content predominates. In addition, if there is a fistular trajectory, it may be seen in the sagittal MRI views [196].

– *Hemangioma.* This is a tumor of mesodermal origin that may be capillary or cavernous, and which does not always exhibit a vascular content.

• ***Neoplastic processes in adults:***

– *Inverted papilloma.* These are benign neoplasms with a more papillary, friable and vascularized appearance than the typical nasal polyp, and emerge from the lateral nasal wall. Inverted papillomas are mainly seen in males between 40-70 years of age. The lesion may have radiological features similar to those of more aggressive tumors [193].

– *Encephalocele/meningocele* (see neoplastic processes in childhood).

– *Olfactory Esthesioneuroblastoma.* This is a rare tumor originating in the olfactory epithelium. A mass is observed in the ethmoid ceiling that can spread through the ethmoidal region. The condition is characterized by nasal obstruction, epistaxis, anosmia and pain. There may be cervical metastases in 8-10% of all cases. This possibility must be considered in the presence of any mass that traverses the cribiform lamina of the ethmoid bone, extending towards the nasal passage and intracranially. The presence of cysts along the intracranial margin of the tumor is a very typical finding [193].

– *Chondrosarcoma*. The typical location is on the midline, with the origin in the nasal septum. The CT findings are characteristic, with central, curvilinear and irregular calcifications.

– *Chordoma.* These lesions appear in patients between 30-50 years of age and are accompanied by headache, vision alterations, facial pain, hypoacusia, tinnitus, and vertigo. The lesion grows in the nasopharynx or para-nasopharyngeal area, spreading towards the cranial base, brainstem and neurovascular structures.

– *Lymphoma.* It is important to confirm the diagnosis, since treatment in this case is not surgical. The lesions are usually necrotic gray-yellowish masses located in the septum or midline of the palate. One type of lymphoma that proves difficult to diagnose from the clinical perspective is polymorphic reticulosis (midline lethal granuloma or lymphomatoid granulomatosis), since immunohistochemical techniques are required [197].

– *Teratomas.* These are generally benign tumors composed of different types of tissues, some of them ectopic in relation to the nasal cavities, distributed without a pattern, and exhibiting different degrees of maturation. The most common components are neuroglia and neurogenic tissue.

– *Melanoma.* These lesions appear between the fifth and eighth decades of life. Melanoma can manifest as a benign-appearing endonasal polypoid mass, or alternatively may tend to invade neighboring structures. There are no pathognomonic radiological signs, though melanotic melanomas can show an intense signal in T1-weighted sequencing without contrast, due to the melanin content [193]. Melanomas are usually intensely vascularized and show very good gadolinium contrast uptake.

5.2 Associated diseases

5.2.1. Bronchial asthma

Asthma is a chronic inflammatory disease of the airways. Different cells and inflammatory mediators are implicated in the pathogenesis of the disease, which is also partially conditioned by genetic factors, and is characterized by bronchial hyperresponsiveness and variable airflow obstruction that is totally or partially reversible, either spontaneously or as a result of drug action (definition of the GEMA guide 2009) [198].

As has been commented in the epidemiology section, about 5-15% of all asthmatic patients can develop NP [14, 199]. Late onset asthma is more often associated to the presence of NP [14].

In those patients who present both disorders [200]:

- Asthma precedes NP in 69% of all cases (usually between 9 and 13 years before).
- The two disorders appear simultaneously in 10% of the cases.
- In the rest of the cases NP precedes asthma (between 2 and 12 years before).

A diagnosis of asthma should be considered in the presence of characteristic clinical signs and symptoms such as cough, dyspnea, wheezing and chest oppression. These manifestations are usually variable, are most prevalent at night or in the early morning hours, and are caused by different triggering factors [198]. None of these signs and symptoms are specific of asthma – hence the need to include some objective diagnostic test. Spirometry is the diagnostic technique of first choice. The reversibility of airflow obstruction can be evidenced by means of the bronchodilation test.

The main objective of asthma treatment is to achieve and maintain control of the disease as soon as possible, as well as to prevent the exacerbations or attacks and chronic airflow obstruction, and to reduce the associated mortality.

A global and individualized long-term strategy is followed, based on optimum adjusted drug treatment and supervision measures, environmental control, and patient education in asthma. Drug treatment must be adjusted according to the degree of patient control achieved, without neglecting more effective therapeutic options or safety, and the cost of the different alternatives – taking into account the patient satisfaction achieved with the degree of disease control obtained. The GEMA guide 2009 describes the therapeutic steps in the maintenance treatment of asthma, as well as the management of the asthma attacks [198].

Patients with asthma associated to NP tend to have a poorer perception of control of the disease, due to the persistence and severity of the associated nasosinusal symptoms. As a result, treatment of the upper airway disease must not be neglected. The publication in the year 2001 of the ARIA document ("Allergic rhinitis and its impact on asthma") introduced the concept of the "single airway" or "one airway, one disease" [201]. In this context it should be considered that the background chronic inflammatory process affects the entire airway, and thus conditions the diagnostic and treatment strategy.

5.2.2. NSAID intolerance

Aspirin-exacerbated respiratory disease (AERD) [202, 203] is characterized by intense eosinophilic infiltration of the upper and lower airways. The disease affects mainly middle aged women, and is consistently associated to CRS and NP. The phenotype associated to asthma with AERD usually corresponds to moderate or severe persistent disease [204]. Initially described by Widal [205], AERD is also known as ASA triad or Samter's triad (asthma, NP, NSAID intolerance) [206].

The prevalence of NSAID intolerance in the general population is 0.6-2.5%, versus 4.3-11% in asthmatics [207, 208].

In patients with asthma and NSAID intolerance, NP is observed in 36-96% of all cases [199, 209, 210], and radiological changes of the paranasal sinuses are noted in up to 96% [211]. On the other hand, 5-8% of all patients with NP suffer NSAID intolerance, usually associated to non-allergic asthma [212].

An association has been described between AERD and HLA-DPB 1*0301 in the Polish [213] and Korean population [214]. It has also been reported that the presence of HLAA1/B8 is more frequent in patients with asthma and NSAID intolerance [215].

The key to diagnosis is a history of bronchial spasms associated to the oral, systemic or topical administration of NSAIDs. When the clinical history proves inconclusive, a controlled exposure test is required, involving either the oral dosing of aspirin or the intranasal or bronchial administration of L-ASA [190]. In any case, provocation testing in all cases must be carried out under extreme safety conditions by personnel trained to deal with potential serious adverse reactions.

Therapy is based on prevention of the attacks (avoiding NSAIDs and introducing effective alternative treatments), the management of asthma, and the treatment of CRS / NP. NP relapse after surgery is more common in patients who associate NSAID intolerance than in those who tolerate NSAIDs [216, 217].

In some cases aspirin desensitization can result in a better clinical course of asthma, with a significant reduction in the need for systemic and inhalatory corticosteroids from the first few weeks of treatment [218]. In addition, such improvement persists if desensitization is maintained over time [219, 220]. In some patients, desensitization and prolonged treatment with aspirin improve the clinical course of CRS / NP and of the associated smell disorders, and may even slow NP growth [219, 221].

5.2.3. Allergic rhinitis

Between 0.5-4.5% of all subjects with allergic rhinitis also have NP [14, 21] – this figure being similar to that seen in the general population [13].

Although some studies have reported the prevalence of atopy to be greater in subjects with NP, other authors have observed no such association [14, 21]. Nevertheless, in patients with both disorders, the treatment of allergy has been shown to improve the symptoms of NP [181].

To date there have been few studies offering conclusive evidence of a relationship between food allergy and the initiation and perpetuation of NP.

5.2.4. Bronchiectasis

Bronchiectasis (BE) is a chronic bronchial disorder characterized by destruction of the bronchial wall, with irreversible (permanent) dilatation of the bronchi, the retention of secretions, and recurrent infections that cause inflammation, obstruction and damage of the lower airways [222].

BE is the end result of a range of diseases, though infections and excessive mucus production appear to be the most important contributing factors.

Approximately 50% of all cases of BE are considered to be idiopathic [223]. The causes underlying BE may be congenital (alpha-1-antitrypsin deficiency, cystic fibrosis, immotile ciliary syndrome, Marfan syndrome) or acquired (more common), secondary to obstruction and infection.

A recent study has reported a high prevalence of CRS (77%) and NP (26%) in patients with BE (post-infectious and idiopathic) [224]. In addition, according to the same study, the severity of BE is related to the presence of CRS and NP. The authors conclude that patients with BE always should be evaluated for possible CRS and NP, and *vice versa*.

The diagnosis is based on the clinical history and the

radiological findings – CT allowing a firm diagnosis while also evaluating the location and extent of the disorder.

In relation to treatment, the main aim is to control the infections and secretions, avoiding airway obstruction.

5.2.5. Primary ciliary dyskinesia/immotile ciliary syndrome

This is an autosomal recessive hereditary disease that affects 1/10 000-60 000 individuals [225]. Ciliary immobility implies the absence of mucociliary transport, stasis of the respiratory secretions and therefore chronic infections of the upper and lower airways from birth (chronic cough, rhinosinusitis, rhinorrhea), sterility in males (due to sperm flagellar alterations) and reduced fertility in women (involvement of the cilia of the Fallopian tubes) [226].

The association of sinusitis, bronchiectasis, and situs inversus is known as Kartagener syndrome. However, bronchiectasis does not manifest from birth; rather, it develops at a later stage as a consequence of chronic infection. Consequently, Kartagener syndrome is presently defined as the coexistence of primary ciliary dyskinesia and situs inversus [227], with an estimated prevalence of 1/20 000-40 000 individuals [228].

The definitive diagnosis is based on the clinical data, analysis of the frequency and pattern of ciliary movement, and evaluation of ciliary structure using electron microscopy. Determination of the nasal nitric oxide (NO) levels (strongly reduced in these patients) [229] or measurement of mucociliary clearance (saccharin test) can be used as screening methods. However, other disorders may exhibit similar results.

Treatment is based on respiratory physiotherapy to favor drainage of the secretions, and aggressive management of the airway infections with antibiotics.

5.2.6. Churg-Strauss syndrome

This is an infrequent disease characterized by severe asthma, rhinitis, NP, eosinophilia and necrotizing eosinophilic vasculitis with the formation of granulomas. Churg-Strauss syndrome should be suspected in patients with severe asthma who require frequent oral corticosteroid cycles.

Clinically, the syndrome has three phases [230]: a) allergic, of variable duration and typically associated to asthma, rhinitis and NP (usually preceding the rest of the symptoms by years); b) eosinophilic, with a predominance of symptoms related to tissue eosinophil infiltration (lungs, gastrointestinal tract and heart); and c) vasculitic, with a predominance of skin and peripheral nervous system manifestations.

Nasal and sinusal involvement is frequent, with the presence of nasal symptoms in 69% of the patients, and radiological evidence of pansinusitis in 88% [231]. Seventy percent of the patients have skin alterations: macular or papular exanthema (rash), petechiae, palpable purpura, and cutaneous or subcutaneous nodules distributed symmetrically on the extremities. Peripheral neuropathy is present in up to 80% of all cases. Cardiac disease (10-70%) is the most serious complication and may prove fatal. The gastrointestinal manifestations may be due to mesenteric vasculitis or eosinophilic infiltration of the walls of the digestive tract.

Approximately 50-60% of all patients with Churg-Strauss syndrome show anti-neutrophil cytoplasmic antibody (ANCA) positivity, particularly in those cases with greater systemic involvement.

The American College of Rheumatology [232] has established 6 diagnostic criteria, of which four suffice to establish the diagnosis: asthma; peripheral eosinophilia >10% or >1500 eosinophils/mm3; involvement of the paranasal sinuses; lung infiltrates (possibly transient); histopathological confirmation of vasculitis with extravascular eosinophils; and mono- or polyneuropathy.

Treatment is based on the control of vasculitis and inflammation, with the administration of corticosteroids. Immune suppressors are held in reserve for the more serious forms of the disease.

5.2.7. Cystic fibrosis

This disease is extensively reviewed in chapter 8 about NP in Pediatrics.

Key points

- When polypoid formations are unilateral, the possibility of a neoplastic process always must be considered.
- In the case of unilateral polyposis of upper nasosinusal origin or of a vascular appearance, the imaging studies should precede the obtainment of a biopsy.
- Aspirin-exacerbated respiratory disease (AERD) is associated to bronchial asthma (usually moderate or severe persistent asthma), CRS and NP, and episodes of bronchospasm associated to NSAID administration.
- Patients with bronchiectasis and/or asthma always should be evaluated for possible CRS and NP, and vice versa.

6. Medical treatment

6.1 Corticosteroids

The usefulness of corticosteroids as first line treatment for CRS with NP is undeniable, as has been reflected in the most recent European and North American consensus documents [125, 233, 234].

Different types of topical nasal corticosteroids are currently available. In Spain the available drugs are budesonide, beclomethasone, triamcinolone, fluticasone propionate, fluticasone furoate and mometasone furoate. These substances all have a similar chemical structure (perhydrocyclopentanophenanthrene) composed of four carbon rings. The variations in positions 16, 17 and 21 of ring D define the differences among the different molecules as regards increased affinity for the glucocorticoid receptors, increased tissue presence and increased first-pass liver metabolism - which implies a reduction in the associated adverse effects of treatment [235, 236].

The oral corticosteroids marketed in Spain for the treatment of NP are prednisone (which is transformed in the liver to prednisolone, which is the active drug form), methylprednisolone and deflazacort. As has been mentioned, all of these molecules share the perhydrocyclopentanophenanthrene structure. The differences are referred to potency in comparison with hydrocortisone or cortisol, and the associated side effects. The antiinflammatory potency of the oral corticosteroids exhibits the following bioequivalence profile: 0.75 mg of dexamethasone is equivalent to 20 mg of hydrocortisone, 5 mg of prednisone, 4 mg of methylprednisolone, 4 mg of triamcinolone and 6 mg of deflazacort, as specified in the Summary of Product Characteristics which the Spanish Medicines Agency (AEMPS) has authorized for dexamethasone. Deflazacort is an oxazoline derived from prednisolone, and produces fewer side effects [237].

6.1.1. Mechanism of action

The corticosteroids exert dual action. On one hand they act at genetic level, increasing the transcription of antiinflammatory genes and reducing the expression of proinflammatory genes, thereby giving rise to a reduction in inflammatory infiltration and vascular permeability [238], and on the other hand they exert a non-genetic, direct effect on the peripheral nervous system, reducing nasal itching within a few minutes after administration [239]. The genetic action is mediated by activation of the glucocorticoid receptors.

Crystallographic studies have shown that the furoate forms of these drugs spatially adapt best to the ligand binding domain of the glucocorticoid receptor, occupying site 17 [240, 241] and increasing binding affinity [235]. In any case, it must be taken into account that increased affinity for the receptor does not necessarily imply greater clinical efficacy [235], since the potency of the drug (measured by its affinity for the receptor) and its clinical efficacy are not freely inter-exchangeable terms. In effect, a less potent corticosteroid simply needs higher doses at the action site in order to elicit the same pharmacodynamic effect as a more potent drug [242].

From the pharmacokinetic perspective, and in reference to systemic absorption, the furoate forms (mometasone and fluticasone) likewise exhibit lesser systemic absorption, followed by fluticasone propionate, budesonide, beclomethasone and triamcinolone. The important liposolubility of these drugs facilitates tissue permanence for over 24 hours, thus justifying single daily dosing in the case of fluticasone and mometasone [243, 244].

The corticosteroids have demonstrated their effects on polyps both in vitro and in vivo. In the in vitro setting, there have been reports of reductions in eosinophil survival in the polypoid tissue [245], the induction of fibroblast apoptosis [246], reduction of the pro-angiogenic factors (VEGF and angiopoietin 1) and an increase in anti-angiogenic factor (angiopoietin 2) [247, 248], as well as the inhibition of mRNA expression of the MUC4 gene and mucin synthesis [249].

The *in vivo* actions of these drugs in NP are varied and include inhibition of the expression of mRNA encoding for eotaxin, eotaxin 2 and MCP-4 (monocyte-chemotactic protein-4) [250], increased expression of mRNA encoding for COX 2 [251], increased Foxp3 (a regulatory T cell activation marker) [252], promotion of epithelial repair after nasal mucosal damage caused by chronic inflammation via the stimulation of activator protein 1 (AP-1) and its related genes [253], increased mRNA expression corresponding to the glucocorticoid receptors (GRs) which are diminished in NP – this potentially influencing the increase in corticosteroid antiinflammatory action [254] – reduction of the goblet cell counts and of MUC5AC and MUC5B [255], and inhibition of the expression of CCR3, CCL12 and STAT-6, with an increase

in interleukin-1 (IL-1), demonstrating changes in the expression of genes related to the production of cytokines, chemokines and receptors implicated in type Th2 inflammatory responses, as well as an increase in IL-1 expression characteristic of type Th1 responses [256].

From the clinical perspective, topical and systemic corticosteroids have been shown to reduce the nasal symptoms, size of the nasal polyps, and recurrence of NP after surgical polypectomy [257, 258].

6.1.2. Safety

Topical nasal corticosteroids

Topical nasal corticosteroids are generally safe when administered at the doses recommended in the corresponding Summary of Product Characteristics (SPC). Higher doses increase the risk of systemic absorption and thus of adverse effects.

Frequent local adverse effects of nasal corticosteroids include nasal dryness [259] and transient nosebleed [259-261]. Septal perforation is an infrequent adverse effect, and is more characteristic of young women and in the first year of treatment [262]. There also have been reports of oro- and hypopharyngeal candidiasis [263], as well as of allergic contact dermatitis [264] – the main diagnostic difficulty being failure to recognize the problem as the cause of lack of improvement or even of worsening of the nasal symptoms. It has been shown that the increase in intraocular pressure observed after one year of treatment with fluticasone propionate, mometasone furoate and beclomethasone dipropionate is within normal limits [265], and likewise no increase in the incidence of cataracts has been observed [266].

As regards the systemic effects of corticosteroids administered topically via the nasal route, no actions upon the hypothalamic-hypophyseal-adrenal gland axis (HHA) have been reported in adults, adolescents or children [267 269], except when inhalatory or topical corticosteroids are moreover also used for bronchial asthma and atopic dermatitis, respectively [270].

Likewise, no long-term retarded growth has been reported in children administered nasal corticosteroids for allergic rhinitis at the recommended doses during a period of two years [259].

Systemic corticosteroids

The adverse effects of systemic corticosteroids are well known and are fundamentally dependent upon the dose employed and the duration of treatment [271]. The most important such effects are suppression of the HHA axis, alterations in bone metabolism and retarded growth in children.

Daily doses of 5-60 mg of prednisone or equivalent, in treatments lasting less than a week, are unlikely to result in clinically significant suppression of the HHA axis, and full functional recovery is to be expected within about two days [272]. In longer treatments, daily doses of over 15 mg of prednisone or equivalent have been found to cause suppression of the HHA axis, while doses of 5-15 mg produce variable axis suppression [271].

Systemic corticosteroids reduce osteoblast activity, as evidenced by a decrease in serum osteocalcin – this being the first step leading to osteoporosis [273]. A single dose of 2.5 mg of prednisone suffices to alter osteoblast activity [274]. The lumbar spine and proximal femur are the most frequently affected zones. The loss of bone is greater in the first 6 months of treatment; as a result, bone density should be monitored in patients requiring daily prednisone doses of 7.5 mg or more during a period of at least 1-6 months [273].

Retarded growth is observed in children at doses above 0.1 mg/kg/day of prednisone or equivalent, though the effect appears to be less pronounced if dosing can be carried out on alternate days [275].

Other adverse effects are: diabetes mellitus, posterior subcapsular cataract, glaucoma, myopathy, avascular bone necrosis, skin atrophy, delayed wound healing, hypertrichosis, acne, perioral dermatitis, telangiectasias, important sodium retention and potassium excretion, increased appetite with weight gain, Cushing-like appearance, variable psychiatric disorders ranging from emotional lability to psychosis, dyslipidemia, arterial hypertension, gastric ulcer, pancreatitis and increased infection risk – fundamentally caused by latent viruses [276].

Deflazacort has less marked effects in terms of bone metabolism, growth retardation in children, carbohydrate metabolism (glucose intolerance) and Cushing-like manifestations [237].

Pregnancy

The United States Food and Drug Administration (FDA) has classified the topical nasal corticosteroids as corresponding to category C, with the exception of budesonide, which belongs to category B – though to date no studies have been made in pregnant women with CRS. Taking into account the results obtained in patients with bronchial asthma treated with inhalatory corticosteroids, in which no increase in congenital malformations has been noted, such findings could be extrapolated to the topical nasal corticosteroids [238]. Systemic corticosteroid use should be reserved for point situations, since such medication has been associated with cases of high-arched or ogival palate [277, 278], as well as preeclampsia [278] and gestational diabetes [279].

6.1.3. Indications of corticosteroid for nasal polyposis

Topical nasal corticosteroids

There is first-level scientific evidence warranting topical nasal corticosteroid use for reducing the size of nasal polyps [257] and for reducing recurrences after surgical polypectomy [280, 281].

Topical nasal corticosteroids administered as drops have been shown to offer better results than spray formulations, though this effect appears to be attributable to a larger administered total dose when drops are used [282].

There are differences in drug distribution favorable to the nasal drops form when the patient stays for 5 minutes in the head down position [283], though there are no differences

in bioavailability between the drop and spray formulations [284] as a result of faster clearance [285]. Since the nasal corticosteroid doses recommended in the Summaries of Product Characteristics of most formulations are referred to the treatment of rhinitis of different origins, but not to CRS with associated NP, and considering that a dose-dependent effect has been observed in application to the symptoms and to reduction in polyp size with the administration of topical corticosteroids, it seems logical to recommend doses that double those advised in the Summaries of Product Characteristics, depending on the severity of the condition, and for periods of 8-48 weeks, as reflected in different studies [100, 286-289].

As regards intranasal corticosteroid use for avoiding NP recurrence after nasal endoscopic surgery, fluticasone propionate in nasal spray form administered daily at twice the dose recommended in the Summary of Product Characteristics affords statistically significant improvement as determined by the visual analog scale (VAS) of severity. This effect is maintained after 5 years, and for up to four years on the scales relating to NP and edema as assessed by endoscopy [290]. It also has been shown that mometasone furoate treatment after endoscopic sinus surgery (ESS) produces a significant prolongation of the time to recurrence of NP [281].

Nasal polyposis is a chronic inflammatory disorder of the nasosinusal mucosa, and therefore topical nasal corticosteroid therapy must be maintained for long periods of time. A good efficacy-safety ratio has been demonstrated for topical corticosteroids administered daily for 5 years. In this context, it is advisable to use topical corticosteroids with a lesser bioavailability (and therefore systemic absorption), considering that we recommend a doubling of the dose.

The risk of adverse effects with corticosteroids is dependent on the dose administered; as a result, it is essential to use the minimum effective drug dose. It has been shown that olfactory loss is well correlated to the severity of NP as determined by nasal endoscopy or CT [131]; adjusting the drug dose according to the degree of such alterations in smell therefore might be a useful strategy.

Local corticosteroid injection

No randomized studies of sufficient quality are available to allow the recommendation of local corticosteroid injections. In a retrospective study, the injection of corticosteroid (triamcinolone) in the lower turbinate was associated to fewer complications than surgical polypectomy, and to a lesser need for surgery [291], though there have been reports of very important adverse effects such as blindness secondary to thrombosis of the cavernous sinus [292] and local adipose tissue necrosis. As a result, this technique is scantly recommendable [238].

Systemic corticosteroids

In the consensus document of the European Academy of Allergy and Clinical Immunology (EAACI), "EPOS 2007", the administration of systemic corticosteroids is limited to severe NP as short course treatment together with nasal corticosteroids in drop form [125]. The clinical guide "Management of rhinosinusitis and nasosinusal polyposis" of the British Society of Allergy and Clinical Immunology (BSACI) recommends short course oral corticosteroids in the case of severe nasal obstruction, as rescue medication in cases of symptoms not controlled by conventional medication, and as "medical polypectomy" together with nasal corticosteroids in drop form, in the case of a lack of response to initial treatment [234].

Oral corticosteroids have been shown to be effective in reducing the size of NP and in improving the nasal symptoms [293, 294]. A systematic review has been published in which a single clinical trial with sufficient quality to allow evaluation was identified [258], though there is no agreement among the different international guides regarding the precise dosage to be administered in each case - a variable dose of between 0.5-1 mg/kg/day of prednisolone or equivalent having been proposed [125, 234]. Likewise, there is no agreement as to how long treatment is to be maintained – the recommendations being between 10 days and three weeks in total, including the advised gradual dose reduction period. However, this dose reduction period can be obviated if the duration of the treatment cycle is under two weeks, and doses of up to 50 mg/day of prednisolone or equivalent can be maintained [295-297]. Suppression of HHA axis function has been reported with doses of 40 mg/day of prednisolone or equivalent administered over a period of three weeks, though the time to functional recovery is a mere 48-72 hours after suspending the medication [298].

While not designed to only evaluate treatment with systemic corticosteroids, since posterior maintenance periods with topical nasal corticosteroids are added, most studies do assess the effect of systemic corticosteroid therapy prior to switching to topical nasal treatment. The usual tendency is to begin with a decreasing regimen of 30-40 mg/day of prednisolone or equivalent for periods normally lasting 10-14 days. This dosage is used even in more severe NP. Only one study has used 60 mg/day in a descending regimen in severe polyposis [299]. In all cases significant reductions were observed in the size of NP and in the symptoms caused by polyposis. This in turn points to the usefulness of such treatment prior to endoscopic surgery, with a view to improving the outcome, and again after surgery to delay recurrence [297]. No studies of severe NP involving doses of 30-60 mg have been published; as a result, we are unable to affirm which dose is most effective in each situation according to the severity of the disease. Since 50 mg of prednisolone has been found to be useful in cases of massive NP [296], we propose a dose of 50 mg/day during two weeks, with no associated dose reducing regimen. In any case, this recommendation is conditioned to the possible side effects of systemic corticosteroid use, in accordance with the disease history of the patient.

Systemic corticosteroid administration has been shown to be useful to prevent recurrences after surgery. A regimen comprising 30 mg of prednisolone 5 days before endoscopic surgery and 9 days after surgery has been shown to be more effective than placebo for up to 6 months after surgical treatment [297]. Since deflazacort produces fewer side effects, it should be taken into account as an adequate alternative when prescribing oral corticosteroids [237].

6.2. Other non-corticosteroid drugs

In their therapeutic algorithms, the two most recent principal consensus documents addressing the medical management of NP, the EP3OS guide [125] and the BSACI guide [234], recommend topical corticosteroids as first line medical treatment, while the advised other options are nasal lavage/rinses and prolonged antibiotic treatment.

At present there is scientific evidence supporting other options in the treatment of NP, such as antileukotrienes, antihistamines in the case of coexisting allergy, desensitization to L-ASA, treatment with capsaicin or – with lesser supporting evidence – the administration of omalizumab. Other treatment options have been evaluated, though either the clinical trials have not obtained positive results, or the studies have not been of sufficient quality to be able to recommend their use. This is the case of nasal vasoconstrictors, immune modulators, mucolytic agents, proton pump inhibitors, furosemide, or monoclonal antibody targeted to IL-5 [125].

6.2.1. Antimicrobials

Although direct microbial implication in the etiology of NP appears unlikely [300], several clinical studies of sufficient methodological quality have shown the usefulness of antimicrobial treatment, using non-habitual administration regimens, in improving the clinical parameters of NP.

In reference to the efficacy of antimicrobial treatments administered in the context of traditional regimens (short duration), no placebo controlled clinical trials are available to demonstrate their usefulness.

A number of antimicrobials have been evaluated in prolonged treatments, with favorable results. A clinical trial involving 64 patients [301] showed the efficacy of roxithromycin versus placebo, 150 mg every 24 hours for three months, in improving several clinical (SNOT-20 rhinosinusitis quality of life questionnaire and nasal endoscopy) and laboratory test parameters (saccharin test and IL-8 levels in nasal secretions) in patients diagnosed with CRS with and without NP. A prospective study without a control group [302] administered a macrolide antibiotic (roxithromycin or clarithromycin) to 68 adults with CRS, revealing lesser treatment efficacy in patients with NP and more severe disease (presence of asthma, eosinophil infiltrates and more serious findings in the CT study). Another clinical trial [117] compared a strategy comprising surgery followed by topical nasal corticosteroids versus a medical treatment strategy without surgery that included low dose erythromycin (250 mg/day for 3 months). The authors concluded that there were no significant differences in efficacy between the two strategies in the group of patients with NP.

The efficacy of macrolide antibiotics in the treatment of CRS, reported by multiple open clinical trials, has been explained not only in terms of antimicrobial action but also in terms of a possible antiinflammatory effect by reducing different proinflammatory cytokines through action on NF-kB [303].

A recent placebo-controlled clinical trial [294] has compared the effect of doxycycline 100 mg/day for 20 days, beginning the first day with 200 mg, versus methylprednisolone in a descending regimen from 32 to 8 mg every 5 days. A more lasting effect in terms of the reduction of nasal polyp size was observed for doxycycline compared with methylprednisolone – though initially the effect of the latter drug was much greater. Doxycycline had no significant effect on the symptoms of NP.

In treating NP, evaluations have also been made of topical antimycotic use, given the high incidence of fungal-positive cultures of the nasal secretions [304]. However, most of the clinical trials in this field have yielded unfavorable results, with no differences versus placebo [305].

A systematic review [306] of the use of topical antimicrobials (antibacterial or antifungal agents) in treating CRS has concluded that these cannot be regarded as first line treatments, due to the low quality of the scientific evidence, but that the tendency to yield positive results warrants treatment attempts based on such a strategy when other therapies are seen to fail.

6.2.2. Nasal lavage/douching

The efficacy of nasal lavage / rinses or irrigation of the nasal passages with saline solution in the treatment of NP is warranted by the maximum level of scientific evidence, with a systematic review [307] that recommends such treatment based on the pre- and postoperative efficacy results. We have identified no clinical trials evaluating the effect of nasal lavage / rinses on an exclusive basis in treating NP. It therefore does not seem advisable to recommend such treatment as single or sole therapy – though the most recent consensus documents recommend it as concomitant treatment [125, 234]. Such rinses are advisable both before and after surgical treatment.

6.2.3. Antileukotrienes (montelukast)

Several prospective, randomized and controlled clinical trials have demonstrated the efficacy of montelukast [308-311]. It has been found that 10 mg/day of montelukast as sole treatment is as effective as 400 μg of beclomethasone in spray form daily for one year, following endoscopic sphenoethmoidectomy [311], though corticosteroids proved more effective in application to the symptoms of nasal congestion and olfactory loss. In a randomized, placebo-controlled clinical trial, montelukast proved superior to placebo in terms of improvement in patient quality of life – though the improvement in polyp size or reduction in eosinophil cationic protein (ECP) in the nasal lavage failed to reach statistical significance [309].

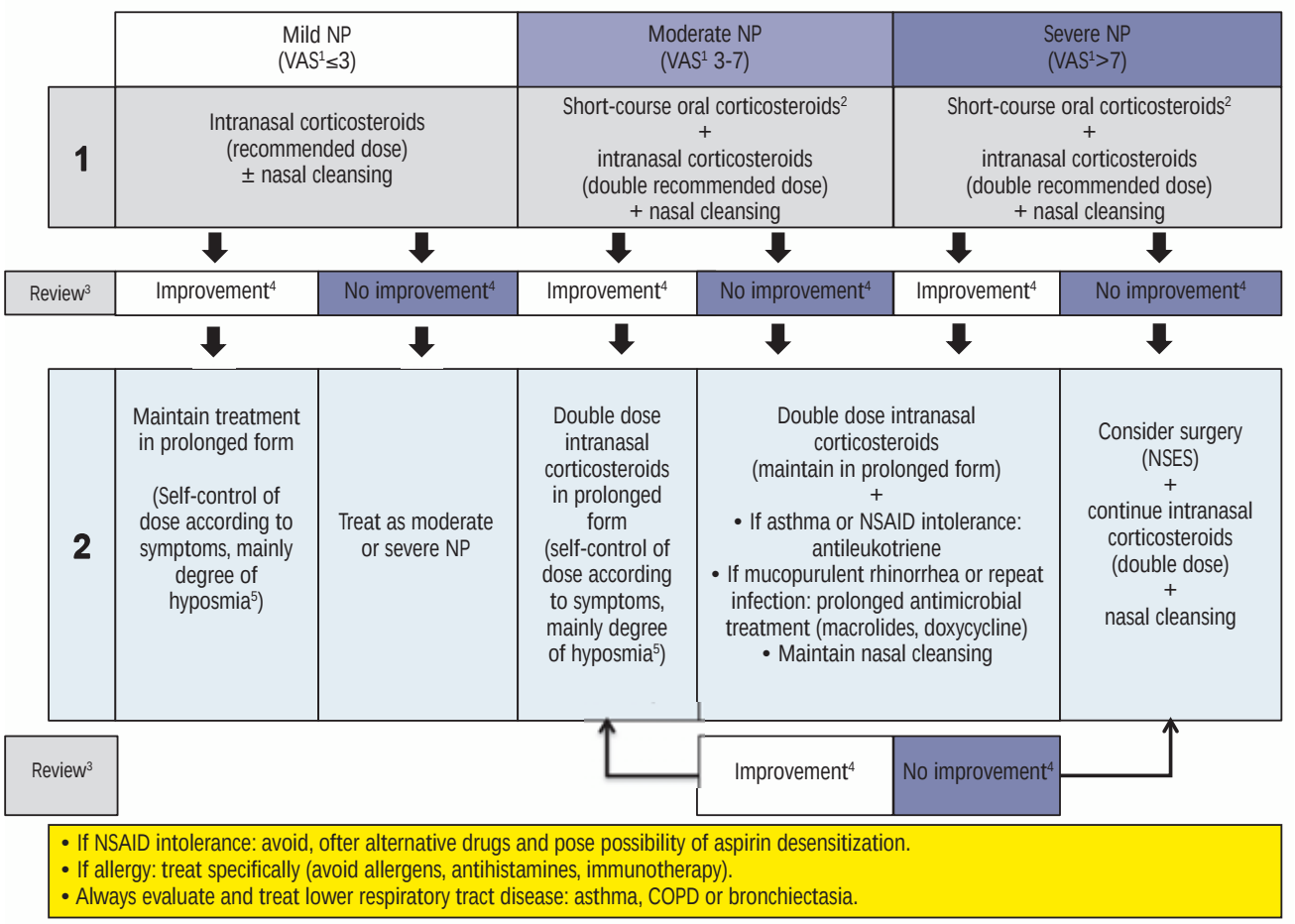
In a clinical trial using montelukast as treatment concomitant to short-cycle oral prednisolone and topical nasal budesonide, the addition of the antileukotriene was seen to improve clinical symptoms such as headache, facial pain or sneezing in the patients with NP [308]. Another clinical trial comparing montelukast with topical nasal beclomethasone, with and without endoscopic polypectomy, revealed no significant differences in terms of nasal or bronchial symptoms between the two treatment options. In contrast, such symptoms proved significantly worse when compared with a combination of loratadine / pseudoephedrine plus beclomethasone without montelukast [310].

6.2.4. Antihistamines

The incidence of allergic sensitization in patients with NP varies from 10-64% [125], though recent studies tend to report higher incidences [23]. A clinical trial [184] has shown that the treatment of allergy in patients with NP can improve the symptoms without changing the size of the polyps.

6.2.5. Aspirin desensitization

Aspirin (acetylsalicylic acid, ASA) desensitizing treatments have been evaluated in patients with NP and aspirin intolerance, based on systemic administration or the topical nasal instillation of L-ASA (the only soluble form). A recent trial [312] has shown that after oral aspirin desensitization



Abbreviations: NP: nasosinusal polyposis. VAS: visual analog scale. ESS: endoscopic sinus surgery. NSAIDs: nonsteroidal antiinflammatory drugs. COPD: chronic obstructive pulmonary disease.

[1]In the treatment of NP, a stepwise approach is advised, based on the severity of the disease. In concordance with the criteria of the EP[3]OS guide [1], we recommend the VAS for assessing severity.

[2]0.5-1 mg/kg/day of prednisone or equivalent for 7-14 days. No gradual dose reduction is required if the dose is under 50 mg/day of prednisone or equivalent.

[3]Although there is no scientific evidence warranting the recommendation of a concrete follow-up period, we initially advise (step 1) follow-up one month after treatment, and posteriorly (step 2) after 3 (moderate or severe) or 6 months (mild or controlled).

[4]We define improvement (control or good response to treatment) as a lowering of one step in severity in moderate or severe NP, or a reduction in VAS score in mild NP.

[5]The degree of hyposmia can be assessed subjectively with a VAS or by olfactometry. It correlates well to the severity of NP, is the most specific symptom of NP, and can be of help in controlling the disease – indicating the need for an increase or reduction in intranasal corticosteroid dose according to whether hyposmia worsens or improves, respectively.

Figure 6.1. Nasal polyposis treatment algorithm.

in patients with NP exhibiting a positive aspirin provocation test, the administration of 300 mg of aspirin a day for one year proves much more effective than treatment with 100 mg in terms of olfactory function, lung function and recurrence rate.

A reduction in tissue inflammation has been demonstrated in patients treated with topical nasal L-ASA in the context of a randomized, placebo-controlled trial, though the small sample size involved did not allow the detection of significant differences in symptoms [313]. A prospective controlled study in which the inclusion protocol (randomized or otherwise) has not been clearly specified has demonstrated the efficacy of topical L-ASA in reducing the NP recurrence rate [314].

6.2.6. Capsaicin

Capsaicin is a neurotoxin that reduces the levels of substance P and other neuropeptides (e.g., the calcitonin gene related peptide, neurokinin A), which have been implicated in possible neurogenic inflammation in NP. A mechanism of action through NF-kB antagonism has also been proposed, as evidenced in vitro for this substance [315]. A randomized, controlled clinical trial compared the efficacy of topical nasal capsaicin versus placebo (control group treated with the vehicle of the topical solution) in patients operated upon for NP – reporting a lesser recurrence rate and significant improvement in subjective nasal obstruction sensation compared with the placebo group [316].

6.2.7. Monoclonal antibody targeted to IgE (omalizumab)

In recent years the role which high levels of polyclonal IgE may have in the pathogenesis of NP has been evidenced. As a result, tests are being carried out with some success, applying treatment with omalizumab - a monoclonal antibody against IgE. There is insufficient evidence to warrant its generalized use, though omalizumab could be a treatment option in patients with severe disease, coexisting asthma and subjects who are unresponsive to other NP treatments [317, 318]. The scientific quality levels for the medical treatment of NP, as well as the degrees of recommendation, are reported in Tables 6.1 and 6.2, while Figure 6.1 presents a treatment algorithm for NP.

Table 6.1. Scientific quality levels for the medical treatment of NP

	Quality level
• Treatment with nasal topical corticosteroid drops at a dose double that recommended in the summary of product characteristics, during 12 weeks, to reduce polyp size	1b
• Treatment with topical corticosteroids at a dose double that recommended in the summary of product characteristics, according to the severity of polyposis, during a period of 8-48 weeks, to reduce polyp size and symptoms	1b
• Prevention of recurrences following endoscopic surgery, using topical corticosteroids at a dose double that recommended in the summary of product characteristics	1b
• Oral corticosteroids for 14 days to reduce polyp size and symptoms, at a dose of 0.5-1 mg/kg/day of prednisone	1a(-)
• Oral corticosteroids to prevent postoperative recurrences	1b
• No gradual oral corticosteroid dose reduction is required if the duration of the treatment cycle is under two weeks and the dosage is ≤ 50 mg/day (prednisone or equivalent)	1b
• Prolonged treatment (3 months) with roxithromycin	1b
• Prolonged treatment (3 months) with erythromycin plus nasal topical corticosteroids	1b
• Prolonged treatment with doxycycline (20 days)	1b
• Topical treatment with antimicrobials	1a(-)
• Nasal lavage as concomitant treatment	1a
• Montelukast as concomitant treatment	1b
• Antihistamines in patients with coexisting allergy	1b
• Prolonged treatment in the form of 300 mg of aspirin in patients with positive provocation after desensitization	1b
• Prolonged treatment with topical nasal capsaicin in patients operated upon due to NP	1b
• Treatment with omalizumab in patients presenting severe disease, failing to respond to other treatments with associated severe asthma	3b

Table 6.2. Recommendations and degree of recommendation in the treatment of NP

Recommendation	Grade of recommendation
• NP is to be treated according to its severity with topical corticosteroids at a dose double that recommended in the summary of product characteristics, in both spray and droplet form, during long periods of time	1
• Moderate and severe NP is to be treated with oral corticosteroids at a dose of 0.5-1 mg/kg/day of prednisone or equivalent, in 14-day cycles, with no need for a dose reduction protocol (cycle under 2 weeks), together with topical nasal corticosteroids at a dose double that recommended in the summary of product characteristics, during long periods of time	1
• Postoperative recurrences are to be avoided with short-course oral corticosteroids and nasal topical corticosteroids at a dose double that recommended in the summary of product characteristics, during long periods of time	1
• Prolonged treatment with roxithromycin 150 mg/day for 3 months can be tested in patients with moderate or severe polyposis	1
• Erythromycin 250 mg/day for 3 months can be added to nasal corticosteroids in patients who fail to reach the desired improvements	1
• Topical antimicrobials can be tested as treatment option in patients failing to respond to conventional therapy	2
• Nasal lavage with saline solution is to be added to usual treatment	1
• Prolonged treatment with montelukast can be tested, added to nasal topical corticosteroids in patients with NP not controlled by conventional treatment	1
• Antihistamines are indicated in patients with allergy associated to NP	1
• Prolonged treatment in the form of 300 mg of aspirin via the oral route can be used in positive provocation patients previously desensitized to aspirin	1
• Treatment with topical nasal capsaicin can be tested in patients operated upon due to NP	2
• Treatment can be tested with omalizumab in patients presenting severe disease, failing to respond to other treatments, and with associated asthma	2

Key points

- Corticosteroids, administered via the topical or systemic (oral) route, are the most effective and safest treatment option for NP. These drugs have been shown to be effective in reducing both the nasal symptoms and polyp size and recurrence after surgical treatment.
- Since NP is a chronic inflammatory disease, the administered topical corticosteroid doses should be up to twice as high as the doses recommended in the Summary of Product Characteristics of the principal drug substances available on the market, depending on the severity of the disease - and treatment is moreover required for prolonged periods of time.
- The administration of systemic (oral) corticosteroids can be carried out in moderate or severe NP at doses of 0.5-1 mg/kg/day of prednisone or equivalent for up to 14 days, without gradual dose reduction or tapering, provided the administered dose is less than 50 mg/day.
- There are other treatment options with sufficient supporting scientific evidence to warrant their use in cases where topical or systemic corticosteroids are insufficient, depending on the clinical characteristics of each individual patient, such as prolonged systemic antibiotic treatment, montelukast, topical antimicrobials, antihistamines in the case of coexisting allergy, aspirin desensitization, topical nasal capsaicin, or omalizumab.

7. Surgery treatment

7.1. Surgery indications

The management of NP requires adequate medical treatment that can be complemented by surgery.

The impact of surgical treatment is difficult to establish with precision, since surgery is performed in those patients who fail to respond adequately to medical management. The concept of poor medical treatment response and the regimen of such treatment (dose and duration) are aspects that can be assessed or interpreted in a relatively diverse number of ways.

The EP^{3}OS 2007 document [42] places surgical indication in the setting of severe NP, with a symptoms VAS score of over 7. It must be pointed out that in order to diagnose poor response to medical treatment, the severity of NP must persist after treatment with topical and oral corticosteroids.

Any nasosinusal surgical procedure requires a CT evaluation of the sinuses to confirm the disorder, a report on lesion extent, and specification of the possible anatomical variants.

7.2. Types of surgery

The surgical treatments historically proposed for NP range from polypectomies as the most conservative option to more radical fronto-ethmoidosphenoidotomy adopting an external approach. However, no surgical procedure has been shown to offer complete healing of the background disease, and it is common for many patients to undergo different surgical operations in the course of their lifetime, with the continuation of medical therapy for prolonged periods of time.

Intranasal polypectomy can be carried out under local or general anesthesia. It is a procedure of very limit scope that eliminates the polyps from the nasal cavity. In the measure to which these polyps are pedicled in portions of the anterior ethmoid region and/or middle turbinate, segments of the lesions can be removed.

Radical surgery of the maxillary sinus or the Caldwell Luc approach was conceived in application to CRS, on assuming that the mucosal lesions present were irreversible. Thus, surgical treatment was taken to imply the need to completely eliminate the entire sinusal mucosa through a window in the anterior sinus wall. At present, it has been seen that on ventilating, draining and re-establishing adequate mucociliary clearance, the sinusal mucosa – regardless of how affected it may seem macroscopically – can be restored to normal, though not in all cases. The Caldwell Luc procedure is practically no longer used in application to NP. Exceptionally, the antral approach may prove useful for eliminating fungal disease colonizing the entire maxillary sinus.

Endoscopic surgery is a crucial element in the surgical management of these patients, making it possible to safely execute from simple polypectomies to very radical surgery in which the entire skull base may be exposed, from the frontal recess to the *planum sphenoidale*, along with both papyraceous laminas laterally, with elimination of the ethmoidal cells, and wide aperture of the maxillary sinus, frontal sinus and sphenoidal sinus.

Two major procedures can be distinguished in the endoscopic sinus approach to NP. Caution is required in analyzing the results, since a large proportion of operated patients are at the limits between both methods. Thus, we can make a distinction between surgery limited to treatment of the lesions in the affected sinuses ("surgery upon demand") and more "radical" surgery characterized by wide elimination of all the ethmoidal cells, exposure of the skull base, aperture of the frontal, maxillary and sphenoidal sinuses, and extensive resection of the middle turbinate, exposing large segments of bone denuded of mucosa [319].

7.3. Results of endoscopic sinus surgery (ESS)

Endoscopic surgery, whether "upon demand" to resolve the sinusal lesions or in its more "radical" form, offers better results than more limited and conservative procedures such as simple polypectomies [320].

Approximately 10% of all patients subjected to endoscopic surgery show a poor response to surgical treatment provided concomitant to medical therapy. When performing revision surgery, situations such as the presence of extensive synechiae in the middle meatus, significant lateralization of the middle turbinate towards the sinusal cavity, non-elimination in first surgery of important segments of the uncinate process, and

the presence of numerous unopened ethmoidal cells are all findings that can underlie a poor response to first surgery [321]. On the other hand, there are aspects related to the clinical expression of NP that have a strong negative impact upon the surgical outcome, such as a massive extent of the disease, the association of bronchial asthma and/or NSAID intolerance, and the association of cystic fibrosis.

Jankowski et al. retrospectively compared a series of patients subjected to surgery "upon demand" according to the lesions present, and another group of individuals subjected to more "radical" surgery. In both groups the preoperative lesions had similar characteristics. "Radical" surgery yielded better results in terms of symptoms assessment and endoscopic exploration of the nasosinusal cavity, as well as fewer relapses [319].

7.4. Complications of surgery

The introduction of endoscopic sinus surgery (ESS) implied a series of advantages with respect to the classical external techniques in the management of NP, such as the absence of facial incisions, lesser morbidity as refers to crusts, postoperative pain and bleeding, and lower economical costs. Nevertheless, ESS is not without certain complications. According to the different published series, the complications rate in patients with NP varies from 4.3-6% [320].

Types of complications

The surgical complications can be classified as hemorrhagic, orbital and intracranial.

a) Hemorrhagic complications. Hemorrhage can manifest as arterial bleeding or suffusion, and the branches of the sphenopalatine artery are the most commonly affected vessels. In the event of damage to the ethmoidal arteries, the orbital zone may be affected in the form of bleeding and/or hematomas. In general, mild nosebleed is observed – with severe bleeding or the need for hospital admission in approximately 2.2% of the cases [322]. Some series have reported isolated and exceptional cases of very serious complications, such as damage to the internal carotid artery following ESS in NP [323].

b) Orbital complications. These occur as a result of direct damage to the optic nerve, the orbital muscles or ethmoidal arteries. Mild lesions can be observed in the form of periorbital emphysema or edema or palpebral ecchymosis, or alternatively more serious problems can develop such as diplopia, diminished visual acuity or blindness. The most common orbital problem is periorbital and/or orbital adipose tissue exposure (2.1%), though when identified intraoperatively such situations in most cases do not give rise to complications [322].

It is also possible to damage the lacrimonasal duct on anteriorly amplifying the middle meatotomy. Wigand and Hoseman reported a 0.5% incidence of epiphora in a series of 600 patients operated upon due to NP [324].

c) Intracranial complications. These complications result from penetration of the skull base. The anatomical regions at greatest risk are the lamina cribosa in its horizontal portion, and the insertion of its lateral portion in the frontal bone. The incidence of postoperative cerebrospinal fluid fistulas varies between 0.2-3% of the cases, while the percentage incidence of meningitis is 0.15% [322].

d) Other complications. Other less frequent complications may also be observed, such as myospherulosis, toxic shock syndrome, the sequelae of secondary atrophic rhinitis, or the presence of facial paresthesias. Some authors consider the appearance of synechiae to be a complication rather than an example of postoperative sequelae. In this case, synechiae would be the most common complication of ESS (10.4%) [322].

All these complications (hemorrhagic, orbital and intracranial) can be classified as mild to serious, depending on the degree of severity. Serious and mild complications have been estimated to occur in about 0.5% and 4% of all ESS procedures, respectively [42].

The risk of complications in sinusal surgery depends on a number of factors such as the existence of anatomical variants, the performance of revision surgery, the extent of the disease, surgery carried out under local or general anesthesia, and surgeon experience. Some studies have demonstrated a greater probability of complications on the right side.

The technique used can influence the percentage of intra- or postoperative complications. Jankowski reported a larger number of complications (all minor in nature) when performing radical surgery (nasalization) compared with conventional ESS (7.7% versus 0%) [319].

7.5. Effect of surgery in asthma

In contrast to classical belief, different studies have shown that polypectomy does not aggravate or induce asthma. To this effect, correct preoperative treatment is necessary – a situation probably not found in the historical series.

Surgical treatment in patients with NP results in subjective patient perceived improvement of asthma, with significantly better results in terms of respiratory function and systemic corticosteroid use. These results progressively worsen over time, however, with poorer performance in patients with asthma and aspirin intolerance [42, 319, 325].

Key points

- Surgery in NP is reserved for severe forms of the disease that fail to respond to corticosteroid therapy.
- ESS (endoscopic sinus surgery) is the technique indicated for the surgical treatment of NP, though it is not a substitute for medical management.
- ESS yields poorer results in cases of massive NP, and when the disease is associated to bronchial asthma and/or NSAID intolerance.
- Complications of ESS are observed in under 5% of all cases, and most of them are mild.
- ESS in patients with NP affords improvements in the subjective and objective assessment of asthma.

8. Nasal polyposis in children

8.1. Epidemiology

Nasal polyposis (NP) is exceptional before puberty. The precise prevalence of the disease in the pediatric population is difficult to establish, due to the few studies that have been made in this field. In any case, the frequency of NP in children is estimated to be 0.1% in the general population [326]. The most frequent cause of pediatric NP is cystic fibrosis (CF). In effect, there is a frequent association between NP and CF in children, varying from 20-58%, depending on the series [326-329]. The incidence of NP in children over 5 years of age with CF ranges between 10% [330] and 56.5% [331]. In the series published by Triglia et al. [328] involving 46 children with NP, 5 were asthmatic, 27 had CF, and 14 suffered neither of these disorders. Forty-three percent of the children included in the study were allergic, specifically, 22% of those with CF, 80% of those with asthma, and 10% of those with neither CF nor asthma. These studies are in conflict with the findings of other authors who found allergy in children with NP to be infrequent, and who identified allergy as a potential risk factor only in patients without CF [327].

Other much less frequent diseases can also be associated to NP [332]. In this sense, ciliary dyskinesia is associated to NP in 5% of the cases, in the same way as Mounier-Kuhn syndrome (characterized by NP, tracheobronchomegalia and bronchiectasis), Kartagener syndrome (NP, situs inversus and bronchiectasis), and Young syndrome (NP and azoospermia). Woakes' disease in turn manifests in children or young individuals in the growing phase, and is characterized by massive polyposis causing dehiscence of the facial bone sutures, widening of the root of the nose and hypertelorism [333].

8.2 Pathogenesis

Chronic inflammation involving any mechanism appears to be the triggering element in the development of NP. Patients with CF have a defect in the small conductance chloride channels, regulated by cyclic adenosine monophosphate (cAMP) – giving rise to anomalous chloride transport across the apical membrane of the epithelial cells. The pathogenesis of NP in patients with CF could be associated to this defect [334].

Two main factors are implicated in the pathogenesis of nasosinusal involvement in patients with CF: alteration of mucus viscoelasticity and the slowing of mucociliary clearance – both conditions leading to mechanical obstruction of the sinus ostium. This is followed by a decrease in oxygen partial pressure (O_2) and an increase in carbon dioxide partial pressure (CO_2), giving rise to ciliary damage, mucosal edema and inflammation. The latter in turn is facilitated by bacterial and viral infections. Both the upper and lower respiratory tracts are habitually and chronically colonized by *Pseudomona aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae* and anaerobes [334].

Recently it has been suggested that mutations of the gene responsible for CF may be associated to the development of chronic rhinosinusitis (CRS) in the general population, and that Delta F508 homozygosis appears to be a risk factor for paranasal sinus disease [335].

8.3 Histopathology

NP found in patients with CF is similar to idiopathic NP as regards hyperplasia of the mucosal glands, mucosal cysts and focal cellular metaplasia of the transitional or squamous epithelium, but differs in that it is characterized by a normal basal membrane without eosinophilic infiltration and a predominance of neutrophils [336], and the fact that the mucosal glands contain more acid than neutral mucins. It has been shown that NP in CF is less responsive to corticosteroid treatment than NP with a greater eosinophil presence [330].

8.4 Inflammatory mediators

An increased expression of human beta-defensin-2 and toll-like receptor-2 has been observed in biopsies of NP in patients with CF compared with patients with NP not associated to CF. IL-5 is not detected in NP among patients with CF, though in contrast it is detected in 80% of all the patients without CF. IL-8 in turn is slightly more elevated in NP in patients with CF. However, the expression of ECP, eotaxin and IgE is significantly higher in patients without CF. Therefore, NP in patients with and without CF is differentiated not only by the inflammatory mediators profile but also by the innate immunity markers [337].

8.5. Clinical manifestations

NP is associated with a worsening of quality of life (QoL), nasal obstruction, anosmia, chronic sinusitis, headache, snoring and posterior rhinorrhea. In children with CF the disease process is so gradual that most patients report no discomfort, since adjustment at such ages is better than in adults – with the added consideration that certain symptoms such as anosmia are difficult to evaluate in children [338].

The clinical manifestations of NP in children depend on the size of the lesions. Small polyps produce no symptoms and may be detected on occasion of a routine examination when located in the anterior portion of the middle turbinate. Those located in the posterior portions of the nasal passages are not seen on occasion of routine explorations with anterior rhinoscopy, and thus remain undiagnosed unless the patient develops symptoms. Small polyps located in areas such as the middle meatus can produce symptoms and block sinus drainage, producing symptoms of sinusitis [339].

Massive NP or the presence of a single large polyp obstructing the nasal cavities, nasopharynx or both, can give rise to sleep apnea or chronic oral breathing [340]. Rarely, patients with CF present invasive NP that can alter the craniofacial structure and produce proptosis, hypertelorism and diplopia (Woakes' syndrome) [333]. However, the presence of a bilateral maxillary pseudomucocele is very characteristic of CF. The bulging of the medial wall of the maxillary sinus caused by the pseudomucocele narrows the nasal passages and largely accounts for the nasal obstruction seen in these children [341].

8.6 Diagnosis

8.6.1 Examination

In Pediatrics, anterior rhinoscopy is not efficient in exploring the presence of NP. Nasal endoscopy [342] is the diagnostic gold standard, allowing visualization of the polyps in the osteomeatal complexes, as well as the mucosal edema, purulent secretions emerging from the ostia of the paranasal sinuses, and dislocation of the lateral wall of the nasal passage characteristic of pseudomucopyoceles. Use is normally made of a 0º rigid endoscope with a diameter of 4 or 2.7 mm [340].

8.6.2 Imaging

CT and MRI are the radiological explorations of choice for evaluating the extent of CRS with NP in children. They are indicated in cases of dissociation between abundant clinical manifestations and poor or doubtful exploratory results. Likewise, when considering the possibility of surgery, CT is the preferred technique, since it allows visualization of the bone septae.

Normally, when neuroimaging guided surgical techniques are contemplated, both explorations are made, since they are complementary. MRI is preferable in those cases where complications of the central nervous system are suspected. The image strongly suggesting CF is demineralization and medialization of the nasal wall adjacent to the maxillary sinus, which is associated to bilateral pseudomucopyocele [343].

8.6.3 Study of the background disease

NP in children is often associated with some background disorder. In this context, CF is the disease most often associated to NP in children [328]; as a result, in pediatric patients with NP, cystic fibrosis is the first diagnosis to be considered. Perspiration testing and/or genetic tests for CF are required in all children with NP.

In children with NP associated to allergic rhinitis, a full allergological study is required, including a guided anamnesis, skin tests and/or serum specific IgE determination using a battery of aeroallergens to determine the cause of allergy and thus decide adequate etiological treatment.

A cytological study of the nasal secretions is indicated to detect eosinophils and thus establish whether the condition corresponds to idiopathic NP or otherwise. If eosinophils are effectively detected in the nasal secretions, corticosteroid treatment is possibly the best treatment option.

8.7. Treatment

8.7.1. Medical

Oral and topical corticosteroid use is the indicated first line treatment in NP (Table 8.1). Antihistamines, decongestants and sodium cromoglycate offer little benefit. Immunotherapy is useful for treating allergic rhinitis, but in itself is unable to resolve NP. Antibiotics are to be employed when bacterial overinfection is suspected [344].

Corticosteroid response appears to depend on the presence or absence of eosinophilia; as a result, patients with NP and allergic rhinitis or asthma respond better to such therapy. Oral corticosteroids are the most effective medical treatment for eosinophilic NP. The recommended maximum dose in children is 1 mg/kg/day for 5-7 days, with evaluation of the effect in 1-3 weeks. Patients with non-eosinophilic NP, as in that associated to CF, may not respond to oral corticosteroids. As a result, prolonged treatment with such medication is not advised, since there may be side effects in children [345].

Some authors have reported important improvement in NP in children with CF following the administration of topical corticosteroids [329]. Controlled studies have shown that topical nasal mometasone [346] and fluticasone do not influence growth [269, 347]; as a result, they should be regarded as first line treatment in children with NP. Nasal corticosteroids are not approved by the United States FDA for use in application to NP among patients under 18 years of age. The doses shown in Table 8.1 are those approved for allergic rhinitis and are based on the corresponding Summaries of Product Characteristics, since no studies are available for drawing scientifically solid conclusions regarding possible indications for the management of NP in children (see chapter 6).

8.7.2. Surgical

Surgical treatment is indicated in those cases where medical management of the symptoms causing worsened quality of life, such as headache or nasal obstruction, is seen to fail. In cases of CF, surgery can slow the gradual worsening of lung function

Table 8.1. Nasal topical corticosteroids and indications in pediatric patients

Years	Mometasone fuorate (50 g/dose)	Fluticasone propionate (50 g/dose)	Fluticasone furoate (27.5 g/dose)	Budesonide (64 g/dose)	Triamcinolone (55 g/dose)	Beclometasone (50 g/dose)
2-11	*1/NP/24 h		1/NP /24 h (morning) 2 /NP/ 12h**			
4-11		1/NP /24 h (morning) 1/NP/12h**				
6-12					1-2 /NP/24 h (morning) 2/NP/12h**	
≥ 6				4/NP/24 h (morning) or 2/NP/12h **		1-2/ NP/12 h**
≥ 12	2 /NP /24h	2 /NP/24 (morning) 2/NP/12 h**	2 NP/24 h		2-4 /NP/24 h**	

* Applications/in each nasal passage/time interval
NP: Nasal passage; H: Hours
**Note: It is possible to increase to this dose and then reduce the dosage when the desired clinical effect has been obtained, to the minimum dose needed to control the symptoms.

secondary to infections of the upper airway. The paranasal sinuses are habitually colonized by *Pseudomona aeruginosa* and *Staphylococcus aureus*.

The indicated surgical technique is endoscopic sinus surgery (ESS), with elimination of the nasal polyps and of the diseased mucosa. ESS is associated with an increase in draining ostial size, improving ventilation of the preserved mucosa and affording better control of the relapses. ESS can be carried out using conventional endoscopic microsurgical instruments or micro-debriding type devices [348] that make it possible to avoid damaging the non-polypoid mucosa, particularly in cases of relapse. Although surgery apparently may have eliminated all the lesions, the associated relapse rate is high (50% after 4 years) [331]. As a result, in recent years the possibility has been offered of combining the endoscopic technique with a navigation system allowing control at all times of the location of the tip of the instrumentation used – correlating the radiological images with endoscopic vision [349].

8.8. Prognosis

The prognosis of NP in pediatric patients depends firstly on whether the disease is similar to adult NP, or whether it is set within the context of CF. In the first case the course is poorer in the presence of severe disease, more advanced stages as determined by CT, and if the patient is exposed to tobacco smoke (actively or passively) [350]. In the cases not associated to CF, topical corticosteroids are more effective in securing control of the disease. In contrast, the prognosis of NP associated to CF is conditioned by the existence of genetic factors that imply a better or poorer course depending on the altered gene [341]; and the associated pathology, since the disease affects organs as important as the lungs or pancreas – the evolution of these alterations making the nasal problems seem irrelevant in comparison.

ESS has been reported to afford a 76% improvement in quality of life [351].

8.9. Criteria for patient's referral

In Pediatrics, patients with clinical manifestations of CRS with headache and/or persistent nasal obstruction should be referred to the specialist. More importantly, any identification of NP via anterior rhinoscopy requires referral to a specialist for nasal endoscopic exploration [338].

In the centers specialized in CF, all the patients are referred, whether symptomatic or otherwise. Complications such as mucoceles and periorbital abscesses are rare in patients with CF, and require urgent referral to the specialist [329].

Key points

- The most frequent cause of NP in children is CF. As a result, in children with NP the possibility of CF must be explored. Likewise, children with CF should be evaluated for possible NP.
- In children with CF, the progression of NP may be so gradual that no symptoms may be observed. Adjustment to the disease is better in children than in adults, and symptoms such as anosmia are difficult to evaluate in children.
- Nasal endoscopy is the gold standard, allowing the visualization of NP.
- The polyps found in patients with CF have a normal basal membrane without eosinophil infiltration, and the mucosal glands contain more acid than neutral mucins.
- Mometasone furoate and fluticasone are the topical corticosteroids of choice in children with NP, since they have been shown to exert no effect upon growth.
- In Pediatrics, any case of suspected NP should be referred to the specialist.

9. Nasal polyposis: criteria for referral from/to Primary Care and interconsultation between ENT and Allergology

9.1. Introduction

Nasal polyposis (NP) is an important health problem, with a high sociosanitary cost. Patients with NP constitute a subgroup within the population diagnosed with chronic rhinosinusitis (CRS), and in turn often suffer associated disorders such as rhinitis, bronchial asthma, NSAID intolerance and bronchiectasis, or cystic fibrosis (CF), among other conditions (Figure 9.1) [1,42]. In each medical intervention consideration is required of the "one airway" concept in both diagnostic evaluation and in planning a unified treatment strategy. As a result, a multidisciplinary approach is not only necessary but essential, with the participation and collaboration of Primary Care physicians (general or family medicine, pediatricians) and specialists (ENT, Allergology, Pneumology).

The purpose of this chapter is to establish a series of criteria for the referral of patients with suspected or confirmed NP among the different levels of medical care in both the primary and specialized settings, with a view to reducing variability in clinical practice and to establish rapid and homogeneous care without contradictory or conflicting messages among the different healthcare levels.

At any level of medical care, decision taking requires good management not only of the clinical definition of the disease but also of its severity and duration – thus allowing flexible and individualized patient care. As in any medical process, adequate control of the variables relating to evaluation, follow-up and referral will serve to increase efficiency, with better use of the existing resources and improved quality of patient care. All this not only secures greater patient satisfaction but moreover also contributes to shorten the time to diagnosis and start of treatment – these being the ulterior objectives of any medical intervention.

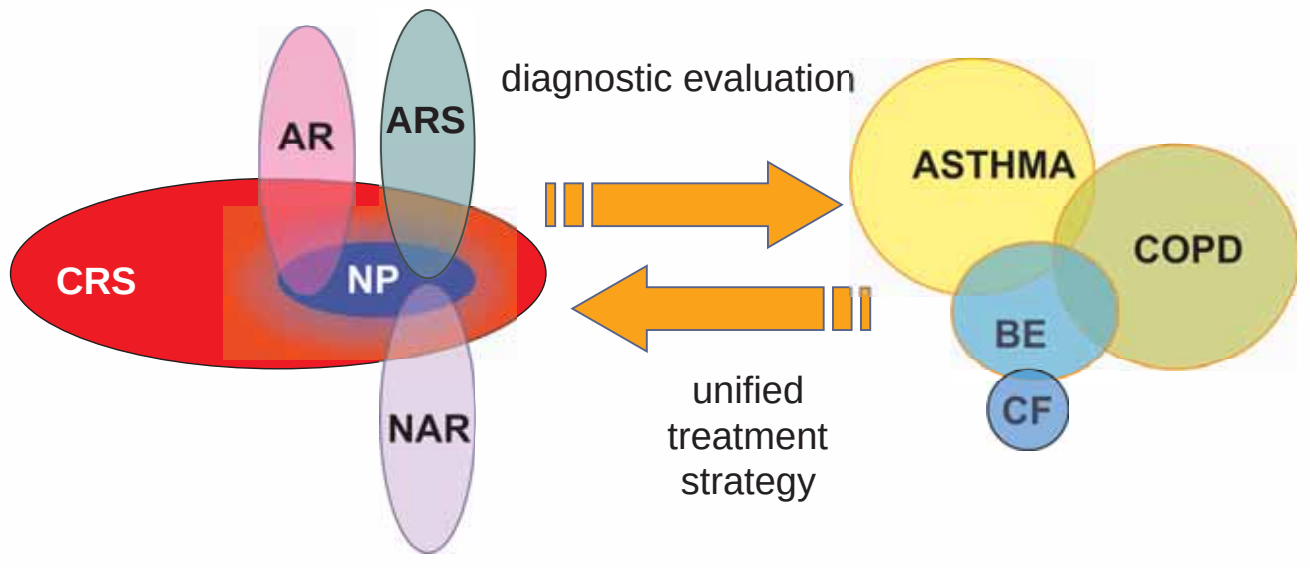


Figure 9.1. Diagnosis and management strategy of nasal polyposis (NP) In the context of "one airway, one disease" [1,42,185,224,357].
CRS, chronic rhinosinusitis; ARS, acute rhinosinusitis; AR: allergic rhinitis; NAR, non-allergic rhinitis; COPD, chronic obstructive pulmonary disease; BE, bronchiectasis; CF, cystic fibrosis.

9.2 Evaluation in Primary Care

In Primary Care, the clinical suspicion should begin when the patient reports with a history of 12 continuous weeks of nasal obstruction accompanied by anterior-posterior rhinorrhea and/or diminished or abolished smell sensation [1,42]. Progressive hyposmia or anosmia associated to nasal symptoms is of great clinical usefulness in the suspicion of NP, its severity and associations [99, 224, 293, 352-354].

In adults, the personal antecedents often include clinical manifestations of rhinosinusitis, allergic rhinitis, bronchial asthma, NSAID intolerance, COPD or bronchiectasis. NP should be suspected in any patient with persistent rhinitis, particularly when of a non-allergic nature, and which fails to improve with the usual medical treatment. The existence of hyposmia reinforces the diagnostic suspicion.

In children and adolescents, bilateral NP is often associated to CF or other diagnoses (primary ciliary dyskinesia, Kartagener syndrome or Young syndrome) [355], and an increase is also seen in unilateral polyposis (antrochoanal polyps) [356].

Although the association of rhinitis and asthma with NP has recently been documented in Spain [353, 354], there is no proof of a causal relationship between allergy and NP. Nevertheless, the physician who visits a patient with NP should take this association into account, and make use of all means available (interconsultation, referral) to establish a correct diagnosis and treatment [42, 185, 357].

When physical exploration in the form of anterior rhinoscopy visualizes the polyps (as occurs in grade 3 polyposis), the diagnosis can be confirmed at this healthcare level. In any case, in the Primary Care setting it is not advised to request any radiological exploration (plain X-rays of CT). It should be taken into account that the clinical anamnesis alone is usually not sufficient for diagnosing NP, since definitive confirmation requires nasal endoscopy and/or CT evaluation, and such explorations are usually made in the specialized care setting [42].

The recommendation is to refer from Primary Care to specialized care [42, 344, 358] (Figure 9.2):

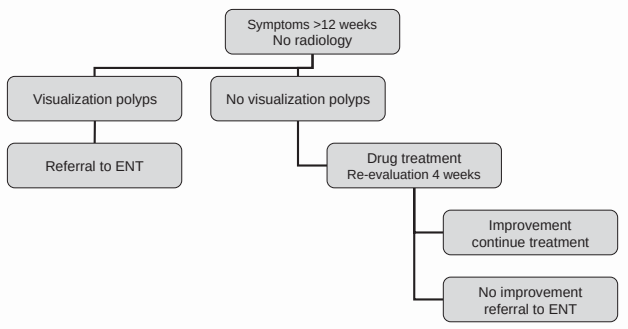


Figure 9.2. Management of NP in Primary Care, where visualization of the polyps (rhinoscopy, endoscopy) is essential for both management (early diagnosis, immediate and continuous treatment) of the patients with NP and their referral to specialized care (ENT, Allergology, Pneumology) [1,42,344].

Table 9.1. Criteria for interconsultation or referral from Primary Care to specialized care: ENT, Allergology, Pneumology [1,42,185,198,344,355,357-359]

To Allergology: suspected or confirmed diagnosis of: • allergic rhinitis • allergic bronchial asthma • NSAID tolerance • other atopic or immunoallergic diseases
To ENT: suspected or confirmed diagnosis of: • non-allergic rhinitis or patients with non-atopic characteristics • diagnostic confirmation by nasal endoscopy • unilateral polyp or mass • acute rhinosinusitis (exacerbation) • NSAID intolerance • ocular and/or endocranial complication • lack of control with medical treatment • indication for surgery • fungal eosinophilic rhinosinusitis
To Pneumology: suspected or confirmed diagnosis of: • non-allergic asthma • cystic fibrosis • bronchiectasia • COPD • Churg-Strauss syndrome or other forms of vasculitis • granulomatous diseases

1) In the presence of a clinical picture compatible with moderate to severe CRS, or when anterior rhinoscopy reveals the presence of polyps (massive polyposis).

2) In the presence of a clinical picture compatible with moderate to severe CRS, where no improvement is achieved after correct drug treatment during four consecutive weeks.

3) In the case where a correct diagnosis cannot be established due to the non-availability of nasal endoscopy or nasosinusal CT.

4) In the case of unilateral NP.

5) In the event of exacerbation and/or ocular or endocranial complications.

The decision to refer the patient to ENT, Allergology or Pneumology can be based on the availability of specialists and on the patient antecedents or associated disease conditions (Table 9.1) [1, 42, 185, 198, 344, 355, 357-359], taking into account that the circuit should be dynamic and flexible, and in all cases considering the repercussions and individual clinical presentation of each patient with NP (Figure 9.3).

9.3. Evaluation in Otorhinolaryngology (Rhinology)

At this healthcare level the Otorhinolaryngology (ENT) specialist should [1, 42]:

1) Confirm the diagnosis of NP and its extent, using nasal endoscopy.

2) Establish the severity of the disease and the existence of associations.

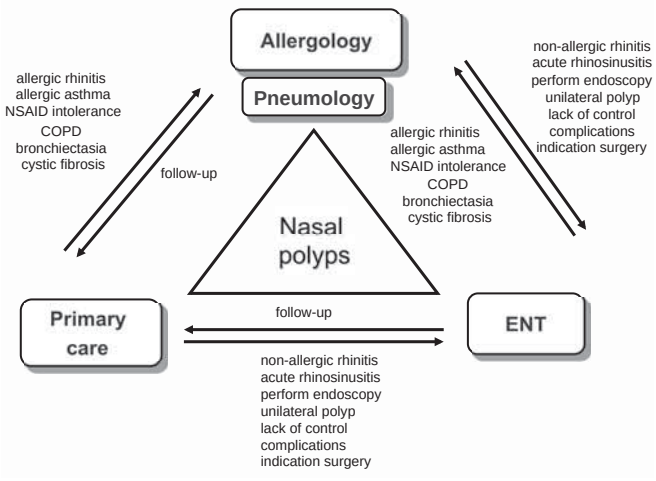


Figure 9.3. Inter-relationship between primary and specialized care in the approach to NP: exploration, complementary tests (endoscopy, CT), diagnosis of NP and its associated conditions, treatment (medical and/or surgical), control and follkow-up [1,42,185,198,344,355,357-359].

Consensus Document on Nasal Polyposis (allergic rhinitis, asthma, COPD, cystic fibrosis, NSAID intolerance) and/or complications (acute rhinosinusitis).

3) Perform the required complementary tests: nasal function (RNM, AR), olfactory function (olfactometry, gustometry).

4) Request imaging tests: for evaluating presurgical disease extent (CT), or where complications are suspected (MRI).

5) Indicate and start treatment (medical or surgical), according to evidence-based medicine.

6) Conduct follow-up of the patients receiving medical treatment or who have undergone surgery:

a) Mild or moderate NP: the appearance of new polyps and the severity of the disease can be evaluated after 6 months.

b) Severe NP: follow-up is advisable after three months, particularly when associating uncontrolled bronchial asthma, anosmia or severe nasal obstruction.

7) Consider interconsultation or referral to Allergology (Figure 9.3) [185, 357]:

a. when allergic disease is suspected

b. to establish adequate control of the associated asthma

c. to assess NSAID tolerance and establish a possible indication of aspirin desensitization

d. when complicated disease is suspected (Churg-Strauss syndrome)

8) Consider interconsultation or referral to Pneumology (Figure 9.3) [198]: when the condition is associated to granulomatous diseases, cystic fibrosis, bronchiectasis, non-allergic asthma or COPD.

9.4 Evaluation in Allergology/ Pneumology

At this healthcare level the allergologist or pneumologist should [185, 198, 357]:

1) Confirm the diagnosis of NP and establish its severity, using nasal endoscopy.

2) Indicate medical treatment (or assess surgical treatment), according to evidence-based medicine.

3) Evaluate and treat the associated diseases in an integral manner: asthma and allergic rhinitis, NSAID intolerance or aspirin-exacerbated respiratory disease (AERD).

4) Patient follow-up:

a. Rhinitis and/or allergic asthma: periodic reviews according to control and indication of medical treatment and/ or specific immunotherapy.

b. NSAID intolerance / AERD: periodic reviews according to asthma control, assessing NSAID tolerance and the need for aspirin desensitization.

5) Consider interconsultation or referral to ENT (Figure 9.3):

a. to corroborate the diagnosis and establish the extent of NP

b. in case of complication (ocular, endocranial)

c. unilateral disease (indication for biopsy)

d. for olfactometry evaluation

e. in case of poor NP control, to establish surgical indications.

9.5 Evaluation in special situations [42, 185, 238]

1) NP in children (cystic fibrosis, antrochoanal polyp): collaboration and multidisciplinary approach among Pediatrics, pediatric ENT and pediatric Pneumology.

2) NP in diabetic patients (corticosteroid use): collaboration and multidisciplinary approach among ENT, Allergology, Pneumology and Endocrinology.

3) NP in patients with ophthalmological disease (glaucoma): collaboration and multidisciplinary approach among ENT, Allergology, Pneumology and Ophthalmology.

4) NP in pregnant patients (corticosteroid use): collaboration and multidisciplinary approach among ENT, Allergology, Pneumology and Obstetrics-Gynecology.

5) NP in patients with bone disease (osteopenia / osteoporosis): collaboration and multidisciplinary approach among ENT, Allergology, Pneumology and Rheumatology.

Key points

- The management of NP requires a multidisciplinary approach, involving the intervention in particular of Primary Care, ENT, Allergology and Pneumology. In special situations the intervention of other medical specialties also may be required.
- In each moment, evaluation is required of the existence of associated diseases, allowing an integral approach from the perspective of the "single airway" concept (Figure 9.1).
- The criteria for referral from Primary Care to the specialist depend on its ulterior purpose: diagnosis and treatment of NP and surgical assessment (ENT), management of rhinitis and allergic asthma (Allergology), management of other respiratory illnesses (Pneumology) (Table, Figure 9.2).
- The criteria for interconsultation among specialists (ENT, Allergology, Pneumology) depend, as in the case of Primary Care, on the ulterior purpose of interconsultation and on the availability of techniques suited for correct diagnosis and follow-up (Figure 9.3).
- Ideally, referral from specialized care (ENT, Allergology, Pneumology) to Primary Care should be possible, in order to conduct patient follow-up once controlled by adequate medical or surgical treatment (Figure 9.3).

10. Research needs in nasal polyposis

Although nasal polyposis (NP) is a prevalent disorder, with a high economical and social cost, and although in recent years many epidemiological, physiopathological and therapeutic studies of NP have been published and a guide has even been presented in 2003 (with posterior revision in 2007), there are still many aspects requiring attention and many questions calling for an answer. In the present chapter we describe some of the issues which we believe require attention.

10.1. Epidemiology

a) Establish the precise prevalence of NP.

b) Establish the precise incidence of NP.

c) Identify the risk factors associated to NP.

d) Establish the precise prevalence of positive allergic tests and specific IgE tests in patients with NP, with the broader objective of studying the possible etiopathogenic relationship between polyposis and allergy.

e) Establish the precise percentage of patients with NP and asthma.

f) Establish the precise percentage of patients with NP and NSAID intolerance.

g) Determine the factors capable of predicting which patients with NP will develop asthma or NSAID intolerance.

h) Determine whether there is a genetic basis underlying NP, and identify which genes may be implicated.

10.2. Pathophysiology

a) Role of infections in the physiopathology of NP.

b) Role of sensitization to allergens in the physiopathology of NP.

c) Role of mucins in the physiopathology of NP.

d) Physiopathological mechanisms of the association of NP to asthma and NSAID intolerance.

e) Histological alterations that may predict the development or course of NP.

f) Exploration of the reasons why some patients with CRS develop NP while others do not.

10.3. Clinical aspects and quality of life

a) Identification of the best method for evaluating the intensity, severity and duration of the symptoms in NP.

b) Identification of the best techniques for evaluating nasal obstruction in NP (AR, RNM, peak nasal inspiratory flow).

c) Design and validation of specific quality of life questionnaires in NP.

d) New indexes for evaluating the severity of NP based on subjective patient assessment and on clinical evaluation according to the nasal endoscopy, CT and olfactory assessment scores.

10.4. Examination and diagnosis

a) Methods for the local detection of specific IgE against bacterial antigens of use in daily clinical practice.

b) Furthered knowledge of the role of bacterial superantigens in NP and associated diseases such as asthma and NSAID intolerance.

c) Role of fungal allergy in NP. Need for the standardization of techniques to assess sensitization to fungal species.

d) Comparative studies of antibiotic therapies versus other types of drug treatments in NP.

e) Determination of which exploratory techniques are ideal for monitoring NP and thus evaluate the response to treatment.

10.5. Differential diagnosis and comorbidities

a) Local and systemic factors implicated in NP relapse in patients with ASA triad.

b) Relationship between NP and food allergy.

c) Confirmation of the relationship between NP and asthma, as well as between NP and bronchiectasis, as regards the epidemiology, etiopathogenesis and severity of the disease.

d) Prospective studies evaluating the effect of surgical and/or medical treatment of NP upon asthma.

e) Role of endonasal desensitization with L-ASA in AERD and its possible use as an alternative to surgery in some patients with NP.

f) Furthering of knowledge of the etiopathogenic mechanisms of AERD with a view to identifying new therapeutic options.

10.6. Medical treatment

a) Role of the antileukotrienes in the treatment of NP.

b) Indications of anti-IgE antibodies (omalizumab) in the treatment of NP.

c) Dose-response evaluation in the use of topical corticosteroids in NP, in order to identify the optimum effective dose.

d) Evaluation based on large series of the local and systemic adverse effects of topical nasal corticosteroids in the treatment of NP.

e) Determination of which oral corticosteroid doses are best, and for how long they should be administered for treating the exacerbations of NP.

10.7. Surgical treatment

a) Definition of clinical criteria for surgical indication in NP.

b) Definition of endoscopic criteria for surgical indication in NP.

c) Definition of a consensus-based universal criterion for endoscopic staging in NP.

d) Consensus-based agreement on the essential need for CT evaluation of the paranasal sinuses in all candidates for surgery.

e) Consensus-based agreement on the drug treatment sequence before and after surgery in NP.

f) Prospective studies are needed to compare the results of surgery in NP involving conservative ("upon demand" according to the existing lesions) and more radical surgical techniques, in homogeneous patient groups.

10.8. Nasal polyposis in children

a) Prospective studies are needed to determine the prevalence of NP in the pediatric population under 12 years of age.

b) Risk factors for the development of NP in the pediatric population. In all children with NP, evaluation should be made of those diseases most commonly associated to NP, and patients with risk disorders should be adequately evaluated to confirm or discard NP.

c) Definition of the treatments best suited to deal with pediatric NP. Well designed studies are needed to evaluate optimum medical and surgical treatment. Regarding topical corticosteroids, studies should focus on defining the dose, duration of therapy, and the short- and long-term efficacy of treatment.

d) Follow-up studies are needed to evaluate the prognosis of NP in children with medical versus surgical treatment.

10.9. Criteria for referral from Primary Care / interconsultation between ENT specialists and allergologists

Evaluation would be required of the proposed interdisciplinary patient referral circuits, in relation to their impact upon:

a) The reduction in time to diagnosis achieved.

b) The timing of adequate treatment.

c) The reduction of exacerbations and the appearance of complications.

d) The reduction of disease severity grades.

e) Improved control of symptoms, quality of life and patient satisfaction.

f) Improved asthma control when the latter disease is also present.

g) The reduction in the number of surgical operations.

h) The reduction in the costs of the disease.

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