REVIEW | Eur Ann Allergy Clin Immunol | Vol 58, N.1, 4-17, 2026

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A clinical update on chronic rhinosinusitis and nasal polyposis

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Key words

Chronic rhinosinusitis; nasal polyps; phenotype; endotype; biologics.

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Doi
10.23822/EurAnnACI.1764-1489.385

Impact statement

Chronic rhinosinusitis causes significant morbidity. This narrative review focuses on the disease's pathophysiology and discusses key aspects of diagnosis and treatment based on the authors' clinical experience.

Summary

Chronic rhinosinusitis (CRS) is a complex heterogeneous disease of the nose and paranasal sinuses that presents different phenotypes and endotypes. CRS is a common health problem associated with significant morbidity, as well as with high health care expenditure. As our knowledge on inflammation, tissue remodeling and pathophysiological mechanisms develops, both diagnosis and therapeutic approaches to CRS improve. This review outlines key drivers in the pathogenesis of CRS with and without nasal polyps, current diagnostic tools clinicians can rely on in clinical practice, and current and future treatment options, while providing a general overview of up-to-date guidelines for CRS diagnosis and management. A better understanding of CRS can pave the way for the optimization and development of novel therapies, benefiting patients who suffer with more severe phenotypes and allowing a personalized approach to the disease.

Introduction

The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) international consensus defines rhinosinusitis in adults as an inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure or reduction or loss of smell, or both. Besides these

symptoms, endoscopic signs of nasal polyps and/or mucopurulent discharge primarily from the middle meatus and/or edema/mucosal obstruction primarily in middle meatus must be present, and/or mucosal changes within the ostiomeatal complex and/or sinuses must be seen by computerized tomography (CT) (1). In children, the definition of rhinosinusitis differs in one criterion: the interference on smell in adults is replaced by the presence of cough in children (1) (**figure 1**) Chronic rhinosinusitis (CRS) is defined as the maintenance of two or more symptoms, one of which should be either nasal blockage or obstruction or congestion or nasal discharge, for at least 12 weeks without complete resolution (1). CRS is associated with a significant impact on quality of life (QoL) and on healthcare costs, particularly indirect costs (1).

In 2011, a large-scale study calculated a CRS prevalence of 10.9% in the adult population of Europe based on EPOS criteria (2). The prevalence of CRS based on symptoms varies between 5.5% and 28%, being more common among smokers than non-smokers (2-5). This variation from 5.5% to 28% corresponds to higher prevalences found in Europe, followed by United States, China, and Brazil, where lower prevalence rates were found (2-5). Several factors may account for this wide variation in prevalence between countries, including differences in healthcare systems and access to medical services, which can influence diagnosis rates. Additionally, environmental factors, such as air pollution and occupational exposures, can vary by region and may contribute to the differences in CRS prevalence (6). Furthermore, different studies may use varying definitions or diagnostic criteria for CRS, which could lead to inconsistencies in reported prevalence (2-5). The prevalence of physician-diagnosed CRS ranges from approximately 1% to 9% of the general population (7).

Traditionally, CRS has been divided into two main phenotypes: with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) (8). According to other clinical features, these may be subdivided into several phenotypes, or divided into endotypes, according to the pathophysiological mechanisms involved (7, 9, 10). EPOS2020 proposed a new classification of CRS into primary and secondary CRS and a division based on anatomic distribution: localized and diffuse disease (8).

This paper aims to review the existing literature on CRS in both adults and children and provide a practical approach and expert considerations on the diagnosis, management, and available therapies for CRS. Several systemic inflammatory disorders can affect the nasosinusal mucosa and present with CRS symptoms, such as Eosinophilic Granulomatosis with Polyangiitis (or Churg-Strauss syndrome) and Granulomatosis with Polyangiitis (or Wegener's granulomatosis) (7). These diseases have distinct pathophysiology and management, and are outside the scope of this review.

Pathophysiology

CRSsNP and CRSwNP are not unique nosological entities, as several phenotypes/endotypes have been proposed, and their classification remains non-consensual (7, 9, 11, 12). A review proposed four distinct (but overlapping) endotype classifications of CRSwNP based on the presence of 1) type 2 cytokines; 2) eosin-

Figure 1 - *The definition of rhinosinusitis in adults and children, as outlined by the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020)) (1).*

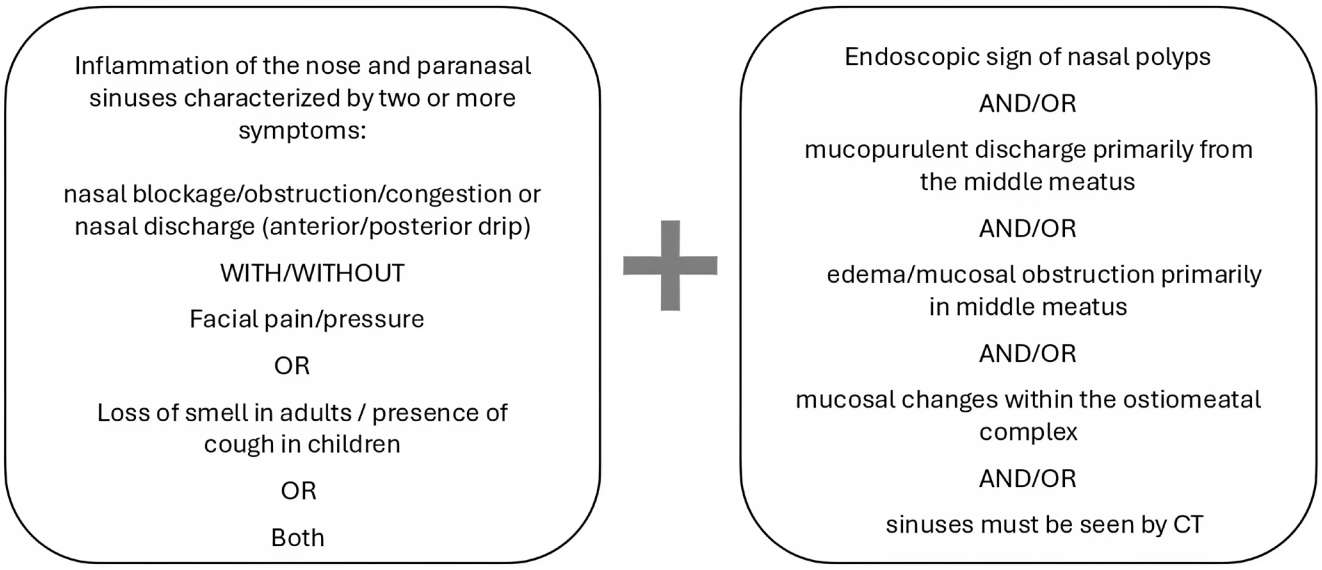
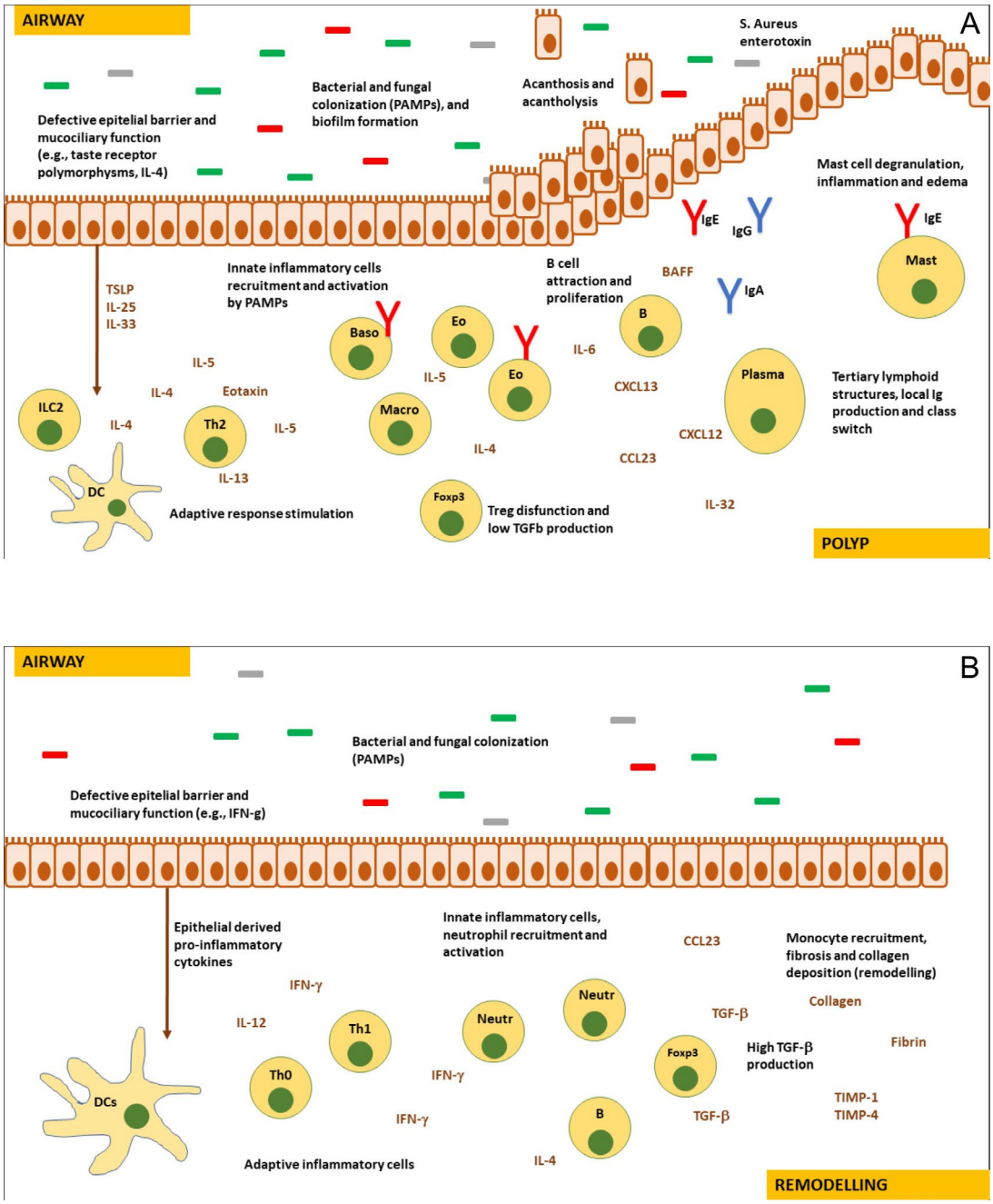


Figure 2 *- Summary of pathophysiological mechanisms of chronic rhinosinusitis (CSR).*



Pathogenesis of CSR with nasal polyps (CSRwNP) and without nasal polyps (CSRsNP) is influenced by microbial, systemic and genetic factors. **(A)** CSR tissues present a variety of innate (eosinophils, neutrophils, basophils, mast cells, type 2 macrophages, and type 2 innate lymphocytes (ILC2s)) and adaptive immune cells. In patients with CRSwNP, both Th2 and eosinophilic inflammation are most often observed together with high levels of cytokines IL-5 and IL-13, eotaxin-2, and monocyte chemoattractant protein (MCP)-4. ILC2 cells are sources of IL-13 in response to IL-33 and contribute to Th2 polarization. IgE promotes eosinophil and mast cell degranulation, maintaining inflammation and edema, while local IgE production may be stimulated by *Staphylococcus aureus* enterotoxin**.** Other mechanisms include bacterial and fungal colonization of the sinonasal tract. *Staphylococcus aureus* biofilms have been associated to recalcitrant CRS. **(B)** Remodelling is driven by induced fibroblast proliferation via TGF-β leading to up-regulation of collagen synthesis. In CRSwNP there is an up-regulation of metalloproteinases (namely MMP7 and MMP9), and down-regulation of natural tissue inhibitors (TIMP1 and TIMP4). Therefore, in CRSwNP, there is a deficit in collagen with degradation of the extra-cellular matrix (ECM) and formation of vacuoles. Deposition of albumin also occurs in CSRwNP, while CRSsNP is characterized by fibrosis.

ophils; 3) immunoglobulin E (IgE); or 4) cysteinyl leukotriene (CysLT) (13). Both phenotyping and endotyping may provide relevant information about the diagnostic, response to treatment, and prognosis. **Figure 2** summarizes the main pathophysiological mechanisms involved in CRS.

Chronic rhinosinusitis pathogenesis

Paranasal sinuses have complex and variable anatomy. The ostiomeatal complex is critical for the correct ventilation and drainage of the maxillary, anterior ethmoidal, and frontal sinuses, and anatomical or inflammatory alterations may predispose to acute and/or chronic sinusitis (14). Viral infections followed by bacterial superinfection are well-established causes of acute rhinosinusitis (most often by *Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis*, and *Staphylococcus aureus*) (15, 16). However, the role of bacterial infection in the pathogenesis of CRS is less clear. Both aerobic and anaerobic bacteria have been found in CRS, but it is unclear whether infection is a primary cause or a consequence of compromised sinus function (17).

Several other local, systemic, microbial, environmental, genetic, and iatrogenic factors may be important for the pathogenesis of CSRwNP and CRSsNP (7, 18) and may contribute in variable degrees to the development of particular endotypes/phenotypes. Despite some efforts (19), there is no established animal model of CRS to help distinguish mechanistic contributions from consequences of CRS uncontrolled inflammation. A review examined six broad theories on the etiology and pathogenesis of CRS. These include the microbiological-based hypothesis which encompass: 1) the "superantigen hypothesis," 2) the "biofilm hypothesis," 3) the "microbiome hypothesis" (all "bacterial-based hypotheses,"); and 4) the "fungal hypothesis". Additionally, the review covered 5) the "eicosanoid hypothesis" and 6) the "immune barrier hypothesis," both of which focus on host-specific factors (20).

CRSsNP vs CRSwNP immunopathology

Polyps are edematous formations of inflammatory tissue grown into the nasal cavity. Etiological differences may determine their occurrence. Remarkably, CRSwNP patients have a higher prevalence of acute rhinosinusitis, allergic rhinitis, and asthma before CRS development, whereas CRSsNP patients have a higher prevalence of upper and lower respiratory tract infections (21).

CRS tissues are rich in innate (eosinophils, neutrophils, basophils, mast cells, type 2 macrophages, and group 2 innate lymphoid cells, ILC2s) and adaptive immune cells (22). Nasal polyposis can be divided into two main types: a neutrophilic polyposis and polyposis associated with conditions such as chronic eosinophilic rhinosinusitis, (23), allergic fungal rhinosinusitis, Nonsteroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (N-ERD) (11, 13, 24), and asthma (11, 13, 25). Traditionally, CRSsNP has been classified as neutrophilic and CRSwNP as eosinophilic. However, neutrophils may be present in normal tissues and also in CRSwNP, and this classification based in the presence of neutrophils has been questioned (26).

On the other hand, Type 2 (T2) inflammation and eosinophilic inflammation are observed in most patients with CRSwNP. Compared to CRSsNP and control subjects, the nasal mucosa of CRSwNP patients shows increased levels of IL-5 (a pivotal cytokine for eosinophils production, maturation, and activation), IL-13, eotaxin-2, and monocyte chemoattractant protein (MCP)-4 (27). CRSwNP also presents higher percentages of innate lymphoid cells (ILC), particularly ILC2, in the diseased mucosa compared to CRSsNP. These cells are important sources of IL-13 in response to IL-33 and contribute to the Th2 polarization of the disease in CRSwNP (27). Blockade of IL-5, IL-4, and IL-13 using monoclonal antibodies showed the importance of these cytokines in CRS immunopathology (28-30). TSLP, an epithelial alarmin, drives Type 2 inflammation, promoting tissue remodeling and nasal polyp formation. The TSLP-blocking antibody Tezepelumab is under investigation for treating CRSwNP (31).

Antibodies of all isotypes have been found in polyps, in strike contrast to CRSsNP (32), and a clear role for IgE in the pathophysiology of CRSwNP was demonstrated in a study using anti-IgE treatment with omalizumab (33). IgE may also lead to eosinophil and mast cell degranulation perpetuating the inflammation and edema observed in CRSwNP (34). Local production of antibodies, in particular specific IgE, may be stimulated by *Staphylococcus aureus* enterotoxin B (35).

Different remodeling processes also differentiate CRSwNP and CRSsNP. CRSwNP is characterized by a deficit in collagen, by degradation of the extra-cellular matrix (ECM), development of vacuoles, deposit of albumin in nasal polyps, and edema. Contrarily, CRSsNP is characterized by fibrosis. Recent data also shows that remodeling in CRSsNP occurs independently from the inflammatory process and precedes it (36).

Diagnosis

According to several guidelines (1, 37-40), the clinical diagnosis of CRS must include symptom assessment and objective documentation of sinonasal inflammation. A position paper from EUFOREA, ARIA, EPOS, and AIRWAYS ICP recommends that CRS clinical diagnosis should be based on the presence of two or more sinonasal symptoms plus a CT scan for non-otorhinolaryngologists, supplemented by allergy tests in case of suspicion of concomitant allergy, and/or nasal endoscopy by otorhinolaryngologists for phenotyping into CRSwNP and CRSsNP (41). The presence of nasal polyps must be confirmed, and it remains a challenge to distinguish between CRSwNP and CRSsNP based on clinical impression alone, since there is considerable overlap of symptoms in patients with and without nasal polyps (42). In children, clinical symptoms are often the primary means of diagnosis due to the difficulty of tolerating nasal endoscopy and the limita-

tions of sinus radiologic imaging in uncooperative patients (43). In the differential diagnosis of nasal masses, age is an important clue: in children aged < 2 years, congenital malformations with a herniated endocranial mass are the most frequent; from 2 to 20 years of age, mucoviscidosis or eosinophilic polyposis must be considered; and in adults > 20 years, inflammatory polyposis is the likeliest cause (44).

The development and validation of questionnaires, along with the resulting diagnostic algorithm may contribute to accurate diagnoses, with high level of sensitivity and specificity (45, 46). However, the correlation between questionnaire-based and clinical-based diagnoses of CRS has shown only moderate agreement, indicating that adjustments to the questionnaires are necessary (47).

Nasal endoscopy or CT scan, remain the gold standard imaging in CRS for documenting sinonasal inflammation (8). **Figure 3** presents an example of nasal endoscopy and CT imaging that is common in clinical practice.

Magnetic resonance imaging (MRI) can complement CT scan for the imaging of paranasal sinuses and diagnosis (48) (**figure 4**). Several challenges limit the broader use of MRI in clinical practice when compared to standard nasal endoscopy and CT scan, including the lower definition obtained for bone structures, longer scanning times and higher costs associated (48). However, MRI has no radiation risks and provides improved soft tissue definition over CT scan, increasing the ability to differentiate between soft tissue masses and retained/obstructed secretions (48, 49). Others recommend MRI only to differentiate benign obstructed secretions from tumors and to assess the spreading to outside the nasal cavity and sinuses (38, 39). We consider that MRI should be performed if eosinophilic CRS is suspected since eosinophilic mucin is only detected by MRI (50).

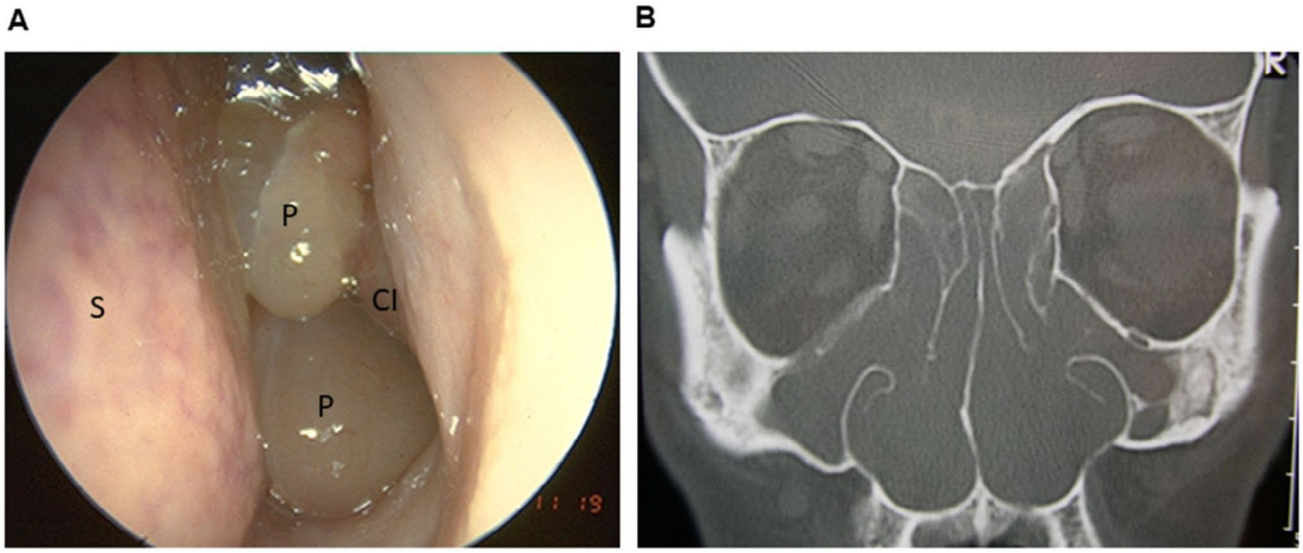
Bacteriology tests are relevant for the etiological diagnosis as specific inflammatory endotypes are associated with the intramucosal presence of specific bacteria (51). Additionally, a relationship between intramucosal microorganisms and inflammatory patterns in subgroups of CSR patients has been reported (51). There is much debate regarding the role of fungi in CRSwNP (1, 38, 39, 49) and whether the diagnostic group of allergic fungal rhinosinusitis (AFRS) truly represents a unique disease.

Nasal NO is a sensitive indicator of inflammation (high values) and ciliary dyskinesia (low levels) (52). However, very low levels in the nose may be related to significant sinus obstruction/severe polyposis, while elevated levels suggest nasal inflammation despite osteomeatal patency. Also, wide variability in the baseline levels of NO limit its value for diagnosis and management (53). NO may, however, be used as an outcome measure to monitor response to therapy (53).

Skin prick tests and/or measurement of specific IgE to aeroallergens in the serum are routinely performed in clinical practice to evaluate respiratory allergy and its contribution to the overall nasal symptoms (1).

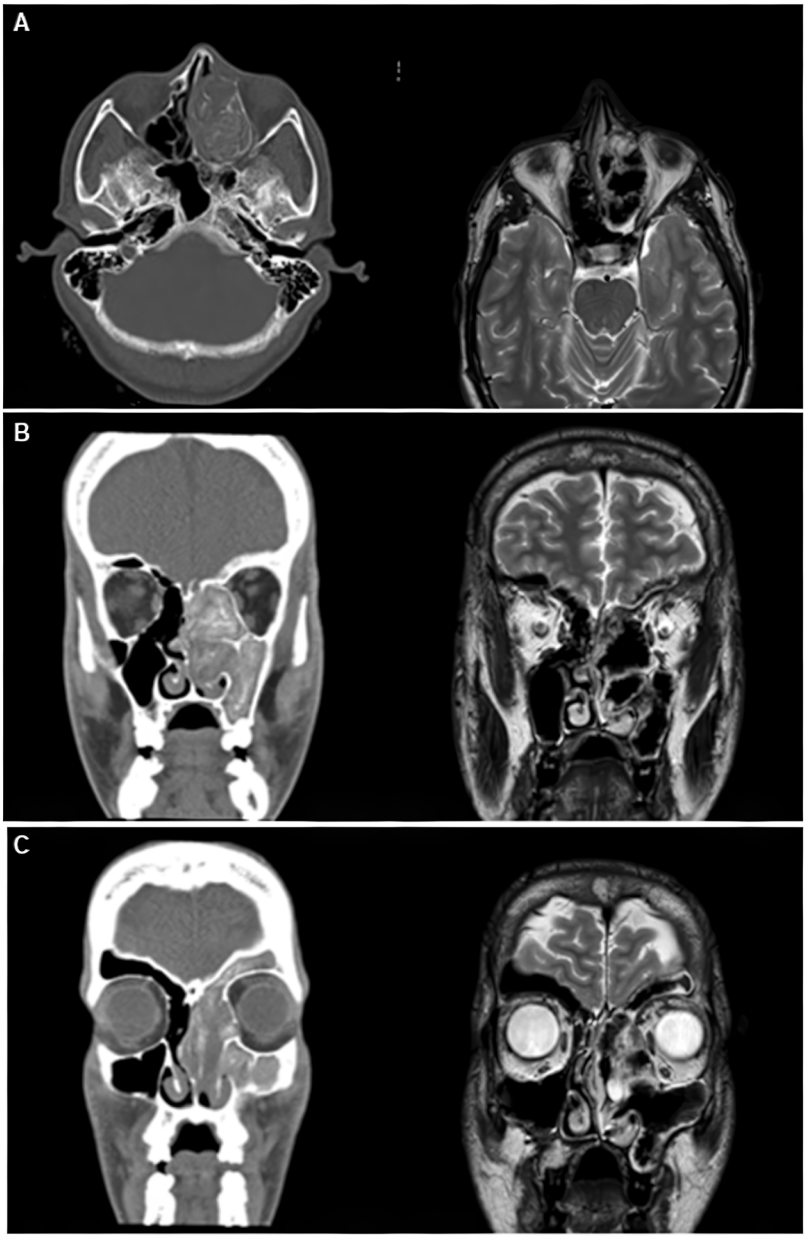
In some patients, a nasal allergen provocation test (NAPT) may be performed (1). This is a safe procedure to demonstrate local mucosal allergy (54), to confirm hyperreactivity to specific allergens before immunotherapy (54), and to identify clinically rel-

Figure 3 *- Nasal endoscopy and compute tomography (CT) are gold standard imaging in chronic rhinosinusitis (CRS).*



(A) Nasal endoscopy of the left nasal fossa. Several inflammatory polyps are visualized. **(B)** CT of the paranasal sinuses in coronal section of a patient with CRS with nasal polyps (CRSwNP). CI: inferior turbinate; P: polyp; S: nasal septum.

Figure 4 - *Magnetic resonance imaging (MRI) often complements computed tomography (CT) in chronic rhinosinusitis (CRS) imaging.*



(A) CT (left) and T2-weighted MRI (right) in axial section of the paranasal sinuses. Filling of the ethmoidal cells and compression of the right eyeball are visible with CT while mucosal hypertrophy is observed with MRI. **(B)** CT (left) and T2-weighted MRI (right) in coronal section of the same patient, encompassing the maxillary sinus and ethmoidal cells. The heterogeneity of the paranasal sinuses is observed in CT. **(C)** CT (left) and T2-weighted MRI (right) in coronal section of the same patient, encompassing the maxillary sinus, ethmoidal and frontal cells.

evant allergens in case of sensitization to multiple allergens (54, 55). Several guidelines aim to standardize this procedure (1, 55). Histopathology is important for differential diagnosis and for CRS endotyping (1, 56). We consider that routine histopathological analysis of nasal polyps, whenever possible, is important to evaluate differential diagnoses such as hamartoma, inverted papilloma or even adenocarcinoma, severe pathologies with an essential impact on therapeutic approach and prognosis. Histopathology may also provide cues regarding endotype, treatment choice and response to treatment. The quantification of eosinophils,

specifically the number of eosinophils per high-powered fields, can be performed, significantly correlates with prognosis and disease severity, and eosinophil-dominance might help direct medical and surgical treatment options, as discussed below (56, 57).

CRS impact and comorbidities

Comorbidities

CRS patients are likely to present with asthma, COPD, primary immunodeficiencies, acquired immunodeficiencies including human immunodeficiency virus (HIV) infection, immunosuppression due to transplant, diabetes mellitus, medications, malignancies, and ciliary dyskinesia (49). In adults, the comorbidities with the highest relative proportions were asthma (38%) and allergy (34%). In CRSwNP, the relative proportions of asthma and allergy were 49% and 36%, respectively, while in CRSsNP, these proportions were 32% for both conditions (43).

It is important to note that comorbidities may differ between pediatric and adult CRS patients, as allergy, chronic otitis media, and tonsils disease were more prevalent among pediatric patients (43).

N-ERD is a type of CRS that requires specific management and should be considered in asthma-associated CRS (49, 58). The relative proportion of N-ERD among patients with CRSsNP and CRSwNP was 1.7% and 6.6%, respectively (59). The oral aspirin challenge remains the gold standard for N-ERD diagnosis (49, 58).

Quality of life

Patients with CRS could experience a complex range of symptoms and therefore CRS related QoL (60) should also be assessed. Several instruments are available to measure CRS related QoL, such as chronic sinusitis survey (CSS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Rhinosinusitis Disability Index (RSDI) and SNOT-22, which is the most widely used questionnaire (1). A recent review showed that the key symptoms reducing quality of life (QoL) include loss or reduction of smell and sleep disturbances, which in turn may lead to additional physical and mental health consequences (59).

Treatment

Treatment should be directed by phenotypes and, whenever possible, by endotypes. However, the EPOS 2020 based treatment in the new classification: localized (often unilateral) or diffuse (always bilateral) (1); the primary classification for the approved therapies is CRSsNP and CRSwNP.

Pharmacological

Intranasal corticosteroids (INCS)

INCS are highly effective and recommended in CRSsNP (1, 7, 18, 61). In CRSwNP, INCS are also recommended (7, 49), but efficacy depends on effectively delivering INCS to the paranasal sinuses. The surgical state of the sinuses treated, *i.e.*, whether the sinuses are open and topical INCS can penetrate the sinus cavity, seems particularly relevant and appears to influence response to treatment significantly (49, 62). In children, INCS is the first-line treatment in CRSwNP and CRSsNP, but caution is needed when long-term treatments and high-doses are prescribed (1).

Systemic corticosteroids

Short term treatment with oral steroids (OCS) may be used in CRSwNP (1, 7, 18, 63, 64). However, it was found that three to six months after the end of the treatment, there is little or no improvement in health-related QoL or symptom severity (64). The risks of short courses of OCS are cumulative over the years, and significant adverse events must be considered (1, 7, 63). OCS should be used cautiously in patients with diabetes, uncontrolled hypertension, and peptic ulcer disease (18). OCS use in CRSsNP is optional due to insufficient evidence (1, 7, 63).

Until recently, it was common to use steroid depot injections. However, in light of the evidence regarding the increased risk of diabetes (65), osteoporosis (65, 66), and secondary adrenal insufficiency (66) associated with these steroid depot injections, we consider that steroid depot injections must be avoided.

Antihistamines

There is no compelling evidence for antihistamine treatment of CRSsNP in adults, and therefore this is not recommended (1). Also, current data yield insufficient evidence to recommend antihistamines in non-allergic patients for the treatment of CRSwNP, although in patients with CSR and concomitant allergic rhinitis, antihistamines may be indicated (1, 25).

The EPOS 2020 guideline recommends using these agents for children with documented allergic rhinitis (1).

Leukotriene modifiers

One meta-analysis concluded that leukotriene receptor antagonist (LTRAs), administered as monotherapy, effectively treated CRSwNP, however have limited benefit when used as an adjunctive therapy to INCS, proposing that additional studies are required to determine the most beneficial strategy for their use (67). EPOS 2020, based on the very low quality of evidence, only recommends its use when patients do not tolerate INCS (1).

No data exists about the potential efficacy and thus usefulness of leukotriene modifiers in the context of CRS in children. The EPOS 2020 guideline recommends the use of these agents for children with documented allergic rhinitis (1).

Antibiotics

Antibiotics should be used if there is enough evidence of infection. However, the evidence regarding the use of short-term antibiotics for CRS, acute exacerbation of CRS, or long-term antibiotic for CRS is very low and conflicting, and further studies

are needed, taking into account the possible secondary effects and the emergence of antibiotic-multiresistant bacteria (68, 69).

Nasal douching

Nasal douching is recommended for both phenotypes (1, 7, 18, 38, 39) and irrespective of age group (1). It is often recommended as an additional non-pharmacological treatment; however, it could also be considered a first-line treatment. Although there is no consensus on the solution to be used, the most suitable device, or the optimal treatment schedule, there is a trend suggesting that once- or twice-daily administration of hypertonic solutions, enriched with the natural minerals and trace elements found in seawater and certain thermal waters, may provide greater clinical benefits, better endoscopic scores, and improved nasal resistance compared to isotonic solutions (70, 71).

Aspirin desensitization

Aspirin therapy after desensitization (ATAD) should be considered in patients with N-ERD (7). ATAD involves the administration of gradually increasing doses of aspirin under medical supervision to induce tolerance, enabling patients to continue daily aspirin therapy. This approach has been shown to alleviate both upper and lower respiratory symptoms and delay the recurrence of nasal polyps (72). More recently, intranasal administration of lysine-aspirin has demonstrated clinical efficacy in improving nasal airflow and sense of smell, with fewer side effects compared to oral aspirin desensitization (73). However, ATAD is associated with potential side effects from daily aspirin intake, and discontinuing the treatment at any stage results in the loss of its clinical benefits (73). Overall, ATAD remains a valid option for carefully selected candidates, taking into account the indications, contraindications, side effects, and patient preferences (74).

Immunotherapy with bacterial lysates

Bacterial lysates are immunostimulants clinically prescribed for the prevention of respiratory tract infections (75). For CRSsNP, bacterial lysates such as oral OM-85 BV treatment may be considered adjunct to standard medical treatment in adults and children (1). Despite these indications and recommendations, the heterogeneity of published studies highlights the need for double-blind, placebo-controlled, multicenter, randomized clinical trials for each specific population (75).

Allergen-specific immunotherapy

For adults with CRSsNP, no data is available regarding the use of this immunotherapy (1). Concerning CRSwNP, few studies investigated the association between sensitization to aeroallergens and NPs, and even fewer tested the efficacy of specific immunotherapy (SIT) in the prevention of relapse after endoscopic sinus surgery (ESS). However, allergen-specific immunotherapy, combined with anti-IgE therapy, might have a promising future for preventing polyps relapse (76, 77). Furthermore, in patients with CRSwNP and concomitant allergic rhinitis symptoms, it is likely that allergen-specific immunotherapy might reduce the global overlapping symptoms.

Surgery

The ideal moment for CRS surgery is debatable (8, 78). A RAND/UCLA appropriateness study concluded that ESS could be appropriately offered to adults with uncomplicated CRSwNP when CT Lund-Mackay score is ≥ 1 and there has been a minimum trial of INCS plus a short-course of a systemic corticosteroid with a post-treatment total 22-item Sinonasal Outcome Test (SNOT-22) score ≥ 20 (78-80). CRSsNP is often treated adequately with surgery (66, 81, 82). ESS is the preferred technique (83) and has been associated with improvements in symptoms scores (especially nasal obstruction and discharge), disease-specific and generic QoL, as well as objective measures. If the adult has CRSsNP, the surgical criteria should include CR Lund-Mackay score ≥ 1, and, at least, one course of INCS plus, either a short-course of a broad spectrum/culture directed systemic antibiotic or the use of a prolonged course of systemic low-dose anti-inflammatory antibiotic with a post-treatment total SNOT-22 score ≥ 20 (78).

Since CRS is a chronic disease, usually related to endonasal anatomical abnormalities, ESS should be considered a step in disease management, correcting these anatomical abnormalities and creating better conditions for local treatment (1).

The most common surgical approach in children with CRS in whom "maximal" medical therapy has failed probably consists of an initial attempt at an adenoidectomy with a maxillary sinus wash plus/minus balloon dilation followed by ESS in case of symptoms recurrence. "Maximal" medical therapy usually includes a course of antibiotics and intranasal and/or systemic steroids and differs widely between practitioners and practice locations (84). Unfortunately, most data supporting this recommendation are not based on randomized prospective studies, and prospective, randomized, controlled clinical trials are required (1).

The long-term efficacy of surgery is influenced by choice of postoperative medical treatment regimen and compliance. Prolonged postoperative medical treatment with INCS improves the outcome post-ESS (1), delays the recurrence after surgery, and postpones the need for a new surgery (18, 85). OCS are strongly recommended in the perioperative period for CRSwNP and AFRS but not for CRSsNP (63).

CRSwNP tends to recur in a high percentage of subjects (18, 66, 81, 82) over 10 years or more and it is often associated with comorbid asthma (86). An investigation into both surgical and medical management strategies is warranted to reduce recurrence (81). Improved CSR phenotyping may allow better tailoring of surgical treatments in the future (83).

Recently, the concept of reboot surgery was introduced for type 2 inflammatory CRSwNP. This approach involves the removal of all inflamed sinus mucosa and allowing the regrowth of func-

tional nasal mucosa (87). This technique has shown a significantly reduced recurrence rate of nasal polyps for 30 months (17% *versus* 45% with the classical approach) (87, 88). Furthermore, this approach significantly improved olfactory function (88, 89). Therefore, reboot surgery should be considered for patients with uncontrolled severe CRSwNP, particularly when ESS has failed, to achieve long-term smell and maintain a polyp-free status (88).

Biologics

The criteria for the use of biologics in CRSwNP, first developed by EPOS 2020 (1), established that biologics are only indicated for CRSwNP patients with a history of previous surgery or, if surgery not appropriate, have three of the following criteria: evidence of type 2 disease; need of at least two courses of systemic corticosteroids per year or long-term (>3 months) continuous use of low-dose systemic corticosteroids; significantly impaired QoL; significantly loss of smell; diagnosis of comorbid asthma. However, the currently updated EPOS/EUFOREA 2023, recommends that evidence of type 2 inflammation should not be mandatory (90). The current EPOS/EUFOREA 2023 also defined five criteria to evaluate the response to biologicals in CRSwNP after 6 months and 1 year of treatment: reduced nasal polyp size; reduced need for systemic oral corticosteroids; improved QoL; improved sense of smell; reduced impact of comorbidities (90). Treatment should be discontinued if no response is observed in any of the criteria (90). Currently, dupilumab, omalizumab and mepolizumab are approved biologics for the treatment of adults with CRSwNP not appropriately controlled with standard therapies, and can be prescribed both in the presence or absence of concomitant asthma (91). Clinical trials with other biologics for the treatment of CRSwNP are ongoing (92).

Dupilumab

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4Rα subunit that is shared by the IL-4 receptor and the IL-13 receptor complexes. Two-phase III randomized clinical trials, Liberty NP SINUS-24 and Liberty NP SINUS-52 evaluated dupilumab added to standard of care in patients with severe CRSwNP (1, 93). An improvement in SNOT-22, rhinosinusitis total symptoms score (VAS), nasal congestion score, sense of smell, nasal polyp score, Lund-Mackay CT score and, asthma control test were observed (1, 93). Dupilumab is well tolerated being the most common adverse event nasopharyngitis, injection-site reactions, and headache (94). A post-hoc analysis of the patients with N-ERD of the phase II study (28) demonstrated that dupilumab reduces sinus opacification across all sinuses and related symptoms (95).

Omalizumab

In adult patients with refractory CRSwNP with inadequate response to nasal corticosteroids, omalizumab is an option as an add-on treatment (96). Omalizumab is an anti-IgE that specifically binds to the high-affinity FcεR1 domain of free circulating IgE. Omalizumab prevents binding of free serum IgE to effector cells, reducing IgE levels and downregulating FcεR1 expression on mast cells and basophils. Consequently, blood eosinophils and nasal tissue eosinophils are decreased. Omalizumab also decreases albumin in the nasal fluid after the allergen challenge, preventing increased vascular permeability. The efficacy of this drug confirms the involvement of IgE as an inflammatory mediator in nasal polyposis (97).

Omalizumab is well tolerated, and adverse events are generally mild-moderate, not significantly different from placebo, and anaphylactic reactions are rare (98).

Omalizumab demonstrated clinical efficacy in treating nasal polyps with comorbid asthma (33, 99-103), irrespective of the presence of allergy (33, 61). A review from 2014 concluded that the use of omalizumab might be an effective therapeutic alternative in CRSwNP, especially in patients with more aggressive forms of the disease, such as those with a history of nasosinusal surgery and those with allergic asthma (104). Some studies also support omalizumab in refractory AFRS with (105) or without concomitant asthma (106).

The recently published results of two replicate phase III clinical trials POLYP 1, and POLYP 2, showed that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes compared to placebo at week 24 and was well tolerated (107). Patients included in these studies were patients with severe CRSwNP, inadequately controlled despite daily INCS therapy (107). An open-label extension study, OLE, including patients from POLYP 1 and POLYP 2 trials, showed gradual worsening of Nasal Polyps Score (NPS), Nasal Congestion Score (NCS), and SNOT-22 after omalizumab withdrawal, even though these remained below pretreatment levels at week 76 (108).

Mepolizumab

Mepolizumab is a humanized monoclonal IgG1k antibody that inhibits the bioactivity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signaling and reducing the production and survival of eosinophils (109). It has been approved as an add-on therapy with INCS for the treatment of adult patients with severe uncontrolled CRSwNP (109). The SYNAPSE phase 3 trial showed that, after 52 weeks, adult patients with severe CRSwNP treated with mepolizumab decreased nasal polyp size and obstruction, improved median endoscopic NPS, and decreased median nasal obstruction VAS scores compared to placebo. Fewer patients on mepolizumab required rescue systemic corticosteroid treatment, showed a significant longer time to first nasal surgery, and demonstrated improvement in sinonasal symptoms via VAS scores and Health-related Quality of Life (HRQoL) via SNOT-22. Adverse events were similar

between mepolizumab and placebo groups (110). Other clinical studies have shown similar results (92).

Due to the lack of head-to-head studies comparing the approved biologics for CRSwNP treatment, indirect comparisons through systematic literature reviews and network meta-analyses (NMA) have been conducted (111-113). These analyses have highlighted the positive effects of various biologics in outcomes such as reducing the need for rescue nasal polyp surgery, lowering the use of oral corticosteroids (OCS), and improving quality of life and the sense of smell, while maintaining a favorable safety profile. While dupilumab has shown favorable results, these findings must be interpreted with caution due to the high heterogeneity of the original studies in terms of patient inclusion criteria, disease severity, and outcomes (111-113). Head-to-head comparisons and real-world evidence are needed to confirm these findings, especially for specific patient subgroups. The personalized choice of biologic may also be influenced by the presence of allergic multimorbidity and other individual factors. Additionally, the availability of biologics can differ across countries and healthcare systems, highlighting the importance of having a diverse range of treatment options to ensure optimal patient care.

We consider that dupilumab, omalizumab, and mepolizumab are effective therapies for CRS. Biologics interfere with significant pathophysiologic pathways and may be disease modifying agents that help prevent remodeling and reduce the need for further surgeries. More data are expected regarding these long-term outcomes.

While taking into consideration that, in the majority of CRSwNP patients, surgery is likely not curative, we still believe that surgery, when possible, is an important clinical intervention for most of the CRSwNP patients and that surgery might be important to guarantee the efficacy of the chronic medical therapy that should be continued after surgery when indicated.

In conclusion, many questions are pending concerning the etiology and inflammatory mechanisms underlying CRS. However, as our knowledge and understanding on the pathophysiological mechanisms of CRS expands, new therapeutic approaches can be envisioned. Although the medical treatment for CRS is currently oriented to different phenotypes, the definition of endotypes with specific biomarkers will be paramount for a tailored clinical application of directed and personalized therapies.

The panel emphasizes the critical role of a multidisciplinary team, including otolaryngologists, pulmonologists, and allergists/clinical immunologists, in collaboratively determining the most effective therapeutic approach tailored to each patient's needs.

Fundings

This work was supported by Novartis via funding for third-party medical writing of this manuscript.

Contributions

EB, JLP, FSR, JPMS: conceptualization. EB, JLP: data curation. EB, JLP, FSR, JPMS: formal analysis. FSR, JPMS: funding acquisition. EB, JLP: investigation. EB, JLP: methodology. FSR, JPMS: project administration. EB, JLP: resources. EB, JLP: software. FSR, JPMS: supervision. FSR, JPMS: validation. EB, JLP, FSR, JPMS: visualization. EB, JLP, FSR, JPMS: writing – original draft. EB, JLP, FSR, JPMS: writing – review & editing.

Conflict of interests

FSR reports speaker and advisory fees from Novartis outside the submitted work. The other authors declare that they have no conflict of interests.

Acknowledgements

This manuscript was prepared with the medical writing support of Irina Duarte, Diana Gaspar and Constança Coelho from X2 Science Solutions, financially supported by Novartis Portugal.

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