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AN UPDATE ON SELECT TOPICS IN CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

INTRODUCTION

Chronic rhinosinusitis affects approximately 5-15% of the population and has an economic burden estimated to be between $22 - $64.5 billion US dollars per year[1, 2]. The condition causes significant reductions in quality of life, productivity and emotional wellbeing for patients.[3] Furthermore it is a top ten leading cause of employee absenteeism.

DIAGNOSIS AND CLASSIFICATION OF CRS

Chronic rhinosinusitis (CRS) is a group of disorders characterized by inflammation of the mucous membranes of the nose and paranasal sinuses. CRS is defined by the presence of two or more of the following symptoms for at least 12 consecutive weeks duration including:

- Mucopurulent drainage (anterior, posterior, or both)
- Nasal obstruction (congestion)
- Facial pain/pressure/fullness, or
- Decreased sense of smell and objective evidence of inflammation identified either by nasal endoscopy or radiologically[4].

Traditionally, diffuse CRS has been categorized into 2 groups based on phenotype: Group 1) CRS with nasal polyps (CRSwNP) and Group 2) CRS without nasal polyps (CRSsNP). Recently, there has been a shift to classify CRS based on *endotype* as either eosinophilic chronic rhinosinusitis (ECRS) or non-eosinophilic chronic rhinosinusitis (Non-ECRS)[5]. This classification is descriptive of the pathophysiology and immune mechanisms involved and is perhaps better suited to help guide management decisions. This is determined histologically via surgical tissue biopsy, or, enumerating the number of eosinophils/per high powered field (HPF) (at 400x magnification). The EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) panel in 2020 has chosen to define ECRS as having ≥ 10 eosinophils/HPF. Published literature has identified that higher numbers of eosinophils from nasal polyp biopsies vary directly with recurrence of nasal polyposis disease. Regarding disease recurrence, a systematic review of 11 articles reporting tissue eosinophilia identified a cut off value of > 55 eosinophils/HPF as being the most predictive of nasal polyp recurrence following combined medical and surgical treatment[6]. When tissue diagnosis is unavailable, serum eosinophil count may serve as a useful surrogate[7]. Numerous markers for identifying and diagnosing eosinophilic chronic rhinosinusitis have been investigated. There is currently no consensus regarding the best tool for the diagnosis of ECRS but using tissue eosinophilia seems to be the most predictive/accurate for recurrence. Regarding serum eosinophilia, there is limited data surrounding its prognostic use. A serum eosinophil count of more than 0.24 × 10/l predicts ECRS with tissue eosinophilia of more than 10 eosinophils/HPF. It has also been shown that a serum eosinophil count of more than 0.45 × 10/l is associated with the need for long-term systemic therapy

following ESS. Unfortunately, serum eosinophil count isn't as well studied as tissue eosinophil count and there is more conflicting evidence surrounding its use as a diagnostic marker for eCRS.[8-10]

ECRS is characterized histologically by a type 2 immune response and is often associated phenotypically with the presence of bilateral or diffuse nasal polyps. The focus of this article will be to briefly discuss the pathophysiology, assessment, and management of patients with CRS with an emphasis on ECRS.

Recently, another distinct endotype has been described and termed central compartment atopic disease (CCAD). This entity is characterized initially by edema of the middle turbinate head (**Figure 1**) and computerized tomography (CT) evidence of inflammatory disease primarily in the middle and superior turbinates, and, with involvement of ethmoid sinuses in more advanced disease. The remainder of the paranasal sinuses are largely spared.[11] While these patients exhibit eosinophilia on tissue histology, further phenotypic evaluation of this population reveals a primary immunoglobulin E (IgE) mediated condition with associated symptoms of atopy consistent with allergic rhinitis, conjunctivitis and childhood onset asthma. This combined eosinophilic-IgE mediated patient population does not typically present with severe infectious exacerbations and often retain good olfactory function despite their nasal polypoid disease.

Overall, the CRS landscape is somewhat heterogeneous, with some subtypes such as those in cystic fibrosis and primary ciliary dyskinesia patients ultimately

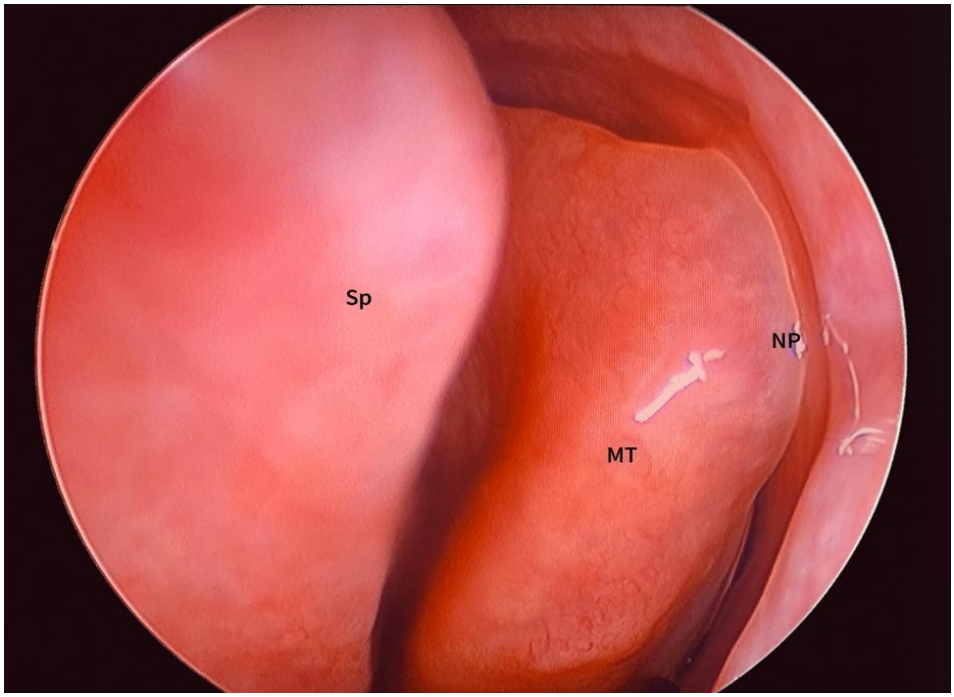

Figure 1: Nasal endoscopy demonstrating polypoid changes on the anterior surface of the middle turbinate. Sp: Septum; MT: middle turbinate; NP; nasal polyp.; courtesy of Tobial McHugh, MD and Doron Sommer, MD

manifesting similar appearing endoscopic and radiologic manifestations with a distinct pathophysiology. Other patterns, possibly more centered in certain geographic regions, may display a more neutrophilic pattern with distinct clinical features and response to therapies. With some non-ECRS patients there is emerging literature noting the efficacy of low dose macrolide therapy in patients with local total IgE less than 5.21 and serum eosinophils less than 2.2%.[10]

PATHOPHYSIOLOGY OF CRS

The pathophysiology of CRS has proven to be complex and multifactorial. Over the past decade, there has been increasing emphasis on investigating inflammation that develops in sinus tissues following a breach in the protective sino-nasal mucosal barrier. When this mucosal barrier is penetrated, an inflammatory response is generated and characterized by one of three cellular and cytokine immune response patterns (type 1, 2, or 3 immune response) or a combination thereof. If the mucosal barrier is breached, there are 3 defensive immunological responses generated with specific cytokines and inflammatory mediators that will target one of three classes of pathogens: type 1 immune responses target viruses; type 2 responses target parasites and type 3 target extracellular bacteria and fungi.[12-13] Recent research efforts have focused on elucidating the role of type 2, often in combination with type 1 and 3 inflammation. This is characterized primarily by inflammatory cytokines including IL-4, IL-5 and IL-13 as well as activation and cellular recruitment of eosinophils and mast cells. This response is coordinated by specific innate lymphoid cells (ILCs), T-helper cells (Th2), and cytotoxic T-cells (CTLs) and is further manifested by IgE-mediated mast cell activation.[14] The presence of chronic sino-

nasal type 2 inflammation results in remodelling of tissues with prominent polyp formation, goblet cell hyperplasia and epithelial barrier abnormalities. These changes result in the typical symptoms associated with CRS. A significant body of evidence suggests that ECRS patients (with type 2 endotype) present with more significant disease burden that is more resistant to current therapies including surgery with higher rates of recurrence compared to type 1 or type 3 endotypes. As a result, monoclonal antibody-based biologics specifically targeting type 2 inflammatory mediators have been shown to be a useful adjunct option in the management of these patients.

ASSESSMENT OF CRS

A detailed clinical history and physical exam focusing on the symptoms of CRS should be performed in patients with suspected CRS. Questions regarding allergic symptoms such as: sneeze, lacrimation, nasal pruritus, and itchy eyes should be included. Conditions associated with eCRS should also be explored and include allergic rhinitis, asthma, atopic dermatitis and aspirin/NSAID allergy. A nasal endoscopy should also be performed to formally diagnose and assess the severity of disease. (**Figure 2**).

Non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD)

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is a chronic type 2 inflammatory disorder of the respiratory tract where patients present with a triad of 1) asthma, 2) CRS and 3) NSAID intolerance. The ingestion of NSAIDs and other salicylates exacerbate patients' upper and lower airway symptoms. The underlying pathology is related to eicosanoid synthesis dysregulation with resulting eosinophilic inflammation and increased leukotriene imbalance that is further exacerbated by NSAIDs.[15] This is a particularly difficult group to manage due to their high polyp recurrence rates. N-ERD patients typically undergo primary sinus surgery at a younger age and have a higher rate of recurrence.[16] Aside from typical systemic and topical steroids, leukotriene modifiers and surgery, specific treatments available to this group include maintenance of a low salicylate diet or aspirin desensitization therapy (ADT).[17]

In a prospective double-blind placebo controlled aspirin desensitization study, after 36 months, individuals in the treatment arm had less nasal polyp relapse compared to control with significantly fewer overall sinonasal complaints and improved quality-of-life scores.[18] Recently however, ADT has fallen somewhat out of favour due significant side effects and limited efficacy. Furthermore, newer treatment options have emerged such as biologics which have favourable safety profiles and robust efficacy in resistant cases or those with high recurrence.

Central Compartment Atopic Disease (CCAD)

CCAD refers to a group of patients with allergic airway inflammation that is primarily driven by IgE. These patients will generally present with signs of systemic atopy including allergic rhinitis, conjunctivitis, atopic dermatitis and/or allergic asthma.[19] All of these conditions are exacerbated when the patient is exposed to their specific allergens. The same allergen-induced exacerbation may affect the sino-nasal cavity with an anatomically central predominance. Within the nasal cavity, the anterior surface of the middle turbinate is chronically exposed to inhaled allergens that results in mucosal edema

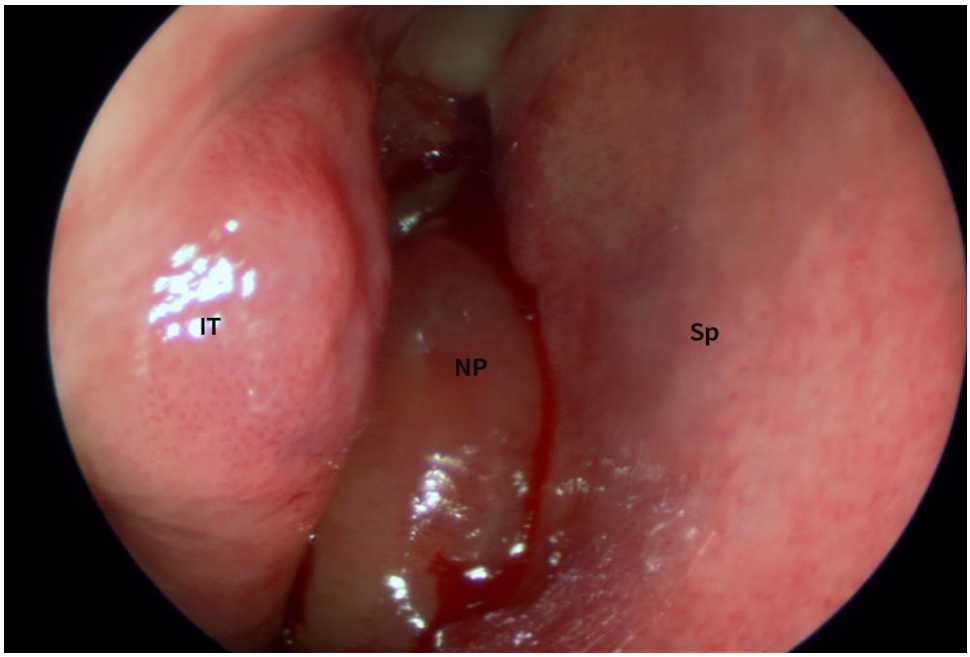

Figure 2: Nasal endoscopy demonstrating severe nasal polyps extending to the nasal floor. IT: inferior turbinate; NP: nasal polyp; Sp: septum; courtesy of Tobial McHugh, MD and Doron Sommer, MD

eventually resulting in polypoid changes. These changes may be clearly visualized and diagnosed on nasal endoscopy (**Figure 1**). With ongoing persistent exposure of inhaled allergens, surrounding nearby structures undergo the same inflammatory changes. These structures include the superior turbinate and posterosuperior nasal septum. Combined with the middle turbinate, this region defines the "central" sino-nasal compartment affected by atopic disease. Persistent allergen exposure is necessary to induce these phenotypic changes. Consequently, seasonal allergens are not generally associated with CCAD, whereas perennial allergens such as dust mites (e.g., *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) are more likely to cause these changes.[19] Radiologically, CCAD patients will demonstrate characteristic central thickening of the turbinates and septum with otherwise unremarkable peripheral sinus mucosa (**Figure 3**).

Diagnostic tools

If the patient has failed medical management and endoscopic sinus surgery (ESS) is being considered, a CT scan of the sinuses should be obtained. Regarding different imaging modalities, a CT scan remains the gold standard in the radiologic evaluation of CRS.[20,21] Conventional sinus X-rays and ultrasound are not indicated for diagnosis or management of CRS. The Lund-Mackay score (LMS) is the most commonly used and validated radiologic scoring system of sinonasal inflammatory changes in CRS.[22] Depending on the amount of sinus opacification (inflammation) identified on CT scan, the LMS calculates a maximum score of 24 or 12 per side. An LMS of 2 or less has an excellent negative predictive value, and an LMS of 5 or more has an excellent positive predictive value.

Patient Reported Outcomes Measures and Quality of life tools

CRS is associated with a significant impact on patient quality of life (QOL). A variety of different QOL questionnaires and patient reported outcome measures (PROMs) have been developed and validated in order to quantify this impact on patient QOL. Of these, a validated and well-studied questionnaire is the Sino-Nasal Outcome Test (SNOT) 22.[23] The SNOT-22 is comprised of 22 questions divided into 5 overall broad categories, some of which assess quality of life. The SNOT-22 can also be a valuable tool in helping inform the clinician and patient decision for proceeding with ESS. The minimal clinically important difference (MCID), that is the smallest change in SNOT-22 score that can be detected by a patient, has been established to be a change in score of 9 on the SNOT-22.[23] A preoperative SNOT-22 score of 30 is associated with a greater than 75% chance of achieving this MCID following ESS.[24] A preoperative score of less than 20 is not associated with improved QOL following ESS. In addition, the SNOT-22 may also be used as a postoperative tool to predict recurrence of disease requiring revision ESS. Following primary ESS, a postoperative SNOT-22 score failing to achieve the MCID of 9 at the 3 month follow-up mark and a deterioration of greater than one MCID (> 9 points) from the 3- to 12-month follow-up period is associated with an increased risk of revision ESS.[25]

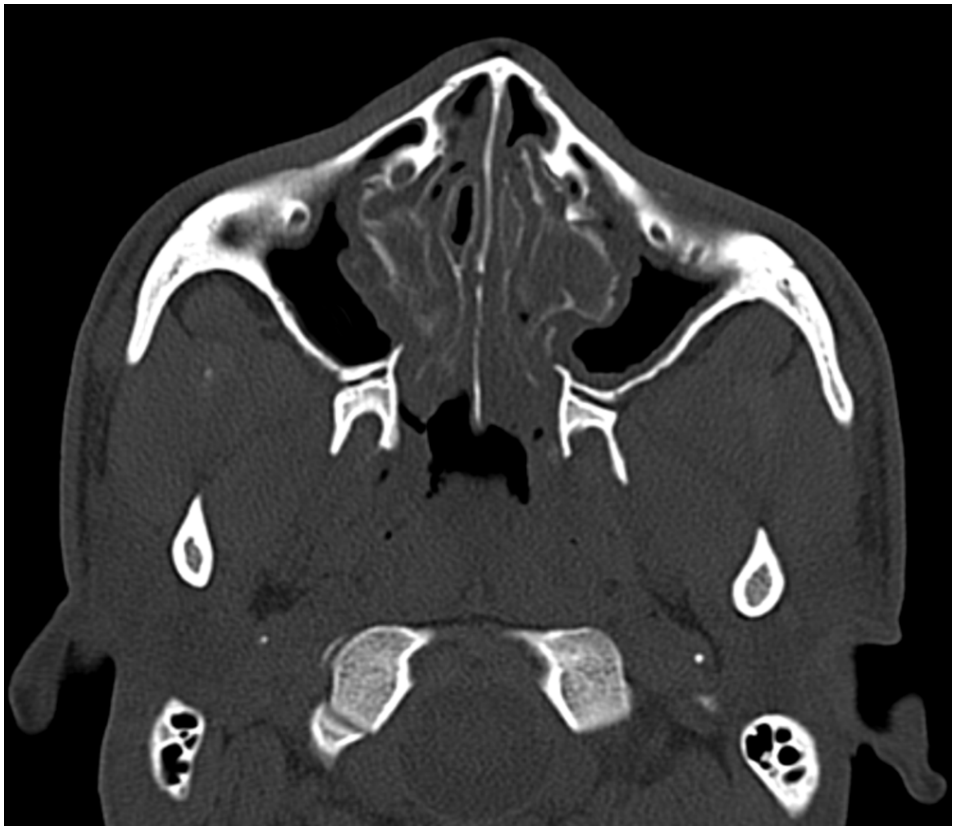

Figure 3: Axial CT image demonstrating advanced inflammation involving primarily the central ethmoid sinuses.; courtesy of Tobial McHugh, MD and Doron Sommer, MD

Thus, objective measures such as PROMs (e.g., SNOT-22) as well as endoscopic scores such as the Lund-Kennedy scoring system that grade visual pathologic states within the nose and paranasal sinuses including polyps, discharge, edema, scarring, and crusting can be important tools for clinicians. The Lund-Kennedy scoring system is most relevant for CRS with polyposis, for assessment pre- and post-endoscopic sinus surgery. Additionally, radiographic scores (Lund-Mackay) may be used to regularly evaluate the effectiveness of current therapies, as well as the need for additional management including surgical intervention and adjunctive use of monoclonal antibody therapies.

MANAGEMENT OF CRS

Previous management guidelines for CRS relied on the phenotypic classification of CRS differentiating between CRSwNP and CRSsNP.[26] However, with greater understanding of pathophysiology and patient outcomes related factors, there has been a shift to using the endotype classification to help guide treatment decisions in CRS.

Medical treatment of CRS

For diffuse, bilateral CRS, regardless of endotype, local intranasal corticosteroids (INCS) and nasal saline rinses (NSR) remain the mainstay of treatment. Appropriate patient education regarding the technique of INCS and NSR use as well as compliance are important elements for success. For severe CRS and to temporarily improve a patient's QOL during an exacerbation, the use of oral corticosteroids may be considered. However, as implied, this is a short-term solution and should not be prescribed repeatedly due to potential corticosteroid side effects. Additional treatment options should be explored, specifically ESS, if initial medical management has failed.

In contradistinction, central compartment atopic rhinosinusitis is primarily IgE mediated and although surgery may be necessary for advanced disease, initial and ongoing treatment with identification of allergen for avoidance measures, in addition to topical nasal steroids and immunotherapy/medical treatment to address the allergy is often successful.

Surgical treatment of CRS

In general, for either type 2 or non-type 2 CRS patients that are not responsive to medical management, surgery should be considered initially. There is currently some debate regarding the extent of surgery that should be performed initially. In general, ESS may be categorized as limited/functional ESS and "full-house". Functional ESS refers to a more limited sinus surgery with the goal of only opening the drainage pathways of the sinuses involved. 'Full-house' ESS refers to a more complete sinus surgery with complete surgical patency of all sinuses and septations removed. There is increasing literature which suggests that a more complete primary full-house ESS for CRS patients with suspected type 2 pathology results in improved long-term outcomes and a decreased likelihood of future ESS. Masterson et al. performed a retrospective review of 149 patients who underwent full house ESS (EESS). SNOT-22 scores were collected pre- and post-op as well as surgical revision rates and perioperative complications and this data was compared with the UK National Audit (in whom the majority underwent a limited ESS). The revision rate at 36 months was significantly lower at 4% as compared to 12.3% in the national audit. There were significant improvements in SNOT-22 scores and no differences were seen in complication rates.[27]

The return of olfaction is not well studied and is generally not a symptom commonly used to measure success of surgery (as opposed to nasal polyp recurrence for example), however, this is gradually changing. The return of sense of smell is somewhat unpredictable following even primary surgery. Duration without any sense of smell also plays a role (i.e.: a patient with 1 year of anosmia has much higher chance of regaining their sense of smell than a patient with > 5 or 10 years of anosmia).

One of the primary goals of surgery is to facilitate penetration of topical steroid irrigations throughout all the sinuses.[28] Like nasal steroid sprays, these have been shown to have minimal bioavailability and a favourable safety profile. Post surgically, their improved sino-nasal penetration results in a normalization of sinus mucus membranes and resolution of edema and polyps. With ongoing use, this helps prevent and control ongoing inflammation and thus, recurrence of disease. Other goals of surgery include the removal of inflammatory load and irreversibly diseased mucosa which promote a return to normal muco-ciliary function.

Patient Education

Patient education about CRS plays a vital role in long-term management to emphasize the importance of long-term medical management even after surgery. It is important that patients understand that, similar to asthma, CRS is truly a chronic disease and generally requires long-term medical treatment with topical steroids for disease control.

Biological (monoclonal antibody) treatment of CRS

Currently, one major challenge to the successful treatment of CRS is finding reliable biomarkers that define type 2 inflammation and reliably predict response to treatment. Although the majority of CRS patients are well managed with the aforementioned treatments, the subgroup of CRS patients whose symptoms are poorly managed despite adequate surgical and medical therapies usually have type-2 pathology. Biologic therapies targeting these type-2 inflammatory pathways have recently been shown to be effective for managing recalcitrant CRS disease. Biologics investigated for the treatment of CRS include reslizumab (anti-IL5), mepolizumab (anti-IL5), dupilumab (anti-IL4/IL13) and omalizumab (anti-IgE).[29-36] Given that the chronicity of CRS requires long-term and continuous use of biologics in order to be effective, cost implications should be considered. The estimated ongoing annual cost of dupilumab is $31,650 CAD[37] resulting in an improvement of 8.95 quality-adjusted life years (QALYs).[38] This is compared to a single one-time cost of $3510.31 CAD for routine outpatient ESS which results in an improvement of 9.80 QALYs. However, this cost of ongoing biologic treatment needs to be considered in light of the possible need for repeat surgery in a select group of CRS patients with recalcitrant disease. This may be particularly relevant in certain populations such as those patients with N-ERD. The extent to which repeat surgery is required is quite variable and depends on numerous factors. There are surgical factors such as extent of surgery. There is also a tendency for patients with high eosinophils to require repeat surgery. Patient non-compliance with postoperative medical care plays a role with revision surgery, etc. The overall number of repeat surgeries required is also not well studied as most studies classify patients into primary surgery vs revision/repeat surgery and not the number of revision/repeat surgeries. However, surgery does appear to be, in general, more cost effective than biologic therapy for the majority of patients.[38]

The Canadian Rhinology Working Group published a consensus statement regarding the use of biologic therapies for CRS.[39] Recommendations include considering biologic therapy only for patients with moderate to severe CRSwNP who have undergone and failed combined adequate ESS and appropriate medical therapy (AMT). Severity of disease should be assessed using a PROM such as the SNOT-22 at initiation of treatment with a biologic agent and periodically to assess management goals. All endotypes of CRSwNP are considered eligible except for primary ciliary dyskinesia and cystic fibrosis. A consideration may also be made for patients who are unfit for surgery and failed AMT. Regarding CRSsNP patients, there is currently insufficient evidence for biologics, however, research is ongoing.

SUMMARY

Over the last decade, there has been a significant shift in the management of CRS. There is a more comprehensive understanding of the underlying inflammatory pathways that cause symptoms associated with CRS. There is greater emphasis for consistent and long-term medical management with topical steroid irrigations. There is also a shift in offering more complete or "full house" sinus surgery, especially if a patient is suspected to have features of type-2 inflammation. Biomarkers including Eos# and total/specific IgE are helpful in assigning diagnostic categories and phenotypes to help with long-term outcome and possible response to biologic therapy. Along with a detailed history and physical exam, nasal endoscopy and CT scans are valuable for patient evaluation and management decisions. The use of PROMs are becoming more wide-spread as instruments to assess severity of disease and monitor treatment efficacy. Finally, for patients with significant recalcitrant CRSwNP which has failed AMT and appropriate sinus surgery, biologics are a safe, effective option and will help further successfully manage this chronic and potentially debilitating disease. A risk-benefit model alongside cost as well as other patient/system factors should be utilized in order to determine what is the best treatment algorithm for patients.

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	**0**	**1**	**2**	**3**	**4**	**5**		○
2. Nasal Blockage	**0**	**1**	**2**	**3**	**4**	**5**		○
3. Sneezing	**0**	**1**	**2**	**3**	**4**	**5**		○
4. Runny nose	**0**	**1**	**2**	**3**	**4**	**5**		○
5. Cough	**0**	**1**	**2**	**3**	**4**	**5**		○
6. Post-nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
7. Thick nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
8. Ear fullness	**0**	**1**	**2**	**3**	**4**	**5**		○
9. Dizziness	**0**	**1**	**2**	**3**	**4**	**5**		○
10. Ear pain	**0**	**1**	**2**	**3**	**4**	**5**		○
11. Facial pain/pressure	**0**	**1**	**2**	**3**	**4**	**5**		○
12. Decreased Sense of Smell/Taste	**0**	**1**	**2**	**3**	**4**	**5**		○
13. Difficulty falling asleep	**0**	**1**	**2**	**3**	**4**	**5**		○
14. Wake up at night	**0**	**1**	**2**	**3**	**4**	**5**		○
15. Lack of a good night's sleep	**0**	**1**	**2**	**3**	**4**	**5**		○
16. Wake up tired	**0**	**1**	**2**	**3**	**4**	**5**		○
17. Fatigue	**0**	**1**	**2**	**3**	**4**	**5**		○
18. Reduced productivity	**0**	**1**	**2**	**3**	**4**	**5**		○
19. Reduced concentration	**0**	**1**	**2**	**3**	**4**	**5**		○
20. Frustrated/restless/irritable	**0**	**1**	**2**	**3**	**4**	**5**		○
21. Sad	**0**	**1**	**2**	**3**	**4**	**5**		○
22. Embarrassed	**0**	**1**	**2**	**3**	**4**	**5**		○

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

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