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The Role of Biologics in Chronic Rhinosinusitis with Nasal Polyps

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39 **Conflict of Interest:**

40 C. Bachert: Speaker and member of advisory boards for Sanofi-Aventis, Regeneron, Novartis,
41 Genentech, Glaxo, Astra-Zeneca, Stallergenes, ALK, Asit Biotech, Mylan, Allakos.

42 M. Y. Desrosiers is on the advisory boards for GlaxoSmithKline, AstraZeneca, and
43 Sanofi/Regeneron; is on the speakers bureau for Mylan; and is founder and major stockholder
44 of Probionase Therapies Inc.

45 P. W. Hellings reports unrestricted research grants from Mylan and GlaxoSmithKline; and
46 reports honoraria for lectures and/or expert boards from Sanofi, Novartis, and Allergopharma.

47 T. M. Laidlaw has served on scientific advisory boards for GlaxoSmithKline and Sanofi-
48 Genzyme, Optinose, and Regeneron.

49

50 **Key words: Chronic rhinosinusitis, Nasal polyps, Biologics**

51

52 **Abbreviations:**

53

- 54 • Chronic rhinosinusitis with nasal polyps (CRSwNP)
- 55 • Chronic rhinosinusitis sans (without) nasal polyps (CRSsNP)
- 56 • *Staphylococcus aureus* enterotoxin (SE)
- 57 • Interleukin (IL)
- 58 • Extracellular eosinophilic traps (EETs)
- 59 • Nasal polyp score (NPS)
- 60 • University of Pennsylvania Smell Identification Test (UPSIT)
- 61 • Sinoasal Outcome Test (SNOT-22)
- 62 • Aspirin-exacerbated respiratory disease (AERD)
- 63 • Allergic fungal sinusitis (AFS)

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Introduction.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common and heterogeneous inflammatory disease of the upper respiratory tract. Advances in our understanding of the immune mechanisms that drive the chronic respiratory inflammation that underlies CRSwNP have led to the generation of several targeted biologic therapies for this disease. However, the optimal evaluation and treatment strategy, including judicious use of systemic corticosteroids, allergen testing, proper surgical approach, appropriateness of antibiotics, and administration of newly approved biologics, is still hotly debated. Here we provide expert opinion and points of view from both allergists and rhinologists who specialize in CRSwNP, and the evaluation and management perspectives offered here are a consensus between the authors.

Endotypes of CRSwNP and CRSsNP and how to identify Type 2 inflammation in these patients.

The first major biomarker for endotyping CRSwNP was identified more than 20 years ago, with the finding that the majority of CRSwNP patients in Europe had increased levels of interleukin (IL)-5,(1) which led to delayed eosinophil apoptosis and was suggested to be a causative mechanism for the observed tissue eosinophilia.(2) These observations were then complemented by publications demonstrating that total and *Staphylococcus aureus* enterotoxin (SE)-specific IgE levels were increased and correlated to each other in a subgroup of patients with CRSwNP;(3, 4) IL-5 and SE-IgE were then also demonstrated to be associated with comorbid asthma in CRSwNP subjects (5) and their elevated levels predicted recurrence of polyps after surgery.(6) These observations are valuable still today, but the field now has expanded knowledge of additional cytokines, mediators and effector cells involved in what is referred to as “type 2 inflammation”.

91 There are also CRSwNP patients with non-type 2 inflammation, in which IL-17 has been
92 identified as a major cytokine involved in the orchestration of the survival of neutrophils in
93 patients with and without cystic fibrosis.(7) These observations were later confirmed by similar
94 findings of non-type 2 inflammation in CRSwNP in Asia.(8) However, there appears to be a
95 recent shift from non-type 2 to type 2 inflammatory CRSwNP in Asia,(9) and also in Europe an
96 increase in type 2 inflammatory patterns has been noted.(10) Recent observations confirmed
97 the increase of neutrophils not only in non-type 2, but also in type 2 disease, perhaps due to the
98 effects of Charcot-Leyden crystals, crystalized galectin 10 derived from eosinophils, which
99 promote neutrophilic inflammation in CRSwNP.(11)

100 These observations have been assembled into one schema in a paper by Tomassen et
101 al.(12) which relates cytokine patterns as derived from a cluster analysis with clinical findings
102 **(Table 1)**.(12, 13) The expression of type 2 inflammation is significantly more frequent in
103 CRSwNP than chronic rhinosinusitis sans/without nasal polyps (CRSsNP), with approximately
104 50% vs. 85%, respectively, of CRS patients in central Europe presenting with type 2
105 inflammation,(13) and is associated with comorbid asthma, ranging from 10% in non-type 2
106 CRSwNP to 70% in severe type 2 CRSwNP patients.(12) In severe type 2 CRSwNP, SE-IgE
107 antibodies could be found in the majority of patients, suggesting prior contact with the bacteria
108 and its products, which have been shown to contribute to type 2 inflammation through a variety
109 of mechanisms.(14-19) Further, *S. aureus* also seems the target of maximal eosinophil
110 activation and death, and the formation of extracellular eosinophilic traps (EETs), comprised of
111 galectin 10, eosinophilic DNA and major basis protein.(20) Thus, the expression of SE-IgE and
112 the formation of EETs are signs of severe type 2 inflammation and point to the presence of
113 bacteria, particularly *S. aureus*, which can persistently stimulate the local immune system.

114 Consequently, endotypes in CRS with or without nasal polyps, as defined by prominent
115 cytokine patterns, the formation of SE-IgE antibodies and Charcot-Leyden crystals as well as

EETs, are useful to differentiate subtypes of CRS with consequences in terms of disease severity, comorbidities, and disease recurrence after surgical or pharmacological treatments.(21-23) Type 2 inflammation was also associated with the presence of nasal polyps, asthma comorbidity, anosmia, and allergic mucin, whereas pus was significantly associated with IL-17 expression in patients with CRS.(24) The diagnosis of endotypes by adequate clinical signs and/or biomarkers may therefore be useful in the optimization of current standard of care, in the selection of surgical procedures, and may even be mandatory for the indication of innovative biologics specifically targeting type 2 cytokines and their down-stream products.

Despite the potential value of biomarker-based endotyping to provide guidance regarding optimal care in CRSwNP, current practice in most rhinology remains largely driven by what has been suggested as treatment options in European and American guidelines, (25) with surgery as one of the key pillars of CRSwNP care.

Clinical data on existing biologics.

The discoveries regarding the upregulation and role of IL-5 in nasal polyps (1, 2) then led to the first small trials using monoclonal antibodies in CRSwNP – today termed “biologics” – which tested the efficacy of reslizumab and mepolizumab, (26) both of which target IL-5. Similarly, the finding of high IgE concentrations in nasal polyp tissue,(3, 4, 27) which is independent of atopy but correlates to the degree of respiratory inflammation and likelihood of recurrence, prompted the first proof-of-concept trials with omalizumab, a monoclonal antibody that binds free IgE.(28) With these early studies, new approaches for recalcitrant CRSwNP were introduced. The next option to be introduced was dupilumab, which inhibits the IL4R α , with a Phase 2 trial in 2016 with 60 subjects that demonstrated that dupilumab provided a significant decrease in nasal polyp score (NPS) of approximately 2 points, out of a maximum score of 8.

(29) This study also showed that dupilumab significantly reduced the CT-scan based Lund-Mackay-Score, and significantly improved sense of smell, measured by changes in the University of Pennsylvania Smell Identification Test (UPSIT) (30) and patient-reported symptoms and quality-of-life, measured by changes in the Sinoasal Outcome Test (SNOT-22).(31) Dupilumab (vs placebo) also resulted in greater improvement in SF-36 (32) and EQ-5D VAS scores and a significantly lower adjusted annualized mean number of sick leave days.(33) Further, it was then demonstrated that dupilumab reduces levels of local and systemic biomarkers, indicating that the drug worked on IL-4-related IgE production, but also on chemokine- and IL-5- related eosinophil migration and activation.(34) The drug was well tolerated; the most common adverse events were nasopharyngitis, injection site reactions and headache.

A further Phase 2 study with mepolizumab in 105 randomized subjects aimed to show reduction in the need of surgery for CRSwNP,(35) again demonstrating a significant improvement of nasal polyposis severity scores, symptom scores, nasal polyp score and SNOT-22. In addition, a significantly greater proportion of patients in the mepolizumab compared with the placebo group no longer required surgery at Week 25 (reduction by 20%), as defined by a composite surgical scoring system. Mepolizumab's safety profile was comparable with that of placebo.

Finally, two Phase 3 studies per drug were performed in larger patient groups to establish the efficacy of dupilumab (36) and omalizumab (37) for the treatment of CRSwNP. The POLYP 1 and 2 studies in adults with CRSwNP with inadequate response to intranasal corticosteroids (INCS) compared the efficacy and safety of omalizumab vs placebo for 24 weeks in patients with severe CRSwNP, who entered the study with a mean NPS of ~6 and a mean SNOT-22 of ~60, reflecting substantial quality-of-life impairment. The co-primary endpoints of NPS and nasal congestion score both improved significantly over the 24-week period, with a

reduction in NPS of ~1 point. Patient-reported symptoms (SNOT-22) and sense of smell (UPSIT) also improved. Thus, not only allergic asthma, but also non-atopic CRSwNP and its comorbidities can be successfully treated with anti-IgE therapy.(38) The LIBERTY SINUS-24 and SINUS-52 studies, which included more than 700 subjects, assessed dupilumab vs. placebo added to standard of care intranasal steroid spray in adults with severe CRSwNP over 52 weeks. More than half of the subjects reported a history of previous sinus surgery, systemic corticosteroid use within the last 2 years, and/or asthma co-morbidity, indicating a high severity of disease in this population. The co-primary endpoints of NPS and nasal congestion score (and Lund-Mackay CT scores in Japan) were highly significantly and clinically meaningfully reduced compared to placebo at 24 weeks, with a reduction in NPS of ~2 points, and were further reduced at 52 weeks. Symptom scores, the UPSIT score, the percentage of anosmic subjects, and the need for systemic corticosteroids and sinus surgery during the 52 weeks of study were all significantly improved in the dupilumab vs placebo treated groups. The drug was generally well tolerated, with a good safety profile.

Collectively, these study results clearly demonstrate the potential for innovative biologics to better control severe CRSwNP with and without comorbid asthma. However, the appropriate timing and placement of biologic treatments within newly developed care pathways, in relation to current standard-of-care medical therapies and surgical interventions, still needs to be determined.(39, 40) Further, due to differences in the inclusion criteria of the trial populations and in the structure of the trials, it is difficult to perform a simple comparison of the results of each trial without adequate statistical considerations, subgroup comparisons, and consideration of potential confounders. To definitively compare efficacy and safety of these biologics, head-to-head trials with sufficient statistical power would need to be performed. As of now, the trials of biologics for CRSwNP have been largely carried out without any biomarker-based subendotyping, which makes choosing the proper biologic for an individual patient difficult.

190

191 **Approach to evaluation and treatment of patients with recurrent CRSwNP**

192 The recommended initial approach to a patient with newly diagnosed CRSwNP is
193 depicted in **Figure 1** and involves consideration of patient perception of symptom severity,
194 comorbidities, biomarkers, and corticosteroid treatment response.

195 However, the patient who presents with recurrent disease represents a medically and
196 technically frustrating problem for both patient and physician. Indeed, well-performed and
197 thorough sinus surgery may relieve most symptoms for a significant interval of time, but there is
198 no guarantee of a cure long-term.(41) Of note, up to 45% of patients undergoing sinus surgery
199 for bilateral inflammatory CRS remain uncontrolled despite adequate surgery, and there are
200 likely multiple reasons for this. (42) (41) Frequently patients with recurrent CRSwNP are
201 younger and may have comorbidities, particularly asthma and concomitant respiratory
202 symptoms. Contributing to patient despair is that recurrence of symptoms can occur rapidly,
203 even after seemingly initially successful surgeries. The patients' needs may then extend beyond
204 the chronic nasal, sinus and pulmonary symptoms to also incorporate psychological issues such
205 as a lack of confidence in the medical system, and a subsequent susceptibility to use of non-
206 evidence-based therapies. Given the high burden of disease on the patient and the lack of
207 success of all other available therapies, it is clear that these high-need patients should be
208 assessed for their suitability to alternate medications, including targeted biologic therapy with
209 monoclonal antibodies.

210 As part of this process, alternate factors potentially contributing to failure should be
211 assessed. Compliance with current therapy must be established and supported by pharmacy
212 records if possible. Clinical phenotype needs to be explored carefully to try and identify the
213 underlying endotype. While there is no absolute biomarker for identifying patients with a strong
214 Type 2 component to their disease process, in addition to serum eosinophil level, presence of

comorbid Type 2 diseases such as asthma, allergic rhinitis, eosinophilic esophagitis, or a history of atopic dermatitis may also suggest Type 2 inflammation-mediated disease. In contrast, association with non-asthma respiratory disorder such as pulmonary fibrosis, with non-Type 2 skin disease such as psoriasis, or presence of an inflammatory disorders such as inflammatory bowel disease or rheumatoid arthritis, may suggest a strong a non-Type 2 mechanistic underpinning. This distinction between Type 2 and non-Type 2 can be quite relevant regarding predicting surgical outcomes and likelihood of post-surgical recurrence, and there are several biomarkers that have been found to be helpful. Both serum eosinophilia and higher polyp tissue eosinophil levels, which correlate with Type 2 inflammation, tend to predict post-surgical recurrence, as does the comorbid presence of asthma and allergic sensitization. Local tissue levels of IL-5 and IgE have also been found to be significant predictors for the need for revision surgery, though these are generally not clinically available tests. (43, 44) Consequently, in patients with severe Type 2 mucosal disease, the recommendation is to adapt the surgical technique and mission away from just anatomic re-installation of ventilation and drainage, and towards a more comprehensive removal of the sinus mucosa, referred to as “reboot surgery”. (23) (45)

It is essential to rule out rare causes potentially responsible for recurrences. To this end, patients with an associated history or previous history of severe infection such as pneumonia should be considered for immune deficiency screening, preferably performed by a clinical immunologist experienced in the area with access to specialized testing. Coexisting bronchiectasis in the absence of asthma may be an indicator of non-Type 2 disease, including undiagnosed cystic fibrosis or common variable immune deficiency, both of which can also present with sinus disease. Any patient presenting with a history of first surgery under the age of 18 years should certainly be screened for cystic fibrosis regardless of other symptoms. Although empiric courses of oral antibiotics have often already been tried in patients with CRSwNP who

present with post-surgical recurrence, bacterial infection is not thought to play a large role in either the chronic persistence of CRSwNP or in the recurrence of nasal polyps following surgery. Acute exacerbations of CRS can be infectious, which is often associated with either viral or bacterial infections, (46) (47) and consensus guidelines on CRS treatment recommend, when possible, that antibiotic treatment should be guided by endoscopically obtained cultures.(48) However, antibiotic treatment is unlikely to prevent the recurrence of nasal polyps.

While technical factors are rarely the sole cause of a surgical failure, it is important to assess extent of previous surgery and occurrence of complications from disease or post-operative scarring. Patients with a history of sinus surgery should be assessed with a CT scan of the sinuses to determine the extent of previous surgery. If it is the assessor's opinion that the surgery had been superficial, with many areas of disease not addressed, a revision surgery may represent a better long-term option for the patient than treatment with a biologic, or may need to be performed in combination with a biologic. CT scans should also be carefully reviewed for evidence of scarring and sinus obstruction. Any revision surgery should only be considered alongside optimal care for comorbidities like asthma, and when occupational or environmental irritating factors have been considered and mitigated where possible.(42) Mucocoeles, which form following obstruction of sinus passages and lead to inadequate drainage, can cause dangerous complications and should be sought out routinely on imaging in patients who have undergone previous surgery.

Biologics can offer an impressive therapeutic benefit for appropriately selected patients and should be prescribed for patients with true refractory disease who are most likely to respond. As experience with these therapies grows, and access to biomarkers increases, patient selection in the future may be biomarker-based, but for the moment, this process requires clinical expertise and judgment.

Should use of biologics ever come before an initial surgery?

In general there is agreement that for most patients with symptomatic CRSwNP who have failed a trial of course of at least 3 months of intranasal steroids, preferably at higher doses or as part of a directly-instilled sinus rinse, a surgical intervention will often be the next treatment of choice. There are several patient-specific reasons why it might be suitable to recommend the use of a biologic for the treatment of uncontrolled CRSwNP, even for a patient who had never undergone sinus surgery. First, for patients with comorbid severe asthma, biologic therapies may provide benefit for both the lower and upper respiratory tract inflammation. As the biologic would otherwise be indicated for asthma treatment, it may be appropriate to begin a biologic and provide 6 months of therapy to determine if the asthma improvement is successful, and if so, if the response in the upper respiratory tract is sufficient enough to prevent the need for surgery. Second, for patients with severe CRSwNP who have limited access to specialized rhinologists, or for whom the wait time for a sinus surgery is more than 6 months, beginning with a biologic for more immediate symptom relief may be the best approach. If, after 6 months of therapy with a biologic, surgery still is needed, the surgical intervention may need to be less extensive, and the healing process after surgery may be faster and better while on the biologic treatment, which should then be continued to secure control and avoid recurrence (49). Finally, there are patients for whom the concept of surgical intervention is terrifying, and/or in whom surgery is associated with a higher than average complication rate given previous trauma, bone erosions or orbital pathology. Although thoughtful education and patient-centered discussions with the surgical team are usually enough to provide comfort and reassurance, there still remain a minority of patients who are entirely unwilling to undergo surgery, for personal or religious reasons. In these select cases, offering medical therapy with a biologic would be appropriate. However, no patients should be prescribed a biologic unless their symptoms are truly recalcitrant despite adherence to a proper daily medical regimen. Simply “I

don't want to use my nasal spray" is not a substantive reason to suggest a biologic as an alternative. One clear gap in the field is knowledge regarding the longer-term use of biologics for the treatment of CRSwNP. The trials to date have not followed patients beyond 1 year of treatment, and therefore a direct comparison of the "long-term" value of surgical intervention compared to prolonged use of biologics is not yet possible.

Four specific special case scenarios to consider:

1. The patient with AERD

Patient DS is a 35-year-old woman who was diagnosed with asthma at the age of 27 and nasal polyps at the age of 29. She developed a suspected ibuprofen-induced asthma exacerbation at home at the age of 30 and a diagnosis of aspirin-exacerbated respiratory disease (AERD) was subsequently confirmed following a physician-observed provocative oral aspirin challenge that induced a fall in FEV1 of 19%, along with increased nasal congestion, sneezing, and eye watering. For her asthma, she has been treated with high-dose inhaled corticosteroids and a long-acting beta-agonist twice daily for the last 6 years, along with montelukast 10mg daily, and albuterol as needed. She has had two functional endoscopic sinus surgery procedures, one at age 30 and again at age 32. Each time her sense of smell returned temporarily, though waned within 4 months following surgery. She has consistently used intranasally instilled budesonide washes once daily, both before and after her surgeries. Despite these therapies, she has poorly controlled asthma with a recent FEV1 of 71% of predicted, requiring at least 2 courses of oral corticosteroids annually to treat exacerbations, and her nasal polyps have returned and have caused complete anosmia and chronic nasal congestion. Her current peripheral eosinophil level is 477 cells/uL, and her total serum IgE is 140 IU, though she does not report any clinical symptoms of environmental allergies.

This patient would benefit from additional medical management for both her asthma and her CRSwNP. She is wary of proceeding with a third sinus surgery, as the benefit was only temporary. As she has comorbid CRSwNP, uncontrolled asthma, and AERD, and thus a Type 2 inflammatory process, dupilumab would likely be the best choice for her as it may help to control her asthma symptoms, improve her FEV1, decrease her polyp burden, and improve her sense of smell.(49) Therefore, dupilumab would be the first-choice biologic for this patient and may help her avoid more surgery. If after 6 months of treatment with dupilumab her polyps had not improved at all, switching to another biologic or continuing to a third surgery could be recommended; if her polyps had improved but only partially, indicating the appropriateness of the biologic choice but with insufficient benefit, proceeding to a third surgery may be appropriate to debulk the remaining polyps, while continuing the dupilumab treatment.

2. The patient with fungal sinusitis

Patient AA is a 40-year-old female who presented for otolaryngologic consultation due to nasal obstruction and recurrent acute sinusitis. Her past medical history is positive only for mild intermittent asthma, managed with beta agonists. She describes a six-month history of right-sided facial pressure with nasal obstruction and anosmia. She has no personal or family history of immune deficiency of prior sinus surgery and has no known sensitivity to aspirin or other non-steroidal anti-inflammatory drugs. On nasal endoscopy, Grade II/IV nasal polyposis can be seen bilaterally in narrowed nasal passages. CT scan imaging shows sinus opacification involving all sinuses but particularly striking is the expansive aspect of the right maxillary sinus, which displaces the lateral nasal wall medially to obstruct the nasal passage (**Figure 2**). On soft tissue views, the soft tissue density in the right maxillary sinus is characteristic of the eosinophilic mucin seen in allergic fungal sinusitis (AFS). Closer examination reveals the presence of a peri-apical abscess on the right upper molars, suggesting dental involvement as a possible

339 additional factor in disease development. Her current peripheral eosinophil count is 620 cells/uL,
340 and her total serum IgE is 428 IU. The patient's pulmonologist inquires if this situation would be
341 amenable to biologics.

342 The contribution of fungus to "every day" CRSwNP remains debatable, as even healthy
343 individuals carry a fungal load, which is characterized by presence of isolates of potentially
344 pathogenic *Aspergillus* and *Malassezia*.(50, 51)

345 However, in certain situations of high environmental fungal burdens, susceptible patients
346 may present with fungal-associated disease, including AFS.(52) While this can occur on a
347 sporadic basis within areas in the northern reaches of the United States, these are more
348 frequently associated with areas of high heat and humidity along the south eastern coast
349 extending into Texas. Physicians often encounter AFS as characterized by massive involvement
350 of a single sinus, with notable deforming but painless changes, frequently involving the eyes
351 and forehead. While AFS may have manifestations of Type 2 inflammation, other potential
352 contributing factors must be addressed as well, such as in this example where an untreated
353 peri-apical abscess is associated with the AFS-affected sinus. it is believed that the thick
354 "peanut butter"-like mucin within the cavity requires surgical clearance for proper treatment, and
355 many patients with AFS will resolve completely after one sinus surgery. Therefore, use of a
356 targeted biologic therapy in instances of CRSwNP associated with AFS should be reserved only
357 for those patients who fail to achieve a good clinical outcome after an appropriate surgery.

359 **3. The patient with high risk of complications from sinus surgery**

360 Patient WY is a 50-year-old female who was diagnosed with CRSwNP in her 30s but
361 was reluctant to undergo sinus surgery because she considered it to be too risky due to her
362 medical history. During her youth she had been involved in a car accident that had caused facial

and orbital fractures with medialization of the lamina papyracea; these injuries led to a higher risk of orbital complications if she were to undergo elective sinus surgery. In addition, she had spoken to patients in the outpatient clinic who had undergone multiple sinus surgeries for recurrent CRSwNP, without long-term cure.

Her CRSwNP-related symptoms of anosmia, nasal obstruction and post-nasal drip have been only moderately and/or temporarily controlled by nasal rinses and daily INCS use supplemented by frequent courses of oral corticosteroid treatment. She does not have comorbid asthma or any symptoms of environmental allergies. Her current peripheral blood eosinophil level is 355 cells/uL and her total IgE is 98 IU.

For this patient, the option of a non-surgical and non-steroidal treatment plan using a biologic is recommended due to her history of maxillo-facial trauma, and increased risk of complications from sinus surgery according to the international guidelines.(25) As surgery is associated with a higher orbital complication risk in patients after maxillo-facial trauma,(53) a biologic treatment would be the best therapeutic option for this patient with CRSwNP.

4. Does failure of previous surgery always indicate a need for a biologic agent?

Patient PP is a 45-year-old female referred by her pulmonologist for nasal obstruction aggravating underlying sleep apnea. Upon evaluation, she describes bilateral, fixed nasal obstruction, post-nasal secretions producing a cough, and anosmia. There is no history of asthma or NSAID sensitivity. Review of medications shows that she has used an INCS spray intermittently but was not satisfied with the result and abandoned it quickly. She currently uses a topical decongestant nightly, but reports decreasing effect and concerns about side effects. Upon further questioning she describes a 'sinus surgery' performed 18 months ago in an ambulatory surgical facility. This surgery initially improved her nasal obstruction but not her

anosmia, and the nasal obstruction progressively returned to the pre-surgical baseline 6 months later. A subsequent 5-day course of prednisone improved her sense of smell temporarily, but anosmia returned once the prednisone course ended. She describes her condition as bothersome and is seeking lasting relief, but has not required urgent care visits, nor has had to miss work or compromise family activities because of her symptoms.

Physical examination reveals normal septal position and absence of turbinate hypertrophy. Nasal and sinus endoscopy show nasal polyposis extending to the inferior turbinate bilaterally. CT imaging shows opacification of the nasal chambers and sinus cavities with soft tissue swelling, as well as persistence of ethmoid cells and incomplete opening of the maxillary and frontal sinuses. Her current peripheral blood eosinophil level is 310 cells/uL and her total IgE is 141 IU.

This patient, who presents with recurrent symptomatic CRSwNP without asthma, describes her treatment goals as improving anosmia and relieving her nasal obstruction which hinders the success of her continuous positive airway pressure therapy for sleep apnea. With the failure of a previous surgery, she could be a candidate for biologic therapy. However, several factors suggest that a comprehensive repeat surgery, followed by careful and compliant post-operative medical care, may represent a better option. Despite having polyps that recurred following a previous surgery, it is not clear that PP is at a high risk of further failure or recurrence following a proper revision surgery, in large part because her previous surgery was superficial and did not address all of the diseased areas. CT evidence showing persistence of ethmoid cells and incomplete openings to the other sinus passages suggests that the prior surgical approach was not extensive and did not address the disease adequately. Furthermore, her post-operative medical care, which should include use of a daily INCS, was incomplete. Despite blood parameters (mild eosinophilia and elevated IgE) that suggest a mild Type 2 inflammatory profile, she does not have a high-risk phenotype like comorbid asthma or AERD.

Therefore, a thorough and comprehensive revision surgery, along with good compliance with INCS therapy, may be the best recommendation for her.

Patient Perspective.

Patients suffering from CRSwNP are confronted with several medical and societal challenges. Indeed, the condition of severe CRSwNP with smell impairment, nasal obstruction and headaches as major symptoms is not always taken seriously by the physician community nor by society, and it is too often written off as an ordinary self-limiting common cold. This underestimation of the burden induced by smell dysfunction may be somewhat reduced thanks to individuals infected with COVID-19 who have brought media attention to the issues in 2020 regarding how bothersome it is to live without smell and taste. The historic underestimation of the burden of CRSwNP might explain why there is a major delay between disease onset and referral to specialist care.(54, 55) Secondly, patients feel frustrated by both the current care pathways that include only a limited number of treatment options, and the understanding that sinus surgery does not always lead to a definite cure or a complete relief of smell dysfunction.(54) As highlighted by real-life CRS patient data and post-operative analysis after endoscopic sinus surgery, the majority of patients remain symptomatic and with major smell impairment as the most bothersome symptom.(41) Thus, the initiation of a long-term strategy that includes both surgery and innovative biologic treatments is desirable.

Coordinated care with all stakeholders in the respiratory field, along with patient empowerment through proper education on care pathways and personalized therapeutic plans to guide the proper medication choice is extremely important. Areas for cooperation among specialists can include guideline-based confirmation of CRSwNP through endoscopy, subtyping of CRSwNP, identification of coexisting lower airway diseases, and combining surgical and nonsurgical interventional strategies to optimize patient outcomes. (56)

437

438 **Conclusion/Summary.**

439 Historically the mainstays of treatment for patients with CRSwNP have involved a
440 combination of surgery and medical management, which was generally limited to the use of
441 steroids, antibiotics, antihistamines, and allergen avoidance. The use of biologic therapies to
442 specifically target relevant effector cells or cytokines in CRSwNP is a growing area with much
443 potential. Each patient's surgical and medical regimen must be individualized and tailored. For
444 many patients with recalcitrant disease, a combination of sinus surgery and use of a biologic
445 that is targeted to their precise endotype may be the optimal treatment strategy, though which
446 surgical approach and which biologics are best for each patient are debates that remain
447 ongoing.

448

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Table 1. Endotypes of CRS

	CRSsNP		CRSwNP		
% of subgroup	50	50	15	45	40
Endotype	Non-type 2	Type-2	Non-type 2	Moderate Type 2	Severe Type 2
Relevant cytokines	IL-17	IL-4, -5, -13	IL-17	IL-4, -5, -13, IL-17	IL-4, -5, -13
Asthma co-morbidity %	10	30	10	30	50-70
Recurrence %	10	20	10	20-40	>50
Tissue IgE	+	++	+	++	++++ SE-IgE
Tissue IL-5	0	+	0	+	+++
Tissue IL-17	++	+	++	++	0
CLCs	0	+	0	+	+++
Neutrophils	+	+	+	+	++
Eosinophils	0	++	+	++	++++

Figure 1. Evaluation of patient with new diagnosis of CRSwNP.

Figure 2. Fungal Sinusitis. CT imaging shows sinus opacification involving all sinuses with expansion of the right maxillary sinus (**left**), which displaces the lateral nasal wall medially to obstruct the nasal passage. Peri-apical abscess is suggested by bony erosion at dental roots extending superiorly into infected maxillary sinus (**top right**). Mucin removed at surgery with a thick, tenacious consistency (**bottom right**).



