

Rhinosinusitis and Nasal Polyps in Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

- Aspirin • Aspirin desensitization • Aspirin-exacerbated respiratory disease (AERD)
- Chronic rhinosinusitis • Corticosteroids • Nasal polyps
- Nonsteroidal antiinflammatory drugs (NSAID)

KEY POINTS

- Aspirin/nonsteroidal antiinflammatory drug sensitivity is common in patients with chronic rhinosinusitis (CRS) and nasal polyps, causing a more severe disease, referred to as aspirin-exacerbated respiratory disease (AERD).
- The nasal polyps and CRS, which are the cornerstone of the diagnosis of AERD, are generally difficult to treat.
- Medication, particularly intranasal spray or corticosteroids in drops, constitutes the first line of treatment of patients with CRS with nasal polyps and AERD.
- Endoscopic sinus surgery is recommended when medication fails, and a follow-up and medication, including nasal and oral corticosteroids, are recommended after surgery.
- Aspirin desensitization, followed by daily aspirin treatment, is presented elsewhere in this issue in the article on aspirin desensitization in AERD.

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INTRODUCTION

The presence of aspirin-exacerbated respiratory disease (AERD) in a patient with chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma is associated with severe eosinophilic upper and lower airway disease. This article deals with the inflammatory disease of the respiratory tract as it relates to the sinuses. Involvement of the sinuses in AERD is almost universal, depending on the stage of onset of the disease and evaluation by computed tomography (CT). A patient with normal sinus CT, asthma, and rhinitis, almost without exception, does not have a positive, oral, nasal, or inhalation aspirin challenge to aspirin and therefore does not have AERD. Thus, CRS is central to AERD. This article explores the clinical aspects, physiopathology, and treatment of rhinosinusitis as it relates to AERD.

DEFINITIONS

CRS

The diagnosis of CRS with or without NP is mainly based on clinical history (presence and duration for more than 12 weeks of sinonasal symptoms), nasal endoscopy, and CT scan of the paranasal sinuses.¹⁻⁴

In the 2012 update of the EPOS international rhinosinusitis guidelines,^{1,2} CRSwNP was defined as inflammation of the sinonasal mucosa with the presence of at least 2 sinonasal symptoms, one of these being nasal blockage/obstruction/congestion or nasal discharge (anterior rhinorrhea/posterior nasal drip), facial pain/pressure, or reduction or loss of smell for more than 12 weeks. Endoscopic signs of NP, edema/mucosal obstruction in the middle meatus, or CT changes within the ostiomeatal complex or paranasal sinuses help form a definitive diagnosis.

As recorded by CT, CRS in patients with AERD with nasal polyposis is characterized by the involvement of all paranasal sinuses and nasal passages and the thickness of hypertrophic mucosa in up to 100% of the patients, to a greater extent than in aspirin-tolerant patients.⁵ Patients with AERD have significantly worse preoperative CT and nasal endoscopy scores than aspirin-tolerant patients.⁶

EPIDEMIOLOGY AND NATURAL HISTORY

CRS, with or without NP, affects 11% and 14% of the European⁷ and American⁸ general populations, respectively. CRSwNP is an inflammatory condition of the nose and paranasal sinuses of unknown cause, which is present in 2% to 4% of the adult population.^{1,2} CRSwNP is often associated with other respiratory diseases such as asthma,⁹ aspirin sensitivity,¹⁰ and idiopathic bronchiectasis.¹¹ The presence of hypersensitivity to aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) in a patient with CRSwNP^{12,13} is usually associated with a particularly severe, persistent, and treatment-resistant form of the disease, usually coexisting with severe asthma.

AERD has been reported in 8% to 26% of patients with CRSwNP and in 10% to 20% of asthmatic patients.¹⁴ The prevalence of nasal polyposis in aspirin-sensitive asthmatics may be as high as 60% to 70%, compared with less than 10% in the population of aspirin-tolerant asthmatics.¹⁵ The precise prevalence of nasal polyposis in AERD is difficult to document, because tiny polyps in and around the middle meatus may be obscured by swollen turbinates, and nasal endoscopy needs to be performed. In addition, shrinkage of polyps after systemic corticosteroids may give a false-negative conclusion in such studies when examination is not repeated after regrowth of polyps. Thus, in AERD, the true prevalence may be closer to 100%. The increased

severity of the upper airway disease in these patients is reflected by the high recurrence of NP and frequent need for endoscopic sinus surgery.¹⁶

Furthermore, CRS and nasal polyposis have an important impact on the patient's quality of life,¹⁷ which is worsened by the presence of atopy¹⁸ and asthma,¹⁹ although there is a clear improvement after both medical and surgical treatments.²⁰ The socioeconomic burden of CRS and nasal polyposis is also considerable. In the United States, the direct treatment cost of CRS has been estimated at 3.4 to 5 US\$ billion annually,²¹ whereas the average surgical costs of functional endoscopic sinus surgery and postsurgical care have been calculated as 7726 US\$ per patient.²² In consequence, the health care cost is burdensome in patients with AERD, who receive 3 sinus operations on average.²³

In the natural course of the syndrome, a clinical history of rhinitis or CRS usually precedes asthma and the development of aspirin hypersensitivity. In the AIANE (European Network on Aspirin-Induced Asthma) cohort study, the disease followed a typical pattern¹⁰: persistent rhinitis/rhinosinusitis appeared first (mean age 30 years), being related to a flulike infection in half of the patients; this was followed by asthma after 2 years, on average (mean age 32 years), and by aspirin-induced respiratory reactions and nasal polyposis after 4 years (mean age 34 years). The clinical presentation in the different European countries was remarkably similar. In women, who outnumbered men by a ratio of 2.3:1, the onset of symptoms occurred significantly earlier and the disease was more severe than in men. Once developed, RSC and asthma follow a course that is usually independent of the aspirin and NSAID avoidance.²³

PATHOPHYSIOLOGY

Cells and Cytokines

CRSwNP is characterized by an intense inflammatory process with perivascular and subepithelial inflammatory cell infiltration, edematous stroma, and formation of pseudocysts. In most patients with CRSwNP, eosinophils are the predominant infiltrating cells.²⁴ The most intense eosinophilic infiltration is usually found in CRSwNP associated with AERD.²⁵

However, recent studies suggest that the dominant inflammatory cell can vary according to the racial characteristics of the population. In contrast with the predominant eosinophilic infiltration detected in whites, neutrophils seem to dominate in Chinese patients with CRSwNP.²⁶ The mechanisms involved in this difference have yet to be clarified.

The recruitment of eosinophils is regulated by various cytokines and vascular adhesion molecules. Increased production of interleukin 5 (IL-5), eotaxins, and RANTES (regulated on activation, normal T-cell expressed, and secreted) has been reported in CRSwNP.^{25,27–29} The highest production of cytokines involved in eosinophil recruitment and activation, such as IL-5, is found in the nasal tissue of patients with CRSwNP and AERD; this explains why these patients showed the most intense eosinophilic inflammatory process.²⁵ Moreover, increased expression of vascular adhesion molecule 1 (VCAM-1) has been detected in CRSwNP and correlated with the level of tissue eosinophilia, suggesting a role for VCAM-1 in eosinophil recruitment to the inflamed CRSwNP tissue.³⁰

Activated lymphocyte, Th2 polarized infiltration is characteristic of CRSwNP as indicated by the predominance of cytokine signals, such as IL-5, a cytokine associated with the Th2 lymphocyte subset.³¹

Mast cells are also abundant in CRSwNP tissue, especially in those with associated AERD.³² The number of mast cells was correlated with the number of

polypectomies, suggesting that mast cell activity is involved in the pathogenesis of nasal polyposis.

Arachidonic Acid Metabolism in CRSwNP with and Without AERD

Arachidonic acid (AA) is formed from the phospholipids of cell membranes by the action of phospholipase A₂. AA can be metabolized by various enzymes such as cyclooxygenase (Cox), and 5-lipoxygenase (5-LO).³³

Cox is found in different isoforms known as Cox-1 and Cox-2. Cox-1 is generally constitutively expressed and considered a housekeeping gene,³³ whereas Cox-2 is induced under chronic inflammatory conditions.^{34–36} Several prostaglandins (PGs) are synthesized as a result of Cox-2 activation; these are known as PGE₂, PGF_{2α}, and PGD₂. PGD₂ and PGF_{2α} are bronchoconstrictors and PGD₂ is released by mast cells during allergic reactions.³³

PGE₂ can perform contrasting activities, such as bronchodilation and bronchoconstriction in the airways, and antiinflammatory and proinflammatory actions in the lung.³⁷ The origin of the various PGE₂ actions seems to partly depend on the different types of cell surface receptors that may be stimulated by this PG. There are 4 different PGE₂ receptors: EP₁ to EP₄. The stimulation of EP₂ and EP₄ results in relaxing effects. In contrast, EP₁ acts as a constrictor, whereas EP₃ (various isoforms of which are known to result from a splicing process) is considered an inhibitor receptor. The presence or predominance of any given type of receptor in cells could explain the different effects induced by PGE₂.³⁸ The Cox-1 pathway is the target for classic NSAIDs, whereas coxibs are selective Cox-2 inhibitors.³⁹

AA can also be metabolized through the 5-LO pathway. 5-LO is mostly found in cells that are involved in inflammatory responses, such as eosinophils, neutrophils, mast cells, and macrophages. 5-LO is usually located in the cytoplasm; it translocates toward the nuclear membrane to interact with its processing protein, called FLAP, thus enabling it to oxygenate the AA to form a hydroperoxide (5-HPETE), which in turn is converted into leukotriene A₄ (LTA₄) by the 5-LO. In some cells, LTA₄ can be transformed into LTB₄ by an LTA₄ hydrolase or into LTC₄ by an LTC₄ synthase enzyme (LT-C₄S). The LTC₄ is exported toward the exterior of the cells, where it is later metabolized into LTD₄ and LTE₄ by a γ-glutamyl-transpeptidase and a dipeptidase, respectively. LTC₄, LTD₄, and LTE₄ form the so-called cysteinyl leukotrienes (Cys-LTs), previously known as the slow-reacting substance of anaphylaxis. Cys-LTs are powerful bronchoconstrictors, which enhance edema formation and are chemotactic for eosinophils.⁴⁰

Cys-LTs act as agonists to at least 2 receptors: Cys-LT₁ and Cys-LT₂. The former is widely distributed in inflammatory cells and seems to intervene in rhinitis and asthma reactions, whereas the latter is located predominantly in the blood vessels and its function is still unknown.⁴⁰

AA can also be metabolized by a more complex mechanism called transcellular biosynthesis, whereby at least 2 different types of cells work together. The result of this combined activity is the synthesis of lipoxins (LXs) LXA₄, LXB₄, 15-epi-LXA₄, and 15-epi-LXB₄. Their synthesis occurs via 3 transcellular routes: the first involves the generation of LTA₄ by the 5-LO present in cells of myeloid lineage, which are taken up by platelets, where LTA₄ is metabolized by the enzyme 12-LO to form LX₄. A second route involves the generation of 15-hydroxyeicosatetraenoic acid (15 [S]-HETE) by 15-LO of epithelial or monocyte cells, which serves as a substrate for 5-LO in neutrophils to produce LX₄ and LXB₄. There is also a third route involving Cox-2 and 5-LO, in the so-called aspirin-triggered 15-epi-LX pathway. In this pathway, aspirin causes the blockage of the catalytic activity of Cox-2, which becomes unable

to produce PGs. At the same time, the Cox-2 acquires the ability to produce 15(S)-HETE, which is converted by the 5-LO of leukocytes into epimers of LXs (15-epi-LXA₄ and 15-epi-LXB₄).

LXs have powerful antiinflammatory properties, including the inhibition of chemotaxis and the adherence and endothelial transmigration of neutrophils.

AA metabolism in CRSwNP

Cox pathway Various studies have reported low PGE₂ production in CRSwNP of patients with and without aspirin intolerance, compared with control nasal mucosa.^{25,41} The deficient production of PGE₂ was greater in aspirin-intolerant than in aspirin-tolerant patients.

Given the dependence of PGE₂ production on Cox-1 and Cox-2 activity, the expression of both enzymes has been assessed in nasal mucosa and in NP. Cox-1 is usually considered an enzyme that responds to the physiologic needs of cells but is not involved in inflammatory responses. However, some studies have shown mild increases in its expression in inflamed tissues.³³ A substantial upregulation of Cox-1 has been reported in CRSwNP associated with cystic fibrosis, a finding that suggests that airway Cox-1 is sensitive to inflammatory stimuli.³⁵ However, other studies on the regulation of Cox-1 in CRSwNP of patients with and without aspirin intolerance have yielded contradictory results. Some studies have reported no differences at baseline in Cox-1 expression between nasal mucosa and NP from either asthma-tolerant or asthma-intolerant asthmatics,^{42,43} whereas others using proinflammatory stimulation have reported a lower Cox-1 expression in fibroblasts of NP derived from patients with asthma-intolerant asthma compared with healthy nasal mucosa.⁴¹

Because Cox-2 expression increases in inflammatory processes, a concomitant alteration in the expression of Cox-2 would be expected to complement the changes in PGE₂ levels detected in NP. In line with the results reported with PGE₂, Cox-2 expression has been shown to be downregulated in NP of patients with and without aspirin hypersensitivity^{25,41–45} through a potential Nuclear Factor κ B-mediated downregulation.⁴⁶ However, other studies failed to find any difference in the expression of Cox-2 in the NP of aspirin-intolerant, aspirin-tolerant, and control individuals.⁴⁷

There are no clear explanations to account for the discrepancies reported in the regulation of the 2 Cox enzymes in asthma and NP. Differences in the methods used in the identification and quantification of enzymes probably help explain these discrepancies. In general, the studies that used real-time polymerase chain reaction and Western blot techniques found low expression of the enzymes, whereas those using immunohistochemistry found contradictory results, with low or similar expression of Cox-2 in NP compared with nasal mucosa. It has been suggested that discrepancies may result from the use of polyclonal or monoclonal antibodies.⁴⁸ The accuracy of this methodology can also be limited in studies of tissues samples with different cell composition, such as healthy nasal mucosa and inflamed NP infiltrated by numerous inflammatory cells. To overcome these technical limitations, a recent study assessed Cox-2 expression, with enzyme-linked immunosorbent assay, Western blot, and immunostaining in isolated and stimulated fibroblast derived from nasal mucosa and NP from both aspirin-tolerant and aspirin-intolerant patients. The 3 methods confirmed the low expression of Cox-2 expression in NP from both aspirin-tolerant and aspirin-intolerant patients.⁴¹

The expression of the 4 PGE₂ G protein-coupled receptors designated EP₁ to EP₄ has been assessed in CRSwNP. A reduced expression of EP₂ receptor has been

reported in nasal inflammatory cells and fibroblast of NP of aspirin-intolerant patients.^{41,43,49}

Because most of the antiinflammatory effects of PGE₂ seem to be induced by the stimulation of the EP₂ receptor,^{37,38} the association of the reduced release of PGE₂, a substance with antiinflammatory properties in the airways, with the low expression of the PGE₂ receptor involved in the transmission of antiinflammatory signals might contribute to the intensification of the inflammatory process in the upper airways of patients with NP, especially in those with associated aspirin intolerance.⁴¹

Lipoxygenase pathway Some studies have reported increased production of CysLT in CRSwNP of patients with asthma with and without aspirin hypersensitivity.⁵⁰ When the production of CysLT is assessed by measuring the urinary levels of leukotriene E₄, various studies have reported a significant higher urinary excretion of LTE₄ at baseline in patients with CRSwNP and aspirin intolerance compared with CRSwNP from aspirin-tolerant patients.⁵⁰ The baseline levels increase even further when aspirin-intolerant patients are challenged with oral, intravenous, and intranasal aspirin.^{50–52} One recent study reported that severe aspirin-tolerant asthmatics also showed a significantly higher urinary LTE₄ concentration at baseline, compared with mild/moderate patients with aspirin-tolerant asthma.⁵³ This observation suggests that overproduction of CysLTs is closely associated with asthma severity and the presence of CRSwNP. Therefore, an increased production of CysLTs should not be considered a condition exclusively associated with aspirin hypersensitivity. Because most patients with aspirin-intolerant asthma suffer from a severe form of the disease,¹⁰ it is possible that the increased production of CysLT production detected in these patients is related, at least in part, to the severity of the associated asthma.

A recent study found a significant decrease in the urinary LTE₄ concentrations after endoscopic sinus surgery in both CRSwNP aspirin-tolerant and CRSwNP aspirin-intolerant patients with asthma, probably as a consequence of the elimination of many CysLT-producing cells in the sinus.⁵³ This observation suggests that CRSwNP is one of the most important factors involved in CysLT overproduction in asthma.⁵⁰

The increased production of CysLT in CRSwNP is associated with the increased expression of the LTC₄ synthase enzyme, and both CysLT production and LTC₄ synthase expression are significantly correlated with the intensity of the eosinophilic infiltration present in NP tissue.^{25,43} CysLT levels in patients with CRSwNP positively correlate with IL-5 concentrations, a cytokine that primes eosinophils and thereby increases the biosynthesis capacity of these cells to produce CysLT.²⁵ These observations suggest that there is a close link between CysLT overproduction and the accumulation of activated eosinophil in CRSwNP.⁵⁰

Pharmacologic studies in human individuals provide evidence for the existence of at least 3 functional receptors for CysLT, although only 2 have been identified: the so-called CysLT₁ and CysLT₂ receptors.⁵⁴ CysLT₁ has been detected in eosinophils, mast cells, macrophages, neutrophils and vascular cell in human nasal mucosa. CysLT₂ receptors are broadly distributed in leukocytes, heart tissue, brain, adrenal gland, and the vasculature.⁵⁴

Increased numbers of nasal inflammatory cells expressing CysLT₁ have been reported in CRSwNP of patients with aspirin intolerance.^{43,49} Desensitization with lysine-aspirin selectively reduced the number of leukocytes expressing CysLT₁, suggesting that downregulation of CysLT₁ could be a mechanism of therapeutic benefit.⁵⁵

A recent study has also reported an increased expression of CysLT₂ receptor in NP from aspirin-intolerant patients with asthma compared with aspirin-tolerant

asthmatics.⁴³ Because no data on the role of CysLT₂ receptor in asthma and rhinitis have been reported, the biological significance of this observation is not clear.

Transcellular metabolisms (LXs) Levels of LXA₄ have been reported as being higher in patients with CRSwNP compared with control nasal mucosa, but lower in CRSwNP of aspirin-intolerant patients compared with the levels found in CRSwNP of aspirin-tolerant asthmatics.²⁵ A recent study reported that the urinary levels of 15-epi-LXA₄ were significantly lower in aspirin-intolerant asthmatics compared with aspirin-tolerant patients and control nasal mucosa. These findings seem to indicate a deficient regulation of antiinflammatory AA metabolites generated through the transcellular pathway in patients with CRSwNP and aspirin intolerance.

Several observations support the notion that changes in the regulation of AA metabolism are involved in the path physiology of CRSwNP, especially when CRSwNP is associated with aspirin intolerance. Some studies have reported changes at different levels of the Cox pathway, including very low production of PGE₂, alterations in the regulation of both Cox-1 and Cox-2 under inflammatory conditions, and low expression of the EP₂ receptor. Moreover, studies have shown that the 5-LO pathway is very active in CRSwNP, especially when CRSwNP is associated with aspirin intolerance, resulting in an increased production of CysLTs. In contrast with EP₂ receptor, the CysLTs receptor CysLT₁ is unregulated in CRSwNP, and this helps maximize the proinflammatory effects of CysLT.

The impaired regulation of substances (PGE₂) and receptors (EP₂) with antiinflammatory effects, associated with the increased production of proinflammatory products (CysLT) and upregulation of their receptors (CysLT₁) probably plays a part in enhancing and perpetuating the inflammatory process present in CRSwNP. Alterations in the AA metabolisms might also contribute to the development of AERD. The mechanisms involved in the reported altered regulation of AA metabolism remain to be clarified.

DIAGNOSIS

CRS

The diagnosis of CRS with or without NP is based on clinical history (presence and duration for more than 12 weeks of sinonasal symptoms), nasal endoscopy (when available), and CT scan of the paranasal sinuses.¹⁻³ Computed axial tomography is the accepted gold standard for identifying pacifications within the sinuses, with a pattern ranging from bilateral mucosal thickening to complete opacification of all sinuses.

AERD

The diagnosis of aspirin hypersensitivity is based on a history of adverse respiratory reactions precipitated by the intake of aspirin or other NSAIDs. In asthmatic patients with CRS and NP and a negative history or in those who have never been exposed to NSAIDs, provocation testing may be required.⁵⁶

The reference standard for the diagnosis of hypersensitivity to aspirin and other NSAIDs is outlined in detail in the article on "AERD: clinical disease and diagnosis" elsewhere in this issue. The oral aspirin challenge and several protocols have been developed and described.⁵⁷ In Europe, inhalation (bronchial) challenge with lysine-aspirin (a soluble form of acetylsalicylic acid) was introduced more than 30 years ago⁵⁸ and is considered the test of choice for confirming or excluding aspirin sensitivity in patients with bronchial asthma. Although both tests have similar sensitivity

and specificity, the inhalation test is faster and safer to perform than the oral challenge, and the adverse reaction it creates can be easily reversed with nebulized β_2 agonists. A nasal provocation test with lysine-aspirin is also a reliable tool for diagnosing aspirin hypersensitivity, providing that the clinical symptoms are combined with an objective and standardized technique of nasal airflow measurement.^{59,60} The nasal test is rapid and safe and can be performed in an outpatient setting even in asthmatic patients with reduced pulmonary function who are suitable for bronchial provocation. In experienced hands, the sensitivity of intranasal aspirin provocation easily approaches the performance of the bronchial challenge.

In vitro tests measuring aspirin-specific peripheral blood leukocyte activation have recently been proposed for the diagnosis of aspirin sensitivity. These newly developed in vitro tests, involving either peripheral blood leukocytes (Aspirin-Sensitive Patients Identification Test)⁶¹ or basophil activation⁶² seem to show promising performance, but require further investigation and validation before becoming routine tools for confirming the presence of aspirin hypersensitivity.

MANAGEMENT

The management of patients with CRSwNP and AERD is mainly based on patient training, NSAID avoidance, standard medical or surgical treatment of CRS and nasal polyposis, in addition to standard medical treatment of bronchial asthma, and potential aspirin desensitization in selected patients. The treatment also depends on the stage and severity of the disease.^{1,63}

Education and Drug Avoidance

Because aspirin and other NSAIDs can induce severe asthma attacks, the avoidance of these drugs by aspirin-sensitive patients, and their training in this respect, is a hallmark of the management of patients with CRS, NP, and AERD. Physicians should educate patients on various fronts so that they can better understand their disease: first, respiratory problems are not limited to a specific drug but they may appear after the intake of aspirin or any NSAID; second, many compounds for the common cold or flu contain aspirin or other NSAIDs and should be avoided; and third, when analgesic and antipyretic treatment is needed, several safe drugs may be recommended as alternatives, including acetaminophen (up to 1000 mg) and partially selective (meloxicam, nimesulide) or selective COX-2 inhibitors (coxibs).⁶⁴

Medical Treatment

Intranasal corticosteroids^{1,65} and, occasionally, short courses of oral steroids^{66,67} are the most effective drugs for treating CRSwNP and constitute the first line of treatment.^{1,63} Both topical and systemic corticosteroids may affect the eosinophil function by both directly reducing eosinophil viability and activation or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells, in both aspirin-sensitive and aspirin-tolerant patients.⁶³ For safety purposes, and because a patient with AERD receives long-term treatment with intranasal and inhaled steroids as well as short courses of oral steroids during their life span, those intranasal corticosteroids with lower drug bioavailability should be preferred.⁶⁸ Furthermore, topical corticosteroids in nasal drop formulation have shown greater efficacy than those in spray formulation in reducing the need for surgery in patients with severe CRSwNP.⁶⁹

Other medications have proved effective for patients with CRSwNP. Nasal saline irrigation, both isotonic and hypertonic, as well as short-term (before surgery) and

long-term (after surgery) antibiotics may help to alleviate nasal symptoms.^{1,70} Although antileukotrienes do have some effect, they have not proved more effective in aspirin-sensitive than in aspirin-tolerant patients.⁷¹

Several drugs have been investigated in terms of their efficacy in the treatment of CRSwNP (**Table 1**).¹ Although some products have not shown any real efficacy (antihistamines, antimycotics, phytotherapy, capsaicin, nasal decongestants, mucolytics, topical antibiotics, and proton pump inhibitors), others have shown some efficacy but need more investigation to warrant a full recommendation in international guidelines: antileukotrienes, anti-IgE/omalizumab,^{72,73} or anti-IL-5/mepolizumab.⁷⁴

Surgical Treatment

Sinonasal surgery (polypectomy, functional endoscopic sinus surgery, or ethmoidectomy) is reserved for patients with severe or uncontrolled symptoms and for those with inadequate improvement despite intranasal and oral steroid therapy.¹ The aim of endoscopic sinus surgery is to improve nasal symptoms and patients' quality of life but also to reduce bronchial symptoms and requirement for asthma medications.⁵ However, patients with AERD seem to respond less to surgical interventions.^{75,76} Patients with CRS and NP have a high tendency to recurrence after surgery: this recurrence rate is up to 10 times higher in patients with AERD, even after endoscopic sinus surgery,⁷⁷ and patients are more likely to undergo repeated sinus surgical interventions.¹⁶ To prevent or reduce the relapse of NP, international guidelines recommend the continuation of medical management after surgery (**Table 2**).^{1,65} Intranasal corticosteroids have proved their efficacy and safety for up to 5 years of treatment after surgery.⁷⁸

Aspirin Desensitization

Aspirin desensitization is recommended for patients with AERD with severe corticoid-dependent asthma, those with recurrent nasal polyposis requiring more than 1

Table 1
Levels of evidence and recommendations for the management of adults with CRSwNP

Treatment	Level/Grade of Recommendation	Relevance
Oral antibiotics		
Short-term (<4 wk)	Ib and Ib(-), C ^a	Yes Small effect
Long-term (≥12 wk)	III, C	Yes Small effect If IgE level is not increased
Topical corticosteroids	Ia, A	Yes
Oral corticosteroids	Ia, A	Yes
Nasal saline irrigation ^b	Ib, D	Yes For symptomatic relief
Antileukotrienes	Ib(-), A(-)	No
Aspirin desensitization	II, C	Unclear

No data of efficacy or no studies for: topical antibiotics, anti-IL-5 (unclear), anti-IgE, nasal/oral decongestants, mucolytics, phytotherapy, topical/systemic antimycotics, furosemide, immunosuppressants, capsaicin, proton pump inhibitors.

^a One positive and 1 negative study. Therefore recommendation C.

^b No data in single use.

Data from Fokkens WJ, Lund V, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. *Rhinology* 2012;50(Suppl 23):217.

Table 2 Levels of evidence and recommendations for the postoperative management of adults with CRSwNP		
Treatment	Level/Grade of Recommendation	Relevance
Oral antibiotics		
Short-term (<4 wk)	Ib, A	Yes Small effect
Long-term (≥12 wk)	Ib, C ^a	Yes If IgE level is not increased
Topical corticosteroids	Ia, A	Yes
Oral corticosteroids	Ia, A	Yes
Anti-IL-5	Ib, A	Yes
Anti-leukotrienes	Ib(-), A(-) ^b	No

No data of efficacy or no studies for: oral antihistamines in allergic patients (unclear), nasal saline irrigation (unclear), anti-IgE (unclear), aspirin desensitization, furosemide.

^a Indications exist for better efficacy in CRS without NP.

^b Negative study, recommended not to use.

Data from Fokkens WJ, Lund V, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. *Rhinology* 2012;50(Suppl 23):217.

operative intervention, and for patients who require aspirin or NSAID daily therapy for other medical reasons, such as chronic arthritis or coronary artery disease. Although the mechanism of action is still unclear, systemic^{57,79,80} or intranasal^{81,82} aspirin desensitization plays a part in protecting against recurrences of CRSwNP. Aspirin desensitization not only improves nasal symptoms such as the loss of smell but also leads to significant reductions in sinus infections, polyp formation, recurrence rate, need for polyp operations per year, and dosage of intranasal corticosteroids. See the article elsewhere in this issue for a detailed discussion of this subject.

REFERENCES

1. Fokkens WJ, Lund V, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. *Rhinology* 2012;50(Suppl 23):1–298.
2. Fokkens WJ, Lund V, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;50(1):1–12.
3. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy* 2011;1:2.
4. Mullol J, Mariño-Sánchez F, Alobid I, et al. Clinical examination and differential diagnosis in rhinology. In: Georgalas C, Fokkens WJ, editors. *Rhinology and skull base surgery: from the lab to the operating room*. Stuttgart (Germany): Thieme; 2012. p. 134–55.
5. Awad OG, Lee JH, Fasano MB, et al. Sinonasal outcomes after endoscopic sinus surgery in asthmatic patients with nasal polyps: a difference between aspirin-tolerant and aspirin-induced asthma? *Laryngoscope* 2008;118(7):1282–6.
6. Robinson JL, Griest S, James KE, et al. Impact of aspirin intolerance on outcomes of sinus surgery. *Laryngoscope* 2007;117(5):825–30.
7. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA²LEN study. *Allergy* 2011;66(9):1216–23.

8. Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. Current findings, future directions. *J Allergy Clin Immunol* 1997;99(6):S829–48.
9. Alobid I, Cardelús S, Benítez P, et al. The impact of asthma on the sense of smell in patients with chronic rhinosinusitis and nasal polyps. *Rhinology* 2011;49(5):519–24.
10. Szczeklik A, Nizankowska E, Duplaga M. On behalf of the AIANE (European Network on Aspirin-Induced Asthma) Investigators. Natural history of aspirin-induced asthma. *Eur Respir J* 2000;16:432–6.
11. Guilemany JM, Angrill J, Alobid I, et al. United airways: the impact of chronic rhinosinusitis and nasal polyps in bronchiectatic patient's quality of life. *Allergy* 2009;64:1524–9.
12. Widál MF, Abrami P, Lermoyez J. Anaphylaxie et idiosyncrasie. *Presse Med* 1922; 30:189–92 [in French].
13. Samter M, Beers RF Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968;68(5):975–83.
14. Bavbek S, Dursun B, Dursun E, et al. The prevalence of aspirin hypersensitivity in patients with nasal polyposis and contributing factors. *Am J Rhinol Allergy* 2011; 25(6):411–5.
15. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. *J Allergy Clin Immunol* 1977;59(1):17–21.
16. Vento SI, Ertama LO, Hytönen ML, et al. Nasal polyposis: clinical course during 20 years. *Ann Allergy Asthma Immunol* 2000;85(3):209–14.
17. Alobid I, Bernal-Sprekelsen M, Mullol J. Chronic rhinosinusitis and nasal polyps. The role of generic and specific questionnaires on assessing its impact on patient's quality of life. *Allergy* 2008;63(10):1267–79.
18. Alobid I, Benítez P, Valero A, et al. The impact of atopy, sinus opacification, and nasal patency on quality of life in patients with severe nasal polyposis. *Otolaryngol Head Neck Surg* 2006;134:609–12.
19. Alobid I, Benítez P, Bernal-Sprekelsen M, et al. The impact of asthma and aspirin sensitivity on quality of life of patients with nasal polyposis. *Qual Life Res* 2005;14: 789–93.
20. Alobid I, Benítez P, Bernal-Sprekelsen M, et al. Nasal polyposis and its impact on quality of life. Comparison between the effects of medical and surgical treatments. *Allergy* 2005;60:452–8.
21. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat* 10 2009;(242):1–157.
22. Bhattacharyya N, Orlandi RR, Grebner J, et al. Cost burden of chronic rhinosinusitis: a claims-based study. *Otolaryngol Head Neck Surg* 2011;144(3):440–5.
23. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002;89(5):474–8.
24. Bachert C, Gevaert P, Holtappels G, et al. Nasal polyposis: from cytokines to growth. *Am J Rhinol* 2000;14:279–90.
25. Pérez-Novo C, Watelet JB, Claeys C, et al. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. *J Allergy Clin Immunol* 2005;115:1189–96.
26. Zang N, van Zele T, Pérez-Novo C, et al. Different types of T-effector cells orchestrated mucosal inflammation in chronic sinus disease. *J Allergy Clin Immunol* 2008;122:961–8.
27. Beck LA, Stellato C, Beall LD, et al. Detection of the chemokine RANTES and endothelial adhesion molecules in nasal polyps. *J Allergy Clin Immunol* 1996; 98:766–80.

28. Olze H, Forster U, Zuberbier T, et al. Eosinophilic nasal polyps are rich source of eotaxin-1, eotaxin-2 and eotaxin-3. *Rhinology* 2006;44:145–50.
29. Pods R, Ross D, van Hulst S, et al. RANTES, eotaxin and eotaxin-2 expression and production in patients with aspirin triad. *Allergy* 2003;58:1165–70.
30. Jahsen FL, Haraldsen G, Aanesen JP, et al. Eosinophilic infiltration is related to increased expression of vascular adhesion molecule-1 in nasal polyps. *Am J Respir Cell Mol Biol* 1995;12:624–32.
31. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy* 2006;61:1280–9.
32. Kowalski ML, Lewnansowska-Polak A, Wozniak J, et al. Association of stem cell factor expression in nasal polyp epithelial cells with aspirin sensitivity and asthma. *Allergy* 2005;60:613–7.
33. Simmons DL, Botting RM, Hla T. Cyclooxygenase isoenzymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol Rev* 2004;56:387–437.
34. Siegle I, Klein T, Backman JT, et al. Expression of cyclooxygenase 2 in human synovial tissue. Differential elevation of cyclooxygenase 2 in inflammatory joint diseases. *Arthritis Rheum* 1998;41:122–9.
35. Roca-Ferrer J, Pujols L, Gartner S, et al. Upregulation of COX-1 and COX-2 in nasal polyps in cystic fibrosis. *Thorax* 2006;61:592.
36. Xaubet A, Roca-Ferrer J, Pujols L, et al. Cyclooxygenase-2 is up-regulated in lung parenchyma of chronic obstructive pulmonary disease and down-regulated in idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:35–42.
37. Vancheri C, Mastruzzo C, Sortino MA, et al. The lung as a privileged site for the beneficial actions of PGE₂. *Trends Immunol* 2004;25:40–6.
38. Sugimoto Y, Narumiya S. Prostaglandin E receptors. *J Biol Chem* 2007;282:11613–7.
39. Picado C. Mechanisms of aspirin sensitivity. *Curr Allergy Asthma Rep* 2006;6:198–202.
40. Kanaoka Y, Boyce JA. Cysteinyl leukotrienes and their receptors: cellular distribution and function in immune and inflammatory responses. *J Immunol* 2004;173:1503–10.
41. Roca-Ferrer J, Garcia-Garcia FJ, Pereda J, et al. Reduced expression of COXs and production of prostaglandin E2 in patients with nasal polyps with and without aspirin-intolerant asthma. *J Allergy Clin Immunol* 2011;128:66–72.
42. Picado C, Fernández-Morata JC, Juan M, et al. Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. *Am J Respir Crit Care Med* 1999;160:291–6.
43. Adamusiak AM, Stasikowska-Kanicka O, Lewandowska-Polak A, et al. Expression of arachidonate metabolisms enzymes and receptors in nasal polyps of aspirin-hypersensitive asthmatics. *Int Arch Allergy Immunol* 2010;157:354–62.
44. Mullol J, Fernández-Morata JC, Roca-Ferrer J, et al. Cyclooxygenase 1 and cyclooxygenase 2 expression is abnormally regulated in human nasal polyps. *J Allergy Clin Immunol* 2002;109:824–30.
45. Pujols L, Mullol J, Alobid I, et al. Dynamics of COX-2 in nasal mucosa and nasal polyps from aspirin-tolerant and aspirin-intolerant patients with asthma. *J Allergy Clin Immunol* 2004;114:814–9.
46. Picado C, Bioque G, Roca-Ferrer J, et al. Nuclear factor-kappa C activity is down-regulated in nasal polyps from aspirin-sensitive asthmatics. *Allergy* 2003;58:122–6.
47. Adamjee J, Suh YJ, Park HS, et al. Expression of 5-lipoxygenase and cyclooxygenase pathway enzymes in nasal polyps of patients with aspirin-intolerant asthma. *J Pathol* 2006;209:392–9.

48. Sampson AP. Aspirin-intolerant asthma. New insights from bronchial mucosal biopsies. In: Sczceklik A, Gryglewski RJ, Vane J, editors. Eicosanoids, aspirin and asthma. New York: Marcel Dekker; 1998. p. 371–89.
49. Ying S, Meng Q, Scadding G, et al. Aspirin-sensitive rhinosinusitis is associated with reduced E-prostanoid 2 receptor expression on nasal mucosal inflammatory cells. *J Allergy Clin Immunol* 2006;117:312–8.
50. Higashi N, Taniguchi M, Mita H, et al. Aspirin-intolerant asthma (AIA) assessment using the urinary biomarkers, leukotriene E_4 (LTE $_4$) and prostaglandin E_2 (PGD $_2$) metabolites. *Allergol Int* 2012;61:393–403.
51. Micheletto C, Tognella S, Visconti M, et al. Changes in urinary LTE $_4$ and nasal functions following nasal provocation test with ASA in ASA-tolerant and-intolerant asthmatics. *Respir Med* 2006;100:2144–50.
52. Picado C, Ramis I, Rosello J, et al. Release of peptide leukotriene into nasal secretions after local instillation of aspirin in aspirin-sensitive asthmatic patients. *Am Rev Respir Dis* 1992;145:1028–9.
53. Higashi N, Taniguchi M, Mita H, et al. Clinical features of asthmatic patients with increased urinary leukotriene E_4 excretion (hyperleukotrienuria): involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol* 2004;113:277–83.
54. Laidlaw TM, Boyc JA. Cysteinyl leukotriene receptors, old and new: implications for asthma. *Clin Exp Allergy* 2012;42:1313–20.
55. Sousa AR, Parikh A, Scadding G, et al. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* 2002;347:1493–9.
56. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62(10):1111–8.
57. Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep* 2009;9(2):155–63.
58. Bianco SR, Robuschi M, Petrini G. Aspirin induced tolerance in aspirin asthma detected by a new challenge test. *IRCS J Med Sci* 1977;5:129.
59. Milewski M, Mastalerz L, Nizankowska E, et al. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. *J Allergy Clin Immunol* 1998;101(5):581–6.
60. Casadevall J, Ventura PJ, Mullol J, et al. Intranasal challenge with aspirin in the diagnosis of aspirin-intolerant asthma. Evaluation of nasal response by acoustic rhinometry. *Thorax* 2000;55:921–4.
61. Kowalski ML, Ptasińska A, Jedrzejczak M, et al. Aspirin-triggered 15-HETE generation in peripheral blood leukocytes is a specific and sensitive Aspirin-Sensitive Patients Identification Test (ASPITest). *Allergy* 2005;60(9):1139–45.
62. Kim MS, Cho YJ. Flow cytometry-assisted basophil activation test as a safe diagnostic tool for aspirin/NSAID hypersensitivity. *Allergy Asthma Immunol Res* 2012;4(3):137–42.
63. Alobid I, Mullol J. Role of medical therapy in the management of nasal polyps. *Curr Allergy Asthma Rep* 2012;12(1):144–53.
64. Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity: safety of cyclo-oxygenase-2 inhibitors. *Treat Respir Med* 2006;5(6):399–406.
65. Mullol J, Obando A, Pujols L, et al. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. *Immunol Allergy Clin North Am* 2009;29(4):657–68.

66. Mullol J, Alobid I. Combined oral and intranasal corticosteroid therapy: an advance in the management of nasal polyposis? *Ann Intern Med* 2011;154(5): 365–7.
67. Martinez-Devesa P, Patiar S. Oral steroids for nasal polyps. *Cochrane Database Syst Rev* 2011;(7):CD005232.
68. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy* 2008;63(10):1292–300.
69. Aukema AA, Mulder PG, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. *J Allergy Clin Immunol* 2005;115:1017–23.
70. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. *J Allergy Clin Immunol* 2010;125(5): 1069–1076.e4.
71. Ragab S, Parikh A, Darby YC, et al. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. *Clin Exp Allergy* 2001;31:1385–91.
72. Vennera MC, Picado C, Mullol J, et al. Efficacy of omalizumab in the treatment of nasal polyps. *Thorax* 2011;66(9):824–5.
73. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2012. <http://dx.doi.org/10.1016/j.jaci.2012.07.047>.
74. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011;128(5):989–995.e1-8.
75. Batra PS, Kern RC, Tripathi A, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. *Laryngoscope* 2003;113(10): 1703–6.
76. Mendelsohn D, Jeremic G, Wright ED, et al. Revision rates after endoscopic sinus surgery: a recurrence analysis. *Ann Otol Rhinol Laryngol* 2011;120(3):162–6.
77. Kim JE, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. *Ear Nose Throat J* 2007;86(7):396–9.
78. Rowe-Jones JM, Medcalf M, Durham SR, et al. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. *Rhinology* 2005;43(1):2–10.
79. Nucera E, Schiavino D, Milani A, et al. Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax* 2000;55:75–8.
80. Pfaar O, Klimek L. Eicosanoids, aspirin-intolerance and the upper airways—current standards and recent improvements of the desensitization therapy. *J Physiol Pharmacol* 2006;57(Suppl 12):5–13.
81. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. *Laryngoscope* 2005;115:1385–90.
82. Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. *J Laryngol Otol* 2007;121:1156–60.