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REVIEW ARTICLE

Nasal polyposis: an overview of etiology, diagnosis, and modern treatment options

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Summary

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic, heterogeneous inflammatory disease associated with substantial impairment of nasal breathing, olfaction, and patients' quality of life. Its etiology and pathogenesis are multifactorial and involve epithelial barrier dysfunction, impaired mucociliary clearance, dysbiosis, biofilm formation, *Staphylococcus aureus*, eosinophilic/type 2 inflammation, local IgE production, tissue remodeling, environmental factors, and numerous comorbidities. The coexistence of asthma and intolerance to aspirin and/or nonsteroidal anti-inflammatory drugs is particularly important within the unified airway concept. Diagnosis is established by correlating characteristic symptoms with objective findings obtained by clinical and/or endoscopic examination of the nose and computed tomography of the paranasal sinuses. Assessment of disease severity, comorbidities, and relevant differential diagnoses is essential. The cornerstone of treatment is intranasal corticosteroid therapy and nasal saline irrigation, whereas systemic corticosteroids, endoscopic sinus surgery, and biologic therapy are reserved for more severe, recurrent, or uncontrolled disease. The diagnostic and therapeutic approach to CRSwNP requires differentiation between disease phenotypes and endotypes, recognition of type 2 inflammation, active management of associated conditions, and continuous monitoring of treatment response based on symptoms, endoscopic findings, quality of life, and the need for additional interventions. This review summarizes current evidence on the etiology, pathogenesis, clinical presentation, quality of life, diagnostic criteria, and modern treatment options for CRSwNP, based on systematic reviews, clinical guidelines, and original studies. An individualized approach, adequate control of local disease and comorbidities, and regular follow-up are key to improving long-term treatment outcomes.

Keywords: chronic rhinosinusitis with nasal polyps, type 2 inflammation, nasal endoscopy, endoscopic sinus surgery, biologic therapy

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INTRODUCTION

Chronic rhinosinusitis (CRS) is among the most common inflammatory disorders of the upper airways. It represents a major clinical and public health problem because of its substantial impact on quality of life and healthcare costs (1). Data from the United States indicate that approximately 12% of adults are diagnosed with rhinosinusitis each year (2). The annual costs associated with this condition have been estimated at approximately 8.3 billion US dollars, while endoscopic sinus surgery (ESS) is performed nearly 250,000 times per year in the United States (3). In addition to its economic burden, CRS has a profound negative effect on patients' quality of life (3, 4).

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020), CRS in adults is defined by the presence of two or more symptoms lasting for at least 12 weeks, one of which should be nasal obstruction/blockage/congestion or nasal discharge, either anterior or posterior. Facial pain or pressure, and a reduction or loss of the sense of smell, may also be present (5). Importantly, CRS should not be diagnosed solely based on symptoms. Objective evidence of inflammation of the nasal cavity and paranasal sinuses is required, either by clinical findings such as nasal polyps, mucosal edema, or purulent discharge, or by computed tomography (CT), together with symptoms persisting for more than 12 weeks (5-8).

In clinical practice, CRS has traditionally been classified into chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP). Although this classification remains clinically useful, EPOS 2020 proposes a more refined classification of CRS into primary and secondary forms, as well as localized and diffuse disease. Primary CRS is further categorized according to the predominance of type 2 or non-type 2 inflammation. In primary diffuse CRS, clinical phenotypes are additionally classified as eosinophilic or non-eosinophilic, with eosinophilic inflammation defined as the presence of 10 or more eosinophils per high-power field (5).

Sinonasal polyposis is a particularly important phenotype of CRS, as it is associated with more severe nasal obstruction, impaired olfaction, frequent recurrence, and the need for long-term, often combined treatment. Larsen and Tos (9) estimated the incidence of symptomatic nasal polyps to be 6.3 per 10,000 inhabitants in Denmark, whereas autopsy studies have reported the presence of polyps in 26-42% of samples (10). The annual incidence of CRSwNP ranges from 1 to 20 per 1,000 inhabitants, while its prevalence in the general population is estimated at 1-4% in adults and approximately 0.1% in children (11). Nasal polyps are more common in men, with a male-to-female ratio of 2-4:1, and several systemic diseases and comorbidities significantly increase the risk of their development (11).

CRSwNP is now regarded as a chronic inflammatory disease within the unified airway concept. A comprehensive diagnostic assessment of local disease and associated comorbidities is essential for selecting appropriate medical and surgical treatments and for identifying patients who may benefit from modern biologic therapies. Therefore, this narrative review aims to summarize current knowledge on the etiology, diagnostic assessment, and therapeutic options in the management of sinonasal polyposis.

METHODS

This article is a narrative review summarizing current knowledge of sinonasal polyposis, with particular emphasis on etiological factors, diagnostic assessment, and modern therapeutic options. A literature search was conducted using the PubMed and Google Scholar databases, including publications available up to December 2025. The search strategy included combinations of the following terms: nasal polyposis, nasal polyps, chronic rhinosinusitis with nasal polyps, CRSwNP, type 2 inflammation, disease phenotype, endotype, nasal endoscopy, computed tomography, topical corticosteroids, systemic corticosteroids, endoscopic sinus surgery, biologic therapy, dupilumab, omalizumab, mepolizumab, recurrence, disease control, as well as the corresponding Serbian-language terms.

Original clinical studies, review articles, systematic reviews, meta-analyses, clinical guidelines, consensus documents, and relevant book chapters published in English or Serbian were considered for inclusion. The literature selection focused on publications addressing the epidemiology, etiology, and pathogenesis; inflammatory mechanisms; clinical presentation; diagnostic criteria; radiological and endoscopic assessment; and medical, surgical, or biologic treatment of sinonasal polyposis. Studies addressing clinically relevant comorbidities, including asthma, aspirin-exacerbated respiratory disease, allergic rhinitis, and postoperative recurrence, were also considered.

Conference abstracts without available full text, publications outside the scope of this review, and studies published in languages other than English or Serbian were excluded. Studies focusing exclusively on chronic rhinosinusitis without nasal polyps, acute rhinosinusitis, sinonasal neoplasms, or other non-polypoid sinonasal disorders were also excluded, unless they provided relevant background or comparative information. The reference lists of selected publications were additionally reviewed to identify further relevant sources.

ETIOLOGY AND PATHOGENESIS OF SINONASAL POLYPOSIS

Sinonasal polyposis is regarded as a heterogeneous chronic inflammatory disorder, rather than a simple

Table 1. Etiological, pathogenetic, and clinical factors associated with the development and persistence of CRSwNP

Category	Main factors associated with CRSwNP
Mucosal barrier	Epithelial barrier dysfunction, increased epithelial permeability, impaired mucociliary clearance
Inflammatory mechanisms	Type 2 inflammation, eosinophilia, interleukins (IL-4, IL-5, IL-13), local IgE, SE-IgE
Microbial factors	Dysbiosis, biofilm, Staphylococcus aureus, staphylococcal superantigens
Environmental factors	Smoking, passive smoking, air pollution, ozone, occupational exposure, heavy metals
Comorbidities	Asthma, N-ERD/AERD*, allergic rhinitis, atopy, eczema
Secondary causes and special conditions	Cystic fibrosis, primary ciliary dyskinesia, immunodeficiencies, AFRS**
Tissue mechanisms	Stromal edema, fibrosis, basement membrane thickening, angiogenesis, osteitis, polyp formation
Biomarkers and disease-course modifiers	Blood/tissue eosinophils, total IgE, periostin, ECP***, vitamin D

*Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Aspirin-exacerbated respiratory disease
**Allergic fungal rhinosinusitis
***Eosinophil cationic protein

consequence of infection or mechanical obstruction of the nasal cavity and paranasal sinuses (5, 6, 12). It comprises several clinical variants with distinct pathophysiological mechanisms that involve numerous cellular and molecular processes (5). Its etiology is multifactorial and reflects complex interactions among genetic predisposition, environmental influences, occupational exposure, infection, allergy, immune dysfunction, and systemic diseases. Consequently, the development and persistence of CRSwNP result from the combined effects of multiple contributing factors (1, 5, 6, 13). These factors are summarized in **Table 1**.

Epithelial Barrier Dysfunction and Impaired Mucociliary Clearance

The sinonasal epithelium is not merely a passive mechanical barrier; it actively contributes to mucosal homeostasis by producing antimicrobial proteins, peptides, and immune receptors. Impairment of this protective function has been described in CRSwNP, where disruption of the epithelial barrier may increase mucosal permeability to allergens, microorganisms, and other external stimuli. Such dysfunction may represent an early event in disease pathogenesis and contribute to the persistence of chronic inflammation (5).

The mechanisms underlying epithelial barrier disruption have not been fully elucidated. However, genetic and epigenetic influences, alterations in the sinonasal microbiome, viral injury, and systemic signaling disturbances have all been proposed as contributing factors (14, 15). Data regarding pattern-recognition receptors, including Toll-like receptors (TLRs) and nucleotide-binding domain and leucine-rich repeat receptors (NLRs), in CRSwNP remain inconsistent. Nevertheless, an impaired TLR-9-mediated epithelial response may contribute to the chronic inflammatory process (16, 17). Upon stimulation, epithelial cells release cytokines and chemokines that recruit inflammatory cells and shape the subsequent adaptive immune response (18-20). In addition, mucosal edema and impaired mucociliary clearance promote secretion retention, bacterial colonization, and recurrent disease exacerbations (21).

Inflammatory Patterns, Type 2 Inflammation, and Biomarkers

In most patients from Western populations, type 2 inflammation predominates and is characterized by eosinophilic infiltration and activation of the IL-4, IL-5, and IL-13 cytokine pathways (5, 6, 22). By contrast, type 1 inflammation is associated with interferon-gamma, whereas type 3 inflammation involves IL-17 and IL-22 and may reflect a response to bacterial or fungal stimuli (22). Regional differences further support the heterogeneity of the disease, as eosinophilic type 2 inflammation is more commonly reported in Europe and the United States. In contrast, type 1/type 3 and neutrophilic inflammatory profiles are more frequently observed in Asian cohorts (23).

Epithelial-derived cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), may play an important role in initiating the type 2 response by acting on dendritic cells and group 2 innate lymphoid cells, thereby promoting Th2-skewed inflammation (24). Mediators released locally from eosinophils, mast cells, neutrophils, and macrophages contribute to tissue damage, persistent inflammation, and subsequent mucosal remodeling. IL-5-high endotypes show the strongest association with asthma and nasal polyps, highlighting the central role of eosinophilic/type 2 inflammation in the pathogenesis of CRSwNP (25, 26).

Tissue eosinophilia of ≥10 eosinophils per high-power field, blood eosinophil counts of ≥150 cells/μL, and total IgE levels of ≥100 IU/mL are used as practical indicators of type 2 inflammation. However, more reliable biomarkers are still needed (13). Elevated total and specific IgE levels, together with eosinophilic inflammation in nasal polyps, may have pathophysiological relevance in a subset of patients with CRSwNP; however, serum IgE alone is not a sufficiently accurate predictor of the disease (5).

Microbiome, Dysbiosis, Biofilm, and *Staphylococcus aureus*

Microbial involvement in the pathogenesis of CRSwNP primarily involves disruption of the sinonasal microbiome, or dysbiosis, which may initiate or sustain chronic mucosal inflammation (27). Although commensal microorganisms may prevent pathogen colonization and contribute to mucosal homeostasis, the precise nature and clinical significance of dysbiosis in CRS and CRSwNP remain incompletely understood (5).

Biofilms are organized bacterial communities embedded within an extracellular matrix that increase microbial resistance to environmental stressors, host immune defenses, and antimicrobial therapy. Although biofilm formation may be associated with a more severe disease course and a poorer response to conventional treatment, its direct role in the development of CRSwNP remains unclear (5, 6). In some studies, biofilms in CRSwNP have been associated with a more pronounced eosinophilic inflammatory infiltrate, supporting the hypothesis that microbial factors may enhance the type 2 inflammatory response in certain patients (28).

Staphylococcus aureus has a particularly important role, as it is more frequently associated with eosinophilic CRS, especially in patients with CRSwNP and asthma (29). Staphylococcal enterotoxins may act as superantigens, non-specifically activate T lymphocytes, and promote robust cytokine release, local IgE production, and eosinophilic inflammation (30, 31).

Comorbidities, Risk Factors, and Immunomodulatory Factors

Comorbidities and risk factors play an important role in CRSwNP, as they may influence the development of nasal polyposis, the severity of clinical presentation, treatment selection, and the risk of recurrence. Asthma is one of the most important associated conditions, affecting approximately 25-40% of patients with CRSwNP and supporting the concept of shared inflammation between the upper and lower airways (5, 6). In patients with both CRSwNP and asthma, the disease often exhibits a more pronounced type 2 inflammatory pattern, with IL-5-high endotypes showing the strongest association with asthma and nasal polyps (25, 26). The clinical relevance of asthma in CRSwNP is supported by a study showing that asthma in patients with nasal polyposis was associated with longer symptom duration and significantly higher CT scores, but not with a significant effect on overall quality of life or endoscopic scores (32). A particularly important phenotype is N-ERD/AERD, which includes nasal polyposis, asthma, and respiratory reactions to aspirin or other cyclooxygenase-1 (COX-1) inhibitors, and is associated with eosinophilic inflammation and altered arachidonic acid metabolism (33, 34).

Allergic rhinitis and atopy may modify the disease course; however, available evidence primarily suggests an association rather than a proven causal role of allergy in the development of CRSwNP (1, 6). Environmental factors, including smoking, passive smoking, air pollution, ozone exposure, occupational exposure, and exposure to heavy metals, may contribute to epithelial barrier damage and the amplification of the inflammatory response.

In patients with atypical, early-onset, or refractory polyposis, secondary causes should also be considered, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiencies, and granulomatous diseases. Vitamin D has also been proposed as a potential immunomodulatory factor, as 25-hydroxyvitamin D3 deficiency in CRSwNP has been associated with greater mucosal disease severity, the presence of nasal polyps, and bony changes on CT (35).

Tissue Remodeling and Polyp Formation

Tissue remodeling in CRSwNP results from abnormal repair of chronically inflamed and damaged sinonasal mucosa and includes fibrosis, basement membrane thickening, goblet cell hyperplasia, epithelial barrier dysfunction, angiogenesis, osteitis, and the formation of polypoid tissue (36). Persistent inflammation is thought to initiate remodeling, with cytokines, inflammatory mediators, enzymes, and other local factors influencing the type and extent of structural changes (5). Mediators released locally from inflammatory cells may directly contribute to tissue injury and subsequent mucosal remodeling. In CRSwNP, the extent of remodeling increases with disease severity, indicating an association between structural changes and the overall inflammatory burden (37).

In the formation of polypoid mucosa, a primary mucosal abnormality associated with a systemic inflammatory process is likely to play a greater role than simple mechanical obstruction of sinus drainage pathways (6). Molecules such as periostin, transforming growth factor-beta (TGF-β), IL-13, and osteopontin are associated with fibrosis and basement membrane thickening. At the same time, smoking and viral stimulation may further promote polyp remodeling through the TGF-β1 and activin A pathways (38). In line with this, Dudvarski et al. (39), in a postoperative histopathological analysis of sinonasal polyposis, found that edematous/eosinophilic polyps were the predominant histological type, present in 64% of patients. In contrast, fibroinflammatory polyps and polyps with seromucous gland hyperplasia were observed in 24% and 12% of patients, respectively. The same study reported frequent stromal edema, fibrosis, basement membrane thickening, eosinophilic infiltration, and seromucous gland hyperplasia, supporting the concept that CRSwNP involves both inflammatory and remodeling changes of the mucosa (39).

Clinical Significance of the Pathogenesis of Sinonasal Polyposis

The clinical significance of CRSwNP pathogenesis lies in the growing recognition that the disease should not be viewed as a single phenotype defined solely by nasal polyps, but rather as a heterogeneous group of endotypes characterized by distinct inflammatory mechanisms, disease severity, and treatment responses (5, 6). Improved identification of the dominant endotype may allow more individualized therapy, leading to better disease control and a reduced risk of polyp recurrence. Recognition of type 2 inflammation is particularly important, as it explains the favorable response to corticosteroids in many patients and provides the rationale for biologic therapies targeting IL-4, IL-5, IL-13, or IgE (13). The presence of Th2/eosinophilic inflammation, local IgE production, and staphylococcal superantigens may also help explain the association of CRSwNP with asthma, a more severe clinical course, and a tendency toward recurrence (6).

The presence of nasal polyps alone is not sufficient to predict benefit from biologic therapy, particularly in patients with predominantly type 1, type 3, or mixed inflammatory patterns (1). Therefore, in severe uncontrolled nasal polyposis, the selection of advanced therapy should be based not only on endoscopic findings, but also on evidence of type 2 inflammation, the need for systemic corticosteroids, loss of smell, disease-related impairment of quality of life, and the presence of asthma (13). Assessment of treatment response should include patient-reported outcomes, such as the Sino-Nasal Outcome Test-22 (SNOT-22), the severity of nasal congestion and olfactory loss, as well as objective parameters, including the endoscopic nasal polyp score, CT findings, and olfactory testing (13). This approach integrates pathophysiological understanding with modern clinical management. It emphasizes that long-term treatment of CRSwNP requires control of inflammation, comorbidities, and tissue remodeling, rather than mechanical removal of polyps alone (5, 6, 13).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of CRSwNP is based on medical history, objective clinical assessment, and imaging when indicated. Symptoms may be grouped into nasal symptoms (including nasal obstruction, nasal discharge, and impaired olfaction), facial symptoms (such as facial pain or pressure and headache), oropharyngeal symptoms (including postnasal drip, halitosis, dental pain, and cough), and systemic complaints (such as malaise and fatigue) (40). Nasal obstruction is the most common symptom. Although individual symptoms are highly sensitive, their specificity is limited (41). Therefore, CRSwNP should not be diagnosed based on symptoms alone, but rather by correlating at least two characteristic symptoms with objective evidence of disease obtained by nasal endoscopy and/or imaging (5). This approach significantly improves the specificity and positive predictive value of the diagnosis (40).

In clinical assessment, the American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF) Adult Sinusitis Update 2025 particularly emphasizes the importance of identifying nasal polyps, as their presence requires more detailed evaluation and additional investigations for diseases that may be associated with polyposis. The association between asthma, nasal polyps, and aspirin hypersensitivity has long been recognized. In contrast, allergic rhinitis does not appear to be associated with the development of nasal polyps to the same extent (1).

Medical history and symptom assessment represent the first step in the diagnostic algorithm, but have limited diagnostic value when used in isolation. Current diagnostic criteria emphasize four cardinal symptoms: nasal obstruction, nasal discharge, facial pain or pressure, and reduced or absent smell. Previously used "minor" symptoms, such as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness, are no longer considered sufficiently reliable diagnostic criteria (41, 42). Studies have shown that mucopurulent nasal discharge and loss of smell increase the positive predictive value (41, 43). In one prospective study, patients with CRSwNP had significantly more pronounced nasal obstruction, nasal discharge, and hyposmia, as well as higher total symptom, endoscopic, and CT scores than patients with CRSsNP (44). Therefore, reliance on symptoms alone may result in a large number of false-positive diagnoses, with a specificity of only 2-12% and a positive predictive value of 35-54% when CT is used as the reference standard (45).

Unlike anterior rhinoscopy, which can detect only large polyps, nasal endoscopy enables a more detailed assessment of the nasal cavity. In patients with CRSwNP, nasal endoscopy is used to evaluate the location and size of polyps, the degree of mucosal edema, the presence and character of nasal discharge, and possible signs of alternative pathology. When added to characteristic symptoms, nasal endoscopy significantly improves diagnostic accuracy. While a diagnosis based on symptoms alone has a specificity and positive predictive value of 12% and 39%, respectively, the addition of nasal endoscopy increases these values to 84% and 66% (45). However, a negative endoscopic finding does not exclude CRS, as nasal endoscopy has lower sensitivity than CT, with an estimated sensitivity of 30-46% and false-negative rates of 35-70% (45, 46).

Imaging plays an important role in confirming the diagnosis, assessing disease extent, and planning surgical treatment. CT of the paranasal sinuses is the imaging modality of choice and the reference standard, as it provides excellent visualization of anatomical variations across

multiple planes and serves as a surgical roadmap (47). However, CT is not routinely recommended for all cases of CRSwNP. It is most commonly indicated after failure of appropriate medical therapy, in patients with persistent symptoms or abnormal endoscopic findings, and before surgical treatment (5).

The Lund-Mackay system is the most widely used method for standardizing CT findings. It assesses the degree of opacification of the maxillary, ethmoid, frontal, and sphenoid sinuses, as well as obstruction or patency of the ostiomeatal complex, with a maximum score of 24 (48). This scoring system has been validated in several studies (5). In a prospective study, Dudvarski et al. (49) found that patients with CRSwNP had a significantly higher total CT score than patients with CRSsNP (16.05 versus 4.37), with significantly higher scores across all sinus groups and ostiomeatal complexes (49). In adults, a Lund-Mackay score of 3 or higher is highly sensitive for CRS, and a score of 5 or higher strongly supports the diagnosis. By contrast, values of 2 or lower have excellent negative predictive value (45). In children, a Lund-Mackay score of at least 5 is considered a relevant threshold, with a sensitivity of 86% and specificity of 85% (50).

Assessment of olfactory function is an important component of the diagnostic work-up, as olfactory dysfunction is particularly pronounced in CRSwNP. Compared with other sinonasal diseases, CRSwNP is more frequently associated with hyposmia or anosmia (51). Olfactory dysfunction has a dual mechanism: inflammation may damage or alter the olfactory epithelium. In contrast, mechanical obstruction of the olfactory cleft reduces the access of odorant molecules to the olfactory region (52). In many patients, both mechanisms occur simultaneously, which explains why surgical removal of polyps alone may not always result in complete recovery of smell without continued anti-inflammatory treatment.

The diagnostic protocol should also include assessment of relevant comorbidities. Nasal polyps may be associated with asthma, intolerance to acetylsalicylic acid, allergic rhinitis, cystic fibrosis, and primary ciliary dyskinesia (53). The modern understanding of CRSwNP increasingly involves assessing the disease's inflammatory profile. In Western countries, type 2 inflammation most commonly predominates and is associated with IL-4, IL-5, and IL-13 pathways, eosinophilia, and a better response to corticosteroids and biologic therapy. By contrast, type 1 and type 3 inflammatory profiles are more frequently described in certain Asian cohorts (22, 23, 54). Therefore, diagnostic assessment should not be limited to confirming the presence of nasal polyps, but should also include evaluation of disease severity, comorbidities, and potential biomarkers that may influence the choice of advanced therapy.

The symptoms of CRSwNP overlap substantially with those of allergic and non-allergic rhinitis, which represents an important differential diagnostic challenge. EPOS 2020 emphasizes that not all patients who meet symptom-based criteria for CRS have objective evidence of disease on nasal endoscopy or CT. Correlation of symptoms with endoscopic and CT findings may guide the diagnosis, but does not eliminate diagnostic uncertainty (55).

Particular caution is required in patients with unilateral nasal masses or polyps, as these findings require a broader differential diagnosis that includes other benign and malignant conditions (1). The differential diagnosis should include inverted papilloma, lobular capillary hemangioma, cavernous hemangioma, schwannoma, juvenile angiofibroma in adolescent boys, as well as malignant tumors such as squamous cell carcinoma, salivary gland tumors, olfactory neuroblastoma, and lymphoma (6). Features more suggestive of a tumor than inflammatory polyps include unilateral presentation, absence of diffuse sinus inflammation, easy bleeding, and ulceration. Dimitrijević et al. (56) reported a rare case of giant destructive sinonasal polyposis involving all paranasal sinuses, with bone destruction and fungal hyphae in allergic mucin, emphasizing the importance of CT assessment, histopathological verification, and a broad differential diagnosis in atypical or extensive polypoid disease. Encephalocele may mimic a nasal polyp, especially in children, and an antrochoanal polyp should also be considered, as it is typically a large unilateral lesion originating from the maxillary sinus and extending toward the choana (57). Finally, long-standing nasal foreign bodies may lead to rhinolith formation, which may clinically and radiologically resemble a polypoid or even tumor-like lesion (58).

TREATMENT

Several international guidelines guide the diagnosis and management of CRSwNP, and the most relevant documents are summarized in **Table 2**. The American Academy of Otolaryngology–Head and Neck Surgery Foundation Adult Sinusitis Update 2025 includes updated recommendations on advanced therapeutic options for adult rhinosinusitis, including biologic therapy for CRSwNP. In Europe, EPOS 2020 and the European Forum for Research and Education in Allergy and Airway Diseases 2023 recommendations (EPOS/EUFOREA 2023) are particularly relevant, as they address treatment algorithms, indications for ESS, and criteria for initiating biologic therapy.

General Treatment Goals and Therapeutic Approach

Treatment of CRSwNP should be regarded as long-term management of a chronic inflammatory disease, with the primary goals of controlling symptoms, preventing

Table 2. Overview of the most important guidelines for the treatment of CRSwNP

Clinical/methodological purpose	Most relevant guideline or consensus document
Basic diagnostic and therapeutic algorithm for patients with CRSwNP	EPOS 2020
Indications for biologic therapy and criteria for patient selection	EPOS/EUFOREA 2023
Detailed analysis of the level of evidence and comparison of different	ICAR-RS 2021*
Practical, outpatient-oriented algorithm for everyday clinical use	EUFOREA Pocket Guide
American clinical context and general approach to adult rhinosinusitis	AAO-HNSF Adult Sinusitis Update 2025

*International Consensus on Allergy and Rhinology: Rhinosinusitis

recurrence, and improving quality of life. The therapeutic approach should be individualized, as patients differ in phenotype, disease severity, comorbidities, prior treatment response, and risk of adverse effects (6). According to EPOS 2020, the core elements of treatment include patient education, nasal saline irrigation, intranasal corticosteroids, assessment of administration technique and adherence, and avoidance of unnecessary antibiotic therapy. Standard treatment may include long-term topical corticosteroid therapy, short courses of systemic corticosteroids, and surgical treatment in more severe forms of CRSwNP (59). If standard medical and surgical treatment fails to achieve adequate disease control, biologic therapy, aspirin treatment after desensitization in patients with N-ERD, or revision surgery may be considered in selected patients (13).

Local Therapy: Intranasal Corticosteroids and Nasal Irrigation

According to EPOS/EUFOREA 2023, topical therapy forms the basis of long-term CRSwNP management, with intranasal corticosteroids remaining the central component of treatment. Intranasal corticosteroids exert anti-inflammatory effects by reducing proinflammatory gene transcription, inflammatory cell infiltration, and the release of inflammatory mediators, chemotactic factors, and adhesion molecules (60).

Clinical guidelines and systematic reviews support the use of intranasal corticosteroids as an effective treatment for CRSwNP, with improvements in symptoms, endoscopic findings, quality of life, olfactory function, and nasal airway patency (60-62).

Long-term use is generally well tolerated. The most common local adverse effects include epistaxis, nasal irritation, and headache. The meta-analysis included in EPOS 2020 showed an increased risk of epistaxis compared with placebo, but no significant effects on serum or urinary cortisol levels, intraocular pressure, or cataract formation (5).

Nasal saline irrigation is a simple and safe adjunctive measure, and some systematic reviews suggest that hypertonic solutions may provide greater benefit than isotonic solutions (63). Corticosteroid irrigations may be useful postoperatively in selected patients with moderate-to-severe disease that is not adequately controlled with standard nasal sprays. However, the available evidence remains limited because of heterogeneity in protocols, doses, solution volumes, and patient populations (1, 5, 6, 13).

The effectiveness of topical therapy depends on correct administration technique, appropriate hygiene of irrigation devices, and regular use. Therefore, patient education is an integral component of long-term treatment.

The main modalities of topical therapy in CRSwNP, their expected effects, and their principal limitations are presented in **Table 3**.

Table 3. Local therapy in CRSwNP

Therapeutic modality	Main effects	Limitations
Nasal saline irrigation	Removal of secretions, allergens, inflammatory mediators, and potential pathogens; improvement of mucociliary clearance and local hygiene of the nasal cavity.	The effect depends on regular use and proper technique.
Intranasal corticosteroid sprays	Reduction of mucosal inflammation, nasal obstruction, rhinorrhea, and polyp size; long-term symptom control.	Local adverse effects include epistaxis, irritation, and nasal dryness; drug distribution may be poorer in cases of pronounced obstruction.
Corticosteroid drops / non-standard local application	Potentially better drug delivery to the middle meatus and olfactory region in selected patients.	Less standardized protocols, dependence of the effect on proper head positioning, and limited evidence.
Corticosteroid irrigations	Better drug distribution through the nasal cavity and operated sinuses after ESS may improve symptoms and endoscopic findings.	Off-label use, heterogeneous doses and protocols, and the need for further evidence on optimal application.
Corticosteroid implants/ stents	Local prolonged corticosteroid delivery may reduce polyp size and the need for additional intervention in selected postoperative patients.	Cost, availability, and limited long-term data; not routinely recommended in the average patient.

Systemic Corticosteroids

Systemic corticosteroids are used in CRSwNP as a short-term adjunct to topical therapy, particularly in patients with pronounced nasal obstruction, large polyps, or significant olfactory impairment (61). Short courses most commonly last 7-21 days and are generally administered together with intranasal corticosteroids. Prednisolone and methylprednisolone have been the most frequently evaluated agents in double-masked, placebo-controlled randomized studies (5). These studies have shown that short-term systemic corticosteroid therapy is more effective than placebo in patients with CRSwNP, whereas comparable evidence has not been established for CRSsNP.

The clinical effect is reflected in reductions in total symptom score, nasal polyp score, nasal congestion, postnasal discharge, and olfactory loss, although the duration of this effect may be limited (64). Rapid improvement in olfactory function may occur within the first days of therapy, probably due to reduced inflammation of the olfactory mucosa, even in the absence of a clear change in polyp volume (65). However, the benefit-risk profile primarily supports the use of a single short course of oral corticosteroids. In contrast, repeated or prolonged courses may provide no additional benefit and may increase the risk of adverse effects. The need for at least 2 courses per year, long-term low-dose use for more than 3 months, or the presence of contraindications to systemic corticosteroids indicates poor disease control and is one of the criteria for considering biologic therapy (13).

Additional Medical Therapy

Additional medical therapies do not play a central role in the treatment of typical CRSwNP. According to current guidelines, antibiotics should not be used routinely in these patients unless there are clear signs of acute bacterial infection. Topical antibacterial therapy has not demonstrated a clear advantage over placebo, and no randomized studies have confirmed the benefit of intravenous antibiotics in CRS (66).

In CRSwNP, courses of non-macrolide antibiotics lasting less than three weeks are generally not recommended outside acute exacerbations, as the potential benefits do not outweigh the risks of adverse effects, antimicrobial resistance, and anaphylaxis (6).

In the study by Van Zele et al. (64), doxycycline was associated with a reduction in polyp size and postnasal discharge, but did not lead to clear improvement in most other symptoms. Macrolides have potential antibacterial and immunomodulatory properties, and some studies of roxithromycin and clarithromycin suggest possible improvements in symptoms, endoscopic findings, and CT findings. However, the evidence remains limited because of heterogeneous treatment regimens and study designs (6).

There is insufficient evidence to support the routine use of leukotriene receptor antagonists, including montelukast, zafirlukast, and pranlukast, in all forms of CRSwNP. However, they may have a role in selected patients with the N-ERD/AERD phenotype (67). Antihistamines are not part of the core treatment for nasal polyposis, but they may be used for symptom control in patients with concomitant allergic rhinitis. Antifungal therapy is not recommended in typical CRS/CRSwNP, as systematic reviews have not demonstrated significant benefit (1, 5, 6).

Endoscopic Sinus Surgery

Surgical treatment is considered in patients with diffuse CRS/CRSwNP when symptoms persist despite appropriate medical therapy, after reassessment of comorbidities and CT findings. Although the definition of appropriate medical therapy is not fully standardized, ICAR-RS 2021 emphasizes that delaying ESS may adversely affect treatment outcomes (6).

The aim of ESS in CRSwNP is to reduce the polypoid and inflammatory burden, improve nasal patency, restore ventilation and drainage of the paranasal sinuses, and facilitate better postoperative delivery of topical therapy (5). Its clinical benefit is supported by a prospective study of 85 patients with CRSwNP, in which ESS was associated with significant reductions in symptom severity, improvements across all quality-of-life domains, and reductions in endoscopic scores at 6 and 12 months of follow-up (68). However, in the same study, recurrence of nasal polyposis was recorded in 32.9% of patients during one-year follow-up, while the endoscopic score at 12 months was higher than at 6 months. These findings confirm that ESS improves symptoms and quality of life, but does not eliminate the need for long-term postoperative follow-up and maintenance topical therapy (68). Preoperative corticosteroid therapy in CRSwNP may reduce intraoperative bleeding, improve surgical field quality, and shorten operative time, as shown in placebo-controlled studies (69).

After ESS, continuation of medical therapy is necessary, most commonly with nasal saline irrigation and long-term topical corticosteroids. These treatments have the strongest evidence for reducing symptom severity, improving endoscopic findings, and decreasing the risk of polyp recurrence (6). Studies evaluating perioperative and postoperative systemic corticosteroids for the prevention of recurrence after ESS have shown heterogeneous results; therefore, EPOS 2020 does not provide a strong recommendation for their routine use (70). Corticosteroid-eluting stents and dressings may improve local drug delivery immediately after surgery. Still, they are not routinely recommended due to limited evidence quality and concerns about cost-effectiveness. Previous surgical treatment remains an important criterion before

considering biologic therapy, as most patients benefit from medical therapy and ESS, whereas biologic therapy is a long-term, costly treatment modality (71, 72).

Biologic Therapy

Biologic therapy is a treatment option for severe CRSwNP, particularly in patients with predominant type 2 inflammation, polyp recurrence, and insufficient disease control despite standard medical and surgical treatment. Biologic agents target key effectors of the type 2 immune response, including IL-4, IL-5, IL-13, and IgE, making them a rational therapeutic option in selected patients with severe CRSwNP (73-75).

According to EPOS criteria, biologic therapy should be considered in patients with bilateral nasal polyps who have previously undergone surgery or are not candidates for ESS, and who meet at least three additional criteria: evidence of type 2 inflammation, need for systemic corticosteroids, significantly impaired quality of life, loss of smell, and comorbid asthma. Evidence of type 2 inflammation includes tissue eosinophilia ≥10 eosinophils/HPF, blood eosinophils ≥150 cells/μL, or total IgE ≥100 IU/mL, with EPOS/EUFOREA 2023 lowering the blood eosinophil threshold from ≥250 to ≥150 cells/μL (13). However, type 2 inflammation has not been established as an absolute prerequisite, as there is still no precise definition of type 2 inflammation in CRSwNP, and the efficacy of biologic therapy in mixed inflammatory patterns remains unclear (6, 13).

Dupilumab, which targets IL-4Rα signaling, has been shown to significantly reduce nasal congestion and polyp size in the randomized SINUS-24 and SINUS-52 trials (23, 76). Omalizumab, an anti-IgE therapy, has demonstrated benefit in reducing polyp size and improving quality of life. At the same time, mepolizumab, which targets the IL-5 pathway, is intended to reduce eosinophilic inflammation and polyp burden (1).

The high cost of biologic therapy, the uncertain optimal treatment duration, and the established effectiveness of standard medical and surgical treatments require careful, individualized patient selection (77, 78). An overview of the most important biologic agents used or considered for the treatment of severe uncontrolled CRSwNP, including their therapeutic targets, expected effects, and main limitations, is presented in **Table 4**.

Treatment of Comorbidities and a Personalized Approach

Treatment of CRSwNP requires careful assessment of comorbidities, as they may significantly influence treatment selection and therapeutic outcomes. Because CRSwNP is frequently associated with type 2 inflammation and comorbid conditions such as asthma, allergic disease, and N-ERD/AERD, a personalized and often multidisciplinary approach is required. Comorbid asthma is particularly important, as it represents one of the criteria for biologic therapy, especially in patients requiring regular inhaled corticosteroid treatment (13).

N-ERD/AERD is a distinct eosinophilic phenotype characterized by asthma, nasal polyposis, and respiratory reactions to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), together with impaired arachidonic acid metabolism and increased leukotriene activity (33, 34). Recognition of AERD is clinically important, as delayed diagnosis may contribute to persistent disease or early recurrence after ESS (33). In carefully selected patients with AERD, leukotriene modifiers and aspirin desensitization may be considered, with postoperative aspirin therapy associated with better quality of life, lower symptom scores, and a reduced need for revision ESS (79). In patients with suspected immunodeficiency, immunoglobulin therapy or antibiotic prophylaxis may be considered, although the evidence is largely limited to retrospective studies and review articles (80).

Table 4. Biologic therapy in CRSwNP

Biologic drug	Target molecule/ pathway	Main clinical effects	Limitations/notes
Dupilumab	IL-4Rα; inhibition of IL-4 and IL-13 signaling	Reduction of nasal congestion, polyp size, and CT score; improvement in SNOT-22, sense of smell, and asthma in some patients.	High cost, need for long-term treatment, unclear optimal therapy duration, and criteria for discontinuation.
Omalizumab	IgE	Reduction of polyp size and improvement in quality of life, particularly in patients with an IgE-mediated/type 2 pattern.	The effect may depend on the dominant endotype; careful patient selection is required.
Mepolizumab	IL-5	Reduction of eosinophilic inflammation and polyp burden; may reduce the need for systemic corticosteroids or ESS.	Not equally effective across all patients, especially in patients with mixed inflammatory patterns.
Benralizumab	IL-5Rα	Targeting the eosinophilic inflammatory pathway can reduce the burden of eosinophilic inflammation.	In some guidelines, it is listed as an investigational therapy, but its role in the routine treatment of CRSwNP depends on its regulatory status and available evidence.

Follow-up, Disease Control, and Prevention of Recurrence

CRSwNP is a chronic disease that requires long-term monitoring of symptoms and quality of life. Although the concept of disease control is clinically important, there is still no single reference standard for assessing CRS control; therefore, several subjective and objective parameters should be combined (5, 6). In clinical practice, the Sino-Nasal Outcome Test-22 (SNOT-22), visual analog scale (VAS), Short Form 36 Health Survey (SF-36), endoscopic scores, CT scores, olfactory testing, and inflammatory markers may be used, particularly during long-term postoperative follow-up (5).

Assessment of treatment success should include both patient-reported and physician-assessed outcomes, as symptoms, quality of life, endoscopic findings, CT findings, and medication use may not always correlate (81, 82). This is supported by data from a study showing that subjective symptoms and quality of life remained stable at 6 and 12 months after ESS. At the same time, endoscopic scores worsened during this period, and nasal polyposis recurrence was recorded in 32.9% of patients (68). In patients receiving biologic therapy, response is assessed based on improvement in quality of life and olfactory function, reduction in polyp size, decreased need for systemic corticosteroids or ESS, and better control of comorbidities (5). The first assessment of response to biologic therapy is recommended after 6 months, followed by reassessment after one year and annually thereafter. In cases of inadequate response, treatment discontinuation, therapy modification, or revision, ESS should be considered (83).

Prevention of sinonasal polyposis recurrence involves continuing well-tolerated topical therapy, particularly nasal saline irrigation and topical corticosteroids, along with patient education and long-term follow-up (1, 6).

CONCLUSION

Sinonasal polyposis is a chronic, heterogeneous, and multifactorial inflammatory disease involving epithelial barrier dysfunction, dysbiosis, biofilm formation, eosinophilic/type 2 inflammation, tissue remodeling, environmental factors, and multiple comorbidities. Diagnosis cannot be established on the basis of symptoms alone, but requires objective confirmation by clinical and/or endoscopic examination and CT imaging. Assessment of symptom severity, associated comorbidities, and overall quality of life is essential. Modern treatment of CRSwNP focuses on long-term control of inflammation, with intranasal corticosteroids and nasal saline irrigation forming the cornerstone of therapy. In contrast, systemic corticosteroids and ESS are used in more severe or uncontrolled disease. Biologic therapy is an important modern treatment option in selected patients with severe, recurrent CRSwNP characterized by type 2 inflammation. An individualized approach, together with adequate control of local disease and comorbidities, is essential for improving long-term treatment outcomes.

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NAZALNA POLIPOZA: ETIOLOGIJA, DIJAGNOSTIKA I SAVREMENE MOGUĆNOSTI LEČENJA

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Sažetak

Hronični rinosinuzitis sa nazalnim polipima (CRSwNP) predstavlja hronično heterogeno inflamatorno oboljenje koje se karakteriše značajnim narušavanjem disanja na nos, čula mirisa i kvaliteta života bolesnika. Etiopatogeneza je multifaktorijalna i u njoj učestvuju poremećaj epitelne barijere, disfunkcija mukocilijarnog klirensa, disbioza, biofilm, Staphylococcus aureus, eozinofilna/tip 2 inflamacija, lokalni IgE odgovor, tkivno remodelovanje, faktori sredine i brojni komorbiditeti. Posebno se ističe značaj prisustva astme i intolerancije na aspirin i/ili nesteroidne antiinflamatorne lekove u sklopu koncepta inflamacije čitavog disajnog puta.

Dijagnoza se postavlja isključivo na osnovu korelacije karakterističnih simptoma sa objektivnim nalazom kliničkog/endoskopskog pregleda nosa i kompjuterizovane tomografije sinusa. Veoma je važna procena težine bolesti, komorbiditeta i drugih diferencijalno-dijagnostičkih entiteta. Osnovu terapije čine intranazalni kortikosteroidi i ispiranje nosa fiziološkim rastvorom, dok se sistemski kortikosteroidi, endoskopska sinusna hirurgija i biološka terapija koriste kod težih, rekurentnih ili nekontrolisanih oblika bolesti. Dijagnostičko-terapijski pristup kod CRSwNP zahteva razlikovanje fenotipa i endotipa bolesti, prepoznavanje tip 2 inflamacije i aktivno lečenje pridruženih stanja, uz kontinuirano praćenje terapijskog odgovora pomoću simptoma, endoskopskog nalaza, kvaliteta života i potrebe za dodatnim intervencijama.

Ovaj pregledni rad obuhvata aktuelne dokaze o etiopatogenezi, kliničkoj prezentaciji, kvalitetu života, dijagnostičkim kriterijumima i savremenim mogućnostima lečenja CRSwNP, oslanjajući se na sistematske preglede, kliničke vodiče i originalna istraživanja. Individualizovani pristup, dobra kontrola lokalne bolesti i komorbiditeta predstavljaju ključne aspekte za dugoročno poboljšanje ishoda lečenja.

Ključne reči: hronični rinosinuzitis sa nosnim polipima, tip 2 inflamacija, nazalna endoskopija, endoskopska sinusna hirurgija, biološka terapija

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