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AN UPDATE ON SELECT TOPICS IN CHRONIC RHINOSINUSITIS WITH NASAL POLYPS
Doron D. Sommer, MD, FRCSC
Tobial McHugh, MD, FRCSC

MEDICAL MANAGEMENT OF NASAL POLYPS
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THE MEDICAL MANAGEMENT OF EOSINOPHILIC ESOPHAGITIS
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PRIMARY CILIARY DYSKINESIA: A REVIEW
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Rebecca Pratt, MBBS, FRCPC

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EDITOR'S WELCOME



Dear Canadian Allergy and Immunology Community,

Welcome to our final issue of *Canadian Allergy and Immunology Today* in 2021! At the time this publication was first conceived in the spring of 2020, we didn't know how Canada would get through the inoculation campaign required for COVID-19. Despite a difficult year, much work by so many people has resulted in the country having over 85% of eligible citizens fully vaccinated and we are so thankful for that.

In this final issue of the year we discuss some fascinating topics including two articles examining the management of nasal polyps, an article on primary ciliary dyskinesia, another one on medical management of eosinophilic esophagitis and, finally, an article on allergen immunotherapy for the control of allergic rhinoconjunctivitis.

As always, we hope you find these articles informative and helpful. We are grateful for your continued readership, and we look forward to another great year in 2022.

Please let us know how we are doing by suggesting topics and feel free to share our registration link at canadianallergyandimmunologytoday.ca with your peers so that, they too, can subscribe to future issues!

Finally, as this year draws to a close, we wish you and those closest to you a safe, healthy and prosperous 2022.

Best wishes,

Vipul Jain, MD Nikhil Joshi, MD Jason Ohayon, MD Susan Waserman, MD

ABOUT THE AUTHORS

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Dr. Doron Sommer is an otolaryngologist/head and neck surgeon and Clinical Professor at McMaster University. He completed his medical studies and residency in otolaryngology at the University of Toronto and went on to advanced training in Facial Plastic Surgery. He also specializes in rhinology and endoscopic skull base surgery as well as minimally invasive surgical techniques in otolaryngology. He has research interests in surgical techniques in rhinology/skull base surgery, pediatric sleep apnea, smoking cessation and surgical flow and safety measures. He has published many peer reviewed publications as well as several book chapters, and has given numerous lectures, courses and workshops at national and international surgical meetings. Dr. Sommer is an active member of several professional societies and is currently the co-chair of the Royal College of Physicians and Surgeons of Canada otolaryngology examination board.



Tobial McHugh, MD, FRCSC

Dr. Tobial McHugh is dual fellowship trained in pediatric otolaryngology and most recently in rhinology, anterior skull base surgery. He completed otolaryngology, head and neck surgery residency training at McMaster University and his medical degree at McGill University. Research interests include pediatric otolaryngology, anterior skull base pathologies, allergy, and rhinosinusitis. Dr. McHugh will be planning to combine both his fellowships with a special interest in pediatric anterior skull base pathologies and surgery.

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

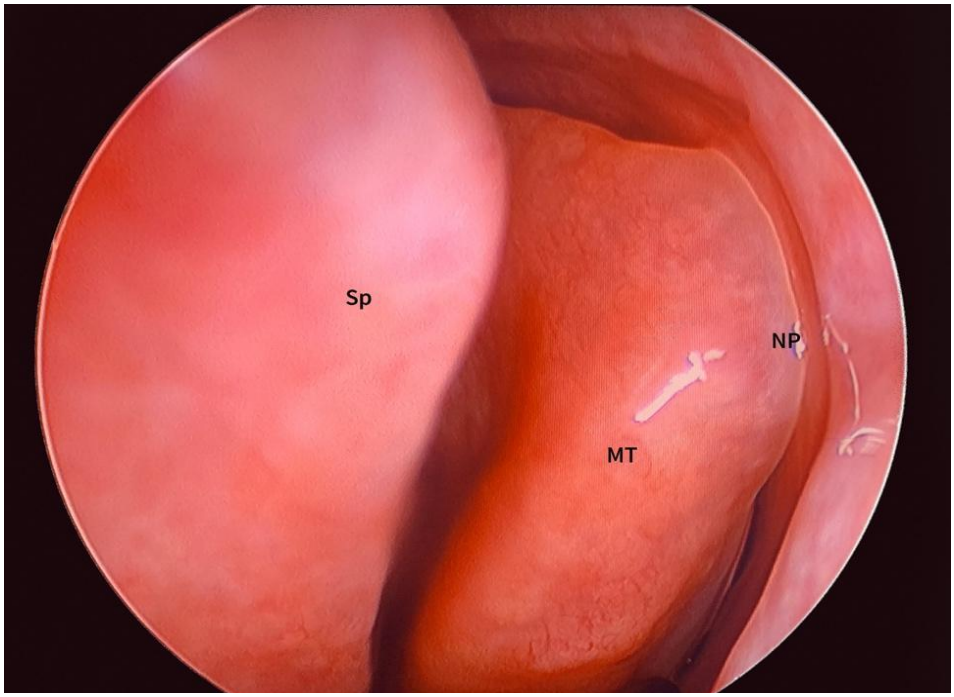


Figure 1: Nasal endoscopy demonstrating polypoid changes on the anterior surface of the middle turbinate. Sp: Septum; MT: middle turbinate; NP; nasal polyp.; courtesy of Tobial McHugh, MD and Doron Sommer, MD

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

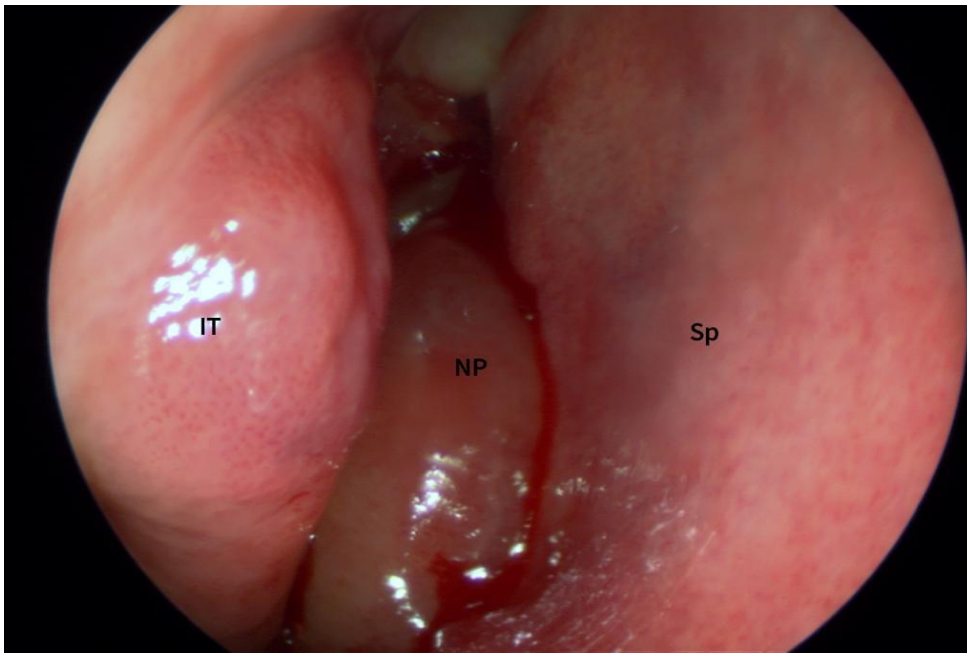


Figure 2: Nasal endoscopy demonstrating severe nasal polyps extending to the nasal floor. IT: inferior turbinate; NP: nasal polyp; Sp: septum; courtesy of Tobial McHugh, MD and Doron Sommer, MD

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)_____ ↑

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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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MEDICAL MANAGEMENT OF NASAL POLYPS

INTRODUCTION

Background on chronic rhinosinusitis

Rhinosinusitis is characterized by inflammation of the nasal mucosa and paranasal sinuses.[1] Chronic rhinosinusitis (CRS) is an inflammatory disease of unclear origin which is typically marked by eosinophilic, neutrophilic and/or lymphocytic cell infiltration, as well as T helper (Th) cell and type 2 cytokine upregulation (TSLP, IL-25, IL-33, IL-4, IL-5, and IL-13).[1] CRS typically presents as either CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP) as noted previously. Unlike CRSsNP, CRSwNP involves the presence of recurring edema-filled nasal polyps and a significant inflammatory cell infiltrate.[1] Biochemically, CRSwNP has a type 2 inflammatory profile mediated by T-helper 2 cells (Th2) while CRSsNP has a type 1 inflammatory profile predominantly mediated by T-helper 1 cells (Th1).[1]

Diagnostic criteria

The diagnostic criteria for both acute and chronic CRS are shown below (**Figure 1**) as depicted in the 2011 Canadian Clinical Practice Guidelines for Acute and Chronic Rhinosinusitis.

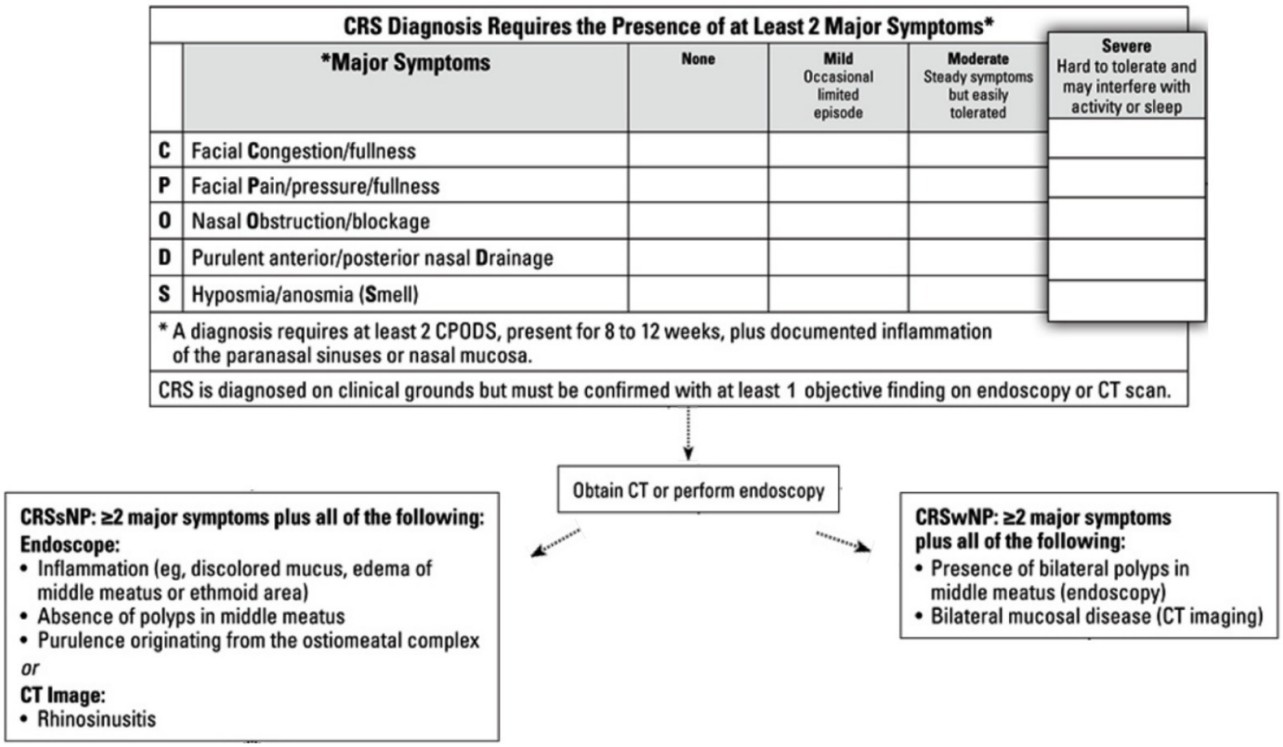


Figure 1. CRSwNP and CRSsNP diagnostic criteria. Figure adapted from the Canadian Clinical Practise Guidelines for Acute and Chronic Rhinosinusitis (Desrosiers et al., 2011).[2]

Prevalence

Due to the subjective and objective nature of a CRS diagnosis, it remains difficult to precisely quantify the population prevalence of CRS, with estimates varying widely from 1% to 12%.[3] CRSwNP is largely a disease of the middle aged, with an average age of onset of 42.[4] Males seem to be disproportionately affected by CRSwNP.[4] There are no established prevalence rates for North America. However, there are studies from South Korea that have found the prevalence in males to be 3.2-3.7% and in females to be 2.0-3.3%.[5,6]

Treatment options

This review will focus on current medical management strategies for the treatment and management of CRSwNP patients. A variety of different medical therapies are currently available for patients with CRSwNP, all with different indications and varying levels of efficacy. The major medical therapies used in CRSwNP discussed in this review are saline irrigation, topical corticosteroids, oral corticosteroids, leukotriene inhibitors, antihistamines, antibiotics and newer emerging biologic therapies.

MEDICAL MANAGEMENT

Saline Irrigation

Saline rinsing is a commonly prescribed, non-pharmacological treatment for patients presenting with CRSwNP. Its excellent short- and long-term safety profile as well as high patient tolerance make it a favourable long-term treatment strategy.[8] Within clinical practice, there remains substantial variation in saline irrigation protocols as they relate to volume, pressure and frequency of use.[9]

A variety of both pre-surgical and post-surgical randomized controlled trials (RCTs) have evaluated the effects of saline irrigation on clinical outcomes in patients with CRSwNP.[8,9] In pre-surgical RCTs, sinonasal saline irrigations are found to be effective at improving patient reported symptoms, health related quality of life (HRQOL) scores and reducing the use of other nasal medications.[9] High volume protocols seem to foster better outcomes than low volume protocols.[10] High volume irrigation is seen with nasal saline squeeze bottles or a neti pot and is typically characterized as greater than 150 mL. Low volume typically refers to mist sprays, which have a per dose volume of less than 5 mL. Saline solutions can be prepared as isotonic (0.9% NaCl) or hypertonic (>3% NaCl) formulations, however neither formulation seems to be more effective than the other.[9] Saline irrigations are also an effective post-surgical treatment regimen, especially after sinus debridement, when mucosal exposure is high.[9] Although intranasal saline irrigation offers a safe and efficacious treatment that should be a first-line recommendation for patients with CRSwNP, its efficacy is limited and may best be used in conjunction with other pharmacological or surgical therapies depending on the severity of disease.[11]

Topical corticosteroids

Currently, intranasal corticosteroid therapy is the backbone of medical treatment for symptomatic CRSwNP patients. There are a variety of different intranasal corticosteroids on the market that vary in steroid structure but generally function in a similar fashion. Topical corticosteroids act to inhibit the production of pro-inflammatory enzymes, cytokines, lymphocyte proliferation and delayed hypersensitivity.[12]

Standard Therapies (Intranasal corticosteroid sprays)

The approved indications for standard topical nasal steroid therapies typically involve low volume (< 5 mL) intranasal corticosteroid sprays. Some of the more commonly used sprays include mometasone furoate (Nasonex), fluticasone propionate (Flonase), fluticasone furoate (Avamys), budesonide (Rhinocort), ciclesonide (Omnaris), beclomethasone dipropionate monohydrate (Beconase), flunisolide (Nasalide), and triamcinolone acetonide (Nasacort).[9] The efficacy and safety of these standard topical steroid treatments have been studied in a variety of randomized control trials and are well summarized in recent meta-analyses.[9,12] Intranasal corticosteroid sprays demonstrate significant improvement in both objective (endoscopic) and subjective (symptomatic) clinical outcome measures in patients with CRSwNP.[9] Many RCTs demonstrate improvement in patient symptom scores (i.e. rhinorrhea, loss of smell, facial pressure), peak nasal inspiratory flow rates and reductions in polyp size.[9] Optimal results with intranasal steroid sprays are observed when used post-operatively, as exposure and penetrance is high.[9] Across the various formulations of intranasal corticosteroid sprays, there seems to be equivalent efficacy, with symptomatic improvement being largely independent of steroid type.[13]

As the risk of systemic side effects for intranasal corticosteroid sprays are extremely low, they can be used in conjunction with saline irrigations indefinitely if patient adherence and response is good.[12] Although intranasal corticosteroid sprays have been the backbone of medical therapy for patients with CRSwNP, low-volume sprays (< 5 mL) are limited by their inability to deeply penetrate the paranasal sinuses.[8] For this reason, many clinicians have begun recommending non-traditional topical steroid protocols that include, but are not limited to, high volume (> 150 mL) corticosteroid-saline irrigations.

Non-standard Therapies

One of the most common non-traditional topical corticosteroid therapies used in the clinic is a budesonide respules sinonasal irrigation.[8] Budesonide respules (Pulmicort) is now widely used as an "off-label" treatment for CRSwNP patients.[12] In Canada, budesonide respules come in either 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1,5 mg or 2 mg / 2 mL nebules.[12] A common protocol is to dissolve 0.25-0.5 mg / 2 mL in 240 mL of saline within a rinse bottle.[9] In published studies, dosages have ranged from one to two daily irrigations for a total of 128 µg-2 mg of budesonide exposure per day.[12] These protocols and dosing regimens are used in adult patients. The lack of an approved indication in CRSwNP has rendered large, quality RCTs scarce, however a number of smaller trials have been performed to assess its efficacy in managing CRSwNP. Studies comparing budesonide-saline irrigation to saline irrigation alone have reported greater improvements in the 22-item Sinonasal Outcome Test (SNOT-22) scores as well as Lund-Kennedy endoscopic polyp scores in both pre-operative and post-operative (12 months) budesonide users.[8] In a small population of CRSwNP patients with asthma, a six-month budesonide irrigation protocol produced substantial reductions in SNOT-22 scores, Lund-Kennedy endoscopic scores, and total oral corticosteroid usage post-treatment compared to pre-treatment.[14] Budesonide respules can also be administered using an intranasal mucosal atomization device (MAD) or as drops. Following endoscopic sinus surgery (ESS), patients administered budesonide respules via either MAD or drops had substantially greater reductions in SNOT-22 and endoscopic Lund-Kennedy polyp scores compared to those who used a daily fluticasone nasal spray regimen, with superior outcomes in the MAD group compared to the drops group.[15]

Similar to saline irrigation, high volume corticosteroid irrigations are preferred due to greater penetrance, especially after ESS, while maintaining low systemic absorption.[12] A number of studies have demonstrated a good short-term safety profile for budesonide respules, with patients showing stable cortisol levels and no markers of adrenal suppression.[16,17] The long-term safety profile looks promising as well. Smith et al. reported no hypothalamic-pituitary-adrenal (HPA) axis suppression in adult patients using 2 mg of budesonide in irrigations every day for an average duration of 3 years.[18] Conversely, one 22-month trial found that 23% of subjects developed signs of HPA axis suppression as noted by low levels of stimulated cortisol.[19] Upon subgroup analysis however, it was found that HPA-axis suppression was highly associated with the concomitant use of pulmonary corticosteroid inhalers, and in most patients, suppression was reversed after stopping budesonide irrigations.[19] Seiberling et al. found that high dose topical nasal steroids (i.e. budesonide irrigations) do not appear to increase intraocular pressure when used for at least 4 weeks.[20] While Soudry et al. later found that longer-term use (mean duration of 22 months) did not elevate intraocular pressures.[19] Caution should still be exercised in patients with open-angle glaucoma, who should have their intraocular pressures measured regularly while on therapy.

As such, budesonide respule sinonasal irrigation presents a safe and efficacious long-term therapy that may be used indefinitely in CRSwNP patients. However, continuous monitoring for any adverse side-effects is advised and care must be taken in patients using multiple topical corticosteroid formulations simultaneously. Clinically, many surgeons report superior outcomes using non-standard steroid irrigations compared to traditional intranasal corticosteroid sprays, which should promote their consideration as both a potential pre- and post-operative treatment option.

Oral corticosteroids

Oral corticosteroid therapy can be used in symptomatic CRSwNP patients that have inadequate response to other topical steroid treatments. However, due to their potential systemic side effects, they should be used at minimal effective doses in short duration courses (~2 weeks) to mitigate any adverse complications.[2]

A number of RCTs have assessed their efficacy in managing CRSwNP both pre- and post-operatively. Typical dosages range from 25-50 mg of daily prednisone (or equivalent) for a duration of 2-6 weeks.[21] In most cases, symptom improvement is noted through the improved SNOT-22 scores, CT and MRI scores, peak nasal inspiratory flow, and endoscopic polyp grading.[22] However, positive outcomes after short course oral steroid therapies are transient, as their effects fade over time.[21] For this reason, combining short oral corticosteroid courses with longer-term topical corticosteroid treatments and saline irrigations is essential for lasting symptom relief and polyp remission.[22] Additionally, oral steroids (30 mg prednisone) may be used 5-7 days preoperatively to enhance operative visibility, reduce surgical bleeding, and shorten operative time.[22] Although effective in short-term symptom reduction, considering the chronicity of CRSwNP, one must consider the potential adverse side effects of prolonged or frequent oral corticosteroid therapy.[23] In the short term, oral corticosteroid use has been associated with mood changes, elevated blood pressure, fluid retention, abdominal pain, sleep disturbance and weight gain.[23] In the longer term, frequent courses of oral corticosteroids pose an increased risk of HPA axis suppression, type 2 diabetes, pneumonia, cataracts, osteoporosis/osteoporotic fractures, GI disturbances and peptic ulcers, infections and more.[23] There have been no studies to suggest that low dose alternate day steroid treatment is safe for longer-term oral steroid treatment. Most studies to date have only had participants on oral steroids for 2-3 weeks at most. In Canada, where the wait times for ESS can be months, the risk of complications of long-term oral steroid use would outweigh the benefits.

Leukotriene inhibitors

Another pharmacological therapy that may have a potential role in the management of CRSwNP are leukotriene receptor antagonists (LTRA) (i.e. leukotriene inhibitors). Montelukast, is a member of a class of anti-inflammatory drugs that act by inhibiting G-protein coupled leukotriene receptors and the potent inflammatory cascade that they mediate.[24] Most studies on leukotriene inhibitors have assessed their effects on Aspirin-Exacerbated Respiratory Disease (AERD) patients (presenting with asthma and CRSwNP) due to their historical use in treating asthma and their known anti-leukotriene effects.[25] A few studies have supported their ability to improve HRQOL scores in a variety of symptoms, nasal airflow, and presence of intranasal inflammatory mediators, yet these agents have failed to demonstrate improvement in endoscopic polyp scores.[26,27] More recent studies have assessed their synergistic effects when combined with traditional intranasal corticosteroid therapy, finding no difference in clinical improvement in patients treated with both leukotriene inhibitors and intranasal corticosteroid sprays compared to those treated with intranasal corticosteroid sprays alone.[25] When directly compared to intranasal corticosteroid sprays in the post-operative management of CRSwNP patients, leukotriene inhibitors seem to be significantly less effective at improving post-operative symptoms like nasal obstruction, rhinorrhea, sneezing/itching, and anosmia over the course of a year.[24] Ultimately, the use of leukotriene inhibitors may be warranted in symptomatic Aspirin-Exacerbated Respiratory Disease (AERD) patients, however they may be only mildly effective as an individual or adjunctive therapy in treating CRSwNP patients. Thus the role of LTRA is limited at best in the maintenance of medical therapy in CRS.

Other treatment options

Antihistamines

There is a paucity of data on the effects of antihistamines in the treatment of CRSwNP patients. One small RCT found no significant improvement in mean symptom scores between patients receiving 20 mg of cetirizine over 3 months relative to patients receiving placebo treatment.[28] However, in this same study, patients did report an improvement in certain allergic symptoms like rhinorrhea and sneezing.[28] As such, there is no evidence to suggest that antihistamines are an effective treatment option in patients with CRSwNP and should be discouraged unless patients present with associated allergic symptoms.

Antibiotics

Antibiotics have also been used in the treatment of CRSwNP for their anti-infectious and anti-inflammatory properties. Although fairly commonly prescribed, the data supporting their use is limited. A systematic review found minimal evidence that systemic antibiotic therapy is effective at mitigating symptoms in CRSwNP and CRSsNP patients.[29] One RCT found slightly lower SNOT-22 scores in CRSsNP patients taking macrolide antibiotics compared to those in the placebo groups immediately after treatment, however no differences were found at the 3-month follow-up timepoint.[29] Another study showed no differences in post-treatment HRQOL scores between patients receiving a 3-month course of macrolide antibiotics + saline irrigation + intranasal corticosteroids compared to patients receiving a placebo + saline irrigation + intranasal corticosteroids.[29] Topical antibiotic therapies are also available; however, most clinical consensus guidelines do not recommend their use due to a lack of evidence supporting their efficacy.[30] Therefore, oral antibiotics also have a limited role in the medical management of CRS.

Biologics

One of the newer approaches to treating patients presenting with CRSwNP involves the use of biologics. Monoclonal antibody therapies have been widely used as effective treatments for other type 2 inflammatory diseases like asthma, atopic dermatitis, chronic spontaneous urticaria, etc.[31] Due to the association between asthma and CRS, studies of biologic therapies in the treatment of CRS have taken off in recent years. For CRS, biologics are administered as periodic subcutaneous injections and work to suppress key mediators in the type 2 inflammatory pathway involved in CRS pathogenesis.[32] Currently, there are a number of biologic agents approved or under study for use in CRSwNP, including: dupilumab (anti-IL-4/13), mepolizumab/reslizumab (anti-IL-5), and omalizumab (anti-IgE).[31] At present, dupilumab is the only Health Canada approved therapy for treatment of nasal polyps.[33] The Canadian Rhinology Working Group consensus statement evaluated the use of various biologic therapies in the treatment of CRSwNP.[32] In summary, certain biologic therapies seem to be quite effective at improving both subjective and objective measures of disease severity in CRSwNP patients.[32] In a small RCT (n=24), reslizumab significantly reduced nasal polyp scores at week 12 and blood eosinophil counts until week 4, however failed to improve disease symptom scores at any time point compared to placebo treatment.[32] Similarly, mepolizumab, another anti-IL5 therapy was found to improve endoscopic/CT scan scores, blood eosinophil counts and nasal cytokine (IL-5Ra, IL-6, IL-1B) levels. However, no difference in disease symptom scores were reported after 8 weeks of treatment.[32] One RCT found that after 16 weeks, patients treated with omalizumab (anti-IgE) had significant reductions in polyp size (improvements in modified Lund-Kennedy polyp scores), symptom scores (nasal congestion, anterior rhinorrhea, hyposmia/anosmia, dyspnea) and no changes in blood or serum markers.[34] The most promising clinical outcomes however, come from dupilumab studies. A multitude of RCTs assessing dupilumab have found significant improvements in SNOT-22 scores, modified Lund-Kennedy polyp scores, patient reported nasal congestion, and UPSIT scores (measures of hyposmia and anosmia) in CRSwNP patients taking dupilumab relative to those receiving a placebo (**Figure 2**).[35,36,37,38] Additionally, lung function (FEV1) was improved in AERD patients treated with dupilumab.[37]

Consensus was reached that short-term biologic use (~12 months) in patients with CRSwNP is safe with few minor adverse effects reported (headache, nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, and injection-site reactions) and no reports of any major adverse effects were noted.[32] Additionally, when studied in relation to other type 2 inflammatory diseases, long-term biologic use is considered safe.[32] There remains the need for patient documentation of SNOT-22 in the application for biologic coverage; hence, clinicians interested in providing biologic therapy will need to familiarize themselves with the SNOT-22 score to administer it in office. However, one major drawback of biologic therapy is its high cost relative to other treatment modalities. Direct costs associated with biologic therapies range from $10,000 to $40,000 annually per patient.[39] As a chronic treatment, this price can be a barrier to access. As such, biologics are generally only considered after topical corticosteroids, oral corticosteroids and ESS fail to provide lasting symptomatic relief and polyp recurrence in CRSwNP patients is evident (**Figure 3**).[40,41] However, there is evidence to suggest that dupilumab treatment reduces the need for systemic corticosteroid therapy as well as ESS, thus the use of monoclonal antibody therapies may actually be cost-effective.[37] Therefore, more robust



Figure 2. CT scans over the course of a year in CRSwNP patients taking dupilumab. Image adapted from Bachert et al., 2020.[38]

longitudinal research is needed to assess their cost-effectiveness, utility in treating different CRSwNP patient populations, and efficacy as an adjunctive therapy with topical corticosteroids, oral corticosteroids, and ESS.

CONCLUSION

Proper medical management of patients suffering from CRSwNP is essential to improve patient quality of life and mitigate disease severity. In summary, high volume saline irrigations are a safe and effective therapeutic strategy that should be recommended to all patients as a first-line treatment for symptom relief. In addition to saline irrigations, intranasal corticosteroid sprays are known to be safe and are likely more effective at improving subjective and objective measures of disease severity in CRSwNP. As such, corticosteroid sprays should also be a first-line treatment option for symptomatic CRSwNP patients. In light of recent evidence, certain non-standard topical corticosteroid treatments like high volume budesonide-saline irrigations may actually offer a more effective topical steroid alternative to intranasal corticosteroid sprays and should be seriously considered by clinicians, especially in the case of corticosteroid spray inefficacy. In some studies HPA-axis suppression was highly associated with the concomitant use of pulmonary corticosteroid inhalers, however this suppression was reversed in most patients after stopping budesonide irrigations. The aforementioned topical therapies are effective at improving disease severity pre-operatively; however, seem to be more essential as post-operative agents to prevent premature polyp recurrence when mucosal sinus exposure and penetrance is optimized. In addition to topical treatments, systemic therapies have been implemented within the clinic with varying levels of efficacy. Oral corticosteroids are an effective treatment modality in patients where topical corticosteroid treatments have failed to provide sufficient symptom relief, as well as pre-operatively to improve surgical efficiency, with attention to dose and duration of treatment. Importantly, steroid course durations should be kept short and infrequent, as long-term side effects can be severe. Other systemic treatments such as leukotriene inhibitors, antihistamines and antibiotics seem to be less effective than those therapies already mentioned and should be avoided unless specifically indicated. Biologics are a promising new therapeutic strategy for patients with CRSwNP, however significant cost barriers still prevent their widespread use.

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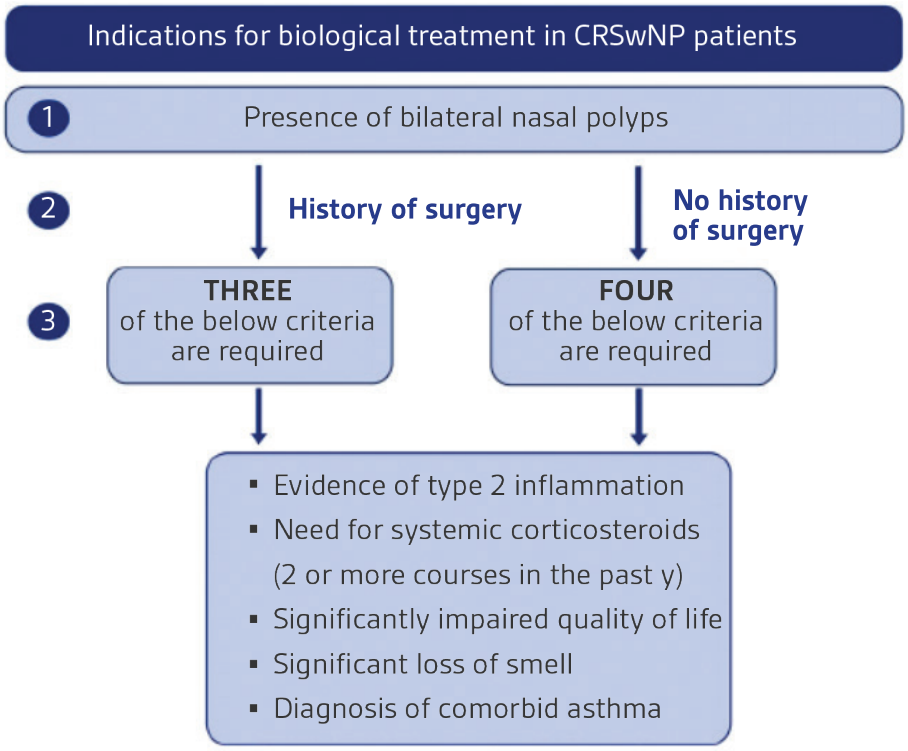


Figure 3. Indications for biological treatment in CRSwNP patients. Image adapted from Fokkens et al., 2019.[41]

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THE MEDICAL MANAGEMENT OF EOSINOPHILIC ESOPHAGITIS

INTRODUCTION

Eosinophilic esophagitis (EoE) was first recognised as a unique condition in the early 1990s. It was described by Alex Straumann[1] who identified 10 children with resistant 'gastro-esophageal reflux disease (GERD) symptoms' with typical endoscopic features and esophageal eosinophilia who achieved resolution of symptoms and esophageal eosinophilia with an elemental formula. While once a rare condition, EoE is being increasingly diagnosed worldwide, with an incidence rate estimated to be 5 to 10 per 100,000[2]. While widely recognised as being a Th-2 inflammatory disorder, predominantly triggered by food allergens, there is a growing body of literature supporting the role of aeroallergens in the condition[3,4]. Management of the condition involves close collaboration amongst gastroenterology and allergy specialists. At least half of affected patients will have other allergic disorders including allergic rhinitis, asthma, eczema and some will also have IgE-mediated food allergies. Workup and management of aeroallergen sensitivities is important as swallowed aeroallergens may be a contributing factor to eosinophilic esophagitis, with many patients noting a seasonal exacerbation in their symptoms[5].

DIAGNOSIS OF EOSINOPHILIC ESOPHAGITIS

EoE is diagnosed when there are ≥ 15 eosinophils/high power field (hpf) in esophageal biopsies in a patient with symptoms of esophageal dysfunction, when other causes of esophageal eosinophilia have been ruled out. Other histologic features should also be present such as thickening of the basal cell layer, eosinophilic layering and possible eosinophilic micro-abscesses. Symptoms can be variable, depending on age of presentation and include nausea, vomiting, heartburn, abdominal pain, dysphagia and food impaction[6,7]. Vomiting and feeding aversion may be more common in very young children, with the more classic dysphagia and food impaction more common in older children, adolescents and adults[8]. Endoscopic features should be described using the EoE Endoscopic Reference Score (EREFS) which characterizes edema, esophageal rings, exudates, linear furrows and strictures[9].

Until relatively recently, it was recommended that diagnostic evaluation be performed following a trial of proton pump inhibitor (PPI) therapy, to remove potential GERD as a cause for the esophageal eosinophilia[7]. It is now recognised that a significant proportion of patients will have PPI-responsive EoE[10]. Therefore, the most recent diagnostic guidelines from the AGREE conference no

longer include the requirement for patients to have a trial of PPI therapy prior to endoscopic evaluation, as this strategy will not distinguish between GERD and PPI-responsive EoE[6].

THERAPEUTIC OPTIONS

Treatments of EoE are aimed at improving symptoms, improving inflammation and preventing complications, mainly stricture development[11].

There are 2 broad therapeutic approaches: 1) dietary-based (elimination diets) or 2) medications (proton-pump inhibitors and swallowed topical steroids). Dilations may be required to manage esophageal strictures. The American Gastroenterology Association Institute and the Joint Task Force on Allergy Immunology Practice Parameters (AGA-JTF) has proposed a guideline for management of EoE and looks at both dietary and medical strategies[3,12].

Dietary Management – Elimination diets

Elimination diets are frequently used to treat EoE. The most effective elimination diet is an elemental diet, with remission rates of up to 90% described[13]. Despite the high efficacy, this is rarely used, except in the youngest children, due to the unpalatability of the amino acid-based formula and the usual need for a nasogastric tube. Therapy with an elemental formula is often prolonged with the need for multiple endoscopic procedures trying to identify the trigger food(s). A more popular approach is the use of empiric elimination diets based on the most common food allergens.

The six-food elimination diet is the most effective of the empiric elimination diets, with remission rates being about 70% in adults and children[14-16]. The most common food allergens in children are milk, followed by wheat, egg, soy, and peanuts[15], whereas in adults, the most common food allergens are wheat, followed by milk, egg, soy and peanut[14].

The six-food elimination diet is quite restrictive. Some physicians will elect to start with a milk-elimination diet, as milk is the most commonly identified food allergen. An improvement in symptoms, endoscopic and histologic features (with eosinophil count < 15/hpf) was noted in just over 50% of children in one study[17].

An interesting approach has been proposed by Molina-Infante et al with a step-up approach to dietary elimination. In their '2-4-6 prospective study', participants including adults (n=105) and children (n=25) first eliminated 2 foods (milk and gluten-containing grains). Forty-three percent (56 patients) achieved clinical and histologic remission with this strategy. Patients not in remission moved to a 4-food elimination diet (also removing eggs and legumes, including soy, lentils, chickpeas, beans, peas and peanuts). Those who failed the 4-food group elimination diet stepped up to a six-food group elimination diet, which also included the removal of all seafood and fish, with remission rates of 60% and 79% described in the 4-food and 6-food groups, respectively. Milk was identified as one of the triggering antigens in 52% of participants, and gluten in 16%. Twenty-eight percent were sensitive to both gluten and milk. Milk was the sole food allergen in 33% of children and 18 % of adults[18].

With all elimination diets, it is preferable to re-evaluate endoscopically as new foods are introduced, as there is a poor correlation between symptoms and histologic disease activity[19]. Eliminating a specific food group should be undertaken for a minimum of 6 weeks[20] with some experts suggesting a longer duration. The need for repeated endoscopies is a significant drawback to dietary elimination strategies, with the consequence of missed work for parents and adult patients, missed school days, need for general anaesthesia (in children) and general increased risk associated with repeated procedures. In my practice, I aim to scope after 8 weeks. In addition, early childhood is a critical period for oromotor development. Interruption to this process can result in significant feeding issues and food aversions[21]. In older children and teens, dietary elimination can have a significant impact on quality of life[22].

Involvement of a registered dietician is very important for any child or adult following an elimination diet. The registered dietician can educate the patient on the elimination diet, while ensuring the diet does not cause micronutrient deficiencies. Nutritional status and growth should be monitored in all patients following dietary restriction.

MEDICAL THERAPY

Proton Pump Inhibitor Therapy

Many adult and pediatric patients will show a histologic response with PPI therapy. A meta-analysis and systematic review of 33 published studies (188 pediatric participants; 431 adult participants), found improvement

in symptoms in 60.8% of patients (95% CI 48.3 - 72.2 %). Histologic remission was noted in 50.5% of participants (95% CI 42.4% - 58.7). The authors did note significant heterogeneity amongst the studies with a publication bias in studies reporting histologic response, indicating that some caution is needed when interpreting the meta-analysis findings[23]. There is no clear recommendation in the literature on PPI dosing, although a prospective study of adult patients, found that the majority of patients who achieved histologic remission on 40 mg omeprazole b.i.d. for 8 weeks, stayed in histologic remission when the dose was reduced to 40 mg daily[24].

The potential mechanism of action of PPI therapy in esophageal eosinophilia (in addition to anti-secretory activity) has been explored. A multicentre study of the EoE transcriptome which included genes for eosinophil chemotaxis (CCL26 (eotaxin-2)), mast cells (CPA3) as well as barrier molecules (DSG1) and tissue remodelling genes (POSTN) showed that the inflammatory molecular signature was nearly completely reversible with PPI therapy25.

Given the relative safety profile and ease of use, some patients may prefer this therapy prior to trying swallowed topical steroids or elimination diets[3].

Swallowed topical steroids

Swallowed budesonide (typically a nebule is used to make a viscous suspension) and swallowed fluticasone (from a metered-dose-inhaler) have been shown to be effective in the treatment of both pediatric and adult patients[26-28]. A double-blind, double-dummy trial comparing swallowed fluticasone with swallowed viscous budesonide found similar efficacy with both medications[29]. To increase contact time of the medication with the esophageal mucosa, patients should not eat or drink for 30 minutes after the dose but may want to rinse out their mouth to help prevent esophageal candidiasis.

Suggested doses for swallowed topical steroids have been proposed in the 2011 consensus recommendation for adult and pediatric patients[7]:

Budesonide: Children < 10 years, budesonide 1 mg per day; for those over 10 years and adults, 2 mg per day was recommended.
Fluticasone: Children 88 to 440 µg 2 to 4 times per day was suggested; Adult dosing 440 to 880 µg twice daily.

Technique: Puff a single puff directly (without use of a spacer-device) into the mouth and swallow. Do not breathe in until the dose is swallowed. After 15 seconds a second puff is administered. A typical dosing regimen is 2 puffs (250 µg per puff) swallowed twice per day. The patient should not eat or drink for 30 minutes after the dose.

Duration of therapy: There is no clear guideline on treatment duration or dosing for the use of swallowed topical steroids in the long-term. The literature shows that when treatment is stopped, symptoms and histologic activity are likely to recur.

More recently trials of an orodispersible form of budesonide have been performed in adult patients, for both induction and maintenance therapy[30,31]. The maintenance trial showed that rates of remission at 48 weeks were 73.5% and 75%, for the 0.5 mg twice daily and 1 mg twice daily dosing, respectively. The rate of clinic-histologic remission was almost 60%, and the rate of histologic remission was just over 90% in patients treated with orodispersible budesonide, 1mg b.i.d. for 6 weeks, in comparison with placebo[32]. Approximately 16% of patients developed oral candidiasis. This medication has become the first approved treatment for EoE and is now available for adult patients in Canada.

Maintenance therapies

Eosinophilic esophagitis is a chronic condition which recurs when treatment is discontinued. Given the concern that untreated esophageal inflammation may lead to fibrostenotic disease, maintenance therapy may be considered[4]. For patients in whom triggering foods are identified, it is preferable to continue avoiding these foods. This is particularly helpful as it avoids the need for swallowed topical steroids, but can be difficult to adhere to, particularly in adult patients[33]. A few studies have explored ongoing use of swallowed topical steroids, showing higher remission rates in those continuing with therapy versus those who use placebo/ no medication[34,35]. The AGA-JTF guideline recommends that patients who achieve remission with topical steroid therapy **continue** with this treatment as maintenance[3]. Further guidance on dosing and use in children will be helpful in future publications.

Adrenal Suppression

Use of steroid therapy raises concern about the risk of adrenal suppression. Symptoms of adrenal suppression are non-specific and include nausea, lethargy, reduced responsiveness (i.e. altered level of consciousness) and can be life-threatening in an adrenal crisis.

While there are guidelines for screening for adrenal insufficiency for asthmatic patients on long-term corticosteroids[36], no such guideline exits for patients with EoE receiving steroid therapy. For patients who continue on daily topical steroid therapy, clinicians may consider screening for adrenal suppression with an 8:00 am cortisol level, on an annual basis. Screening for adrenal suppression amongst EoE patients is not done consistently by treating physicians[37]. Several studies, often small, have shown reduced early morning cortisol and reduced ACTH stimulation tests in patients treated with prolonged use of topical corticosteroid[38,39]. Despite the potential risk of adrenal suppression, a larger study of 106 patients identified true adrenal insufficiency (post ACTH stimulation test) in just 5 patients, all of whom were on additional steroids for other atopic conditions. A larger number in the group had abnormal early morning cortisol levels at one point during follow up[40]. Nonetheless, given that corticosteroids are often used for prolonged periods or for repeated courses and considering that many patients will have other forms of steroid therapy for coexistent atopic conditions, it is important to be aware of this potential adverse effect, particularly as the consequences of a true adrenal crisis can be devastating.

Endoscopic Dilation

For patients with a fibrotic stricture, dilations may be required. Dilations can be done via therapeutic endoscopy or with an interventional radiologist. A retrospective review of 509 patients at a single centre, found that 164 (32%) patients required a dilation over a 12-year follow-up period. More than one dilation was required in almost 60% of patients[41].

Monitoring Treatment Response

Treatment response is determined with endoscopic and histologic re-evaluation. In children, this usually requires general anaesthesia. Repeated endoscopies are inconvenient for the patient and families and utilise hospital resources. Less invasive testing is being explored, and transnasal endoscopy, which does not require sedation, is being used at some centres in the United States for both pediatric and adult patients[42,43]. The scope is thin, measuring 6 mm, and adult patients have reported that a non-sedated transnasal endoscopy is more tolerable than a non-sedated standard endoscopy[44]. In children, the use of virtual reality goggles helps with tolerability of the procedure[45].

Other less invasive tests of disease activity include the esophageal string test and swallowed cytosponge. A multicenter study looked at a one-hour esophageal string test in adult (n=60) and pediatric (n=74) patients. Levels of various eosinophil-derived proteins obtained with the string were comparable with values obtained from mucosal biopsies. There was also good correlation with endoscopic mucosal appearance. The results obtained with the string test were able to distinguish 'active' versus 'inactive' eosinophilic esophagitis. Over 90% of parents and adult patients reported that they preferred the string test over the stand endoscopic procedure[46]. The cytosponge test is less invasive than a standard endoscopy and involves swallowing a gelatin capsule containing a mesh sponge. The test can be performed at the bedside. An adult study found that there was good correlation between eosinophil counts obtained from the sponge and from mucosal biopsies[47].

FUTURE DIRECTIONS

Therapeutic approaches may change in the future. Biologic agents targeting cytokines involved in the EoE inflammatory pathway are currently being studied, as are novel formulations of existing therapies. Less-invasive monitoring methods, though not yet available in Canada outside of a clinical trial, are desirable. When choosing therapies, close collaboration with the patient and their family is important to facilitate joint decision-making and to increase the chance of adherence to the treatment plan.

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PRIMARY CILIARY DYSKINESIA: A REVIEW

PATHOPHYSIOLOGY

Primary ciliary dyskinesia (PCD) is a disease involving the cilia of the body. First identified as Kartagener's syndrome (a constellation of findings of chronic sinusitis, bronchiectasis, and situs inversus), the genetic basis has been increasingly uncovered over time. It is now recognized as an autosomal recessive condition due to a mutation in one of several dozen genes, and more is still being discovered as we continue to have ever-expanding access to genetic sequencing technology. These mutations can affect different parts of the creation, structure, or effector mechanisms of the cilia, with the common result being the impairment of ciliary function. Thus, the primary pathology in PCD is immotile or reduced motility of the cilia in various organs, which leads to the principal manifestation of impaired muco-ciliary clearance in the respiratory tract. These cilia are responsible for the constant movement of mucus upwards, often termed the muco-ciliary escalator, to prevent mucus stasis and eliminate the natural collection of airway debris. When this fails, it provides a nidus for bacterial growth, leading to both chronic bacterial colonization and acute bacterial respiratory exacerbations, defined as an acute worsening of respiratory symptoms. In relation to other manifestations, rotary cilia play a role in embryonal development and lateralization of the organs; hence the possibility of situs inversus/ambiguus developing in PCD. Normal ciliary movement is also required for spermatozoan motility, leading to infertility in males with PCD; females can also experience impaired fertility and higher rates of ectopic pregnancy due to reduced ciliary function in the fallopian tubes.

The respiratory cilia are arranged in a so-called 9+2 fashion, where nine paired microtubules form the outer structure, and a central pair are in the middle. The outer doublets have outer and inner dynein arms, that have enzymes for ATP hydrolysis, responsible for converting chemical energy into motility. Radial spokes connect the outer doublets to the central pair for structural stability. Approximately 200 cilia per cell are able to beat directionally in sync, coordinated with cilia in adjacent cells, to generate a "wave" of upward motion (**Figure 1**). Mutations causing PCD have been identified in each of these parts, indicating the complexity of these tiny structures.

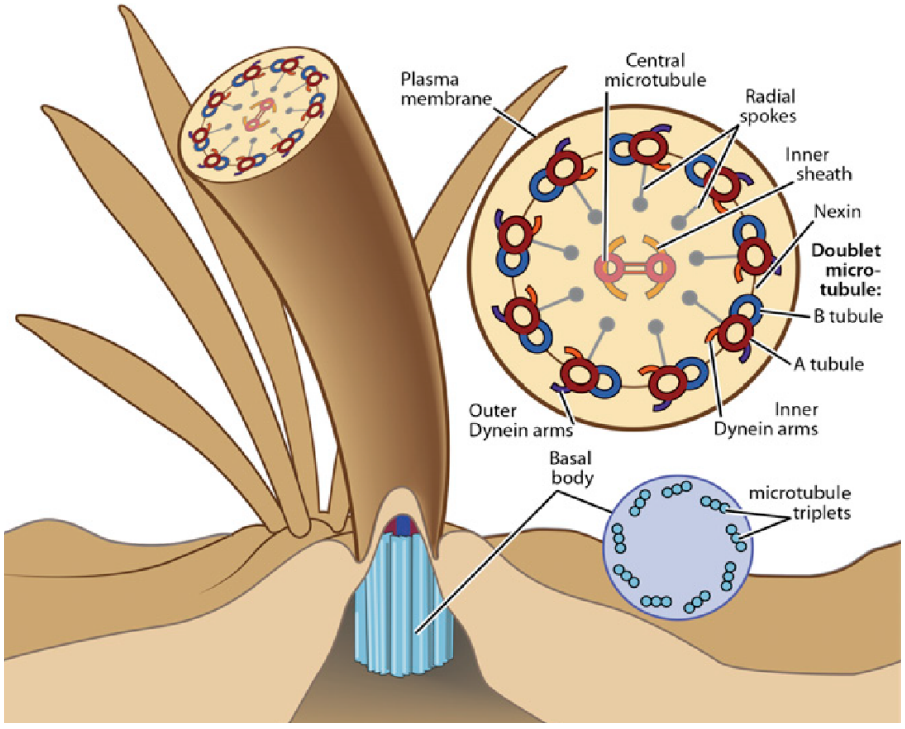


Figure 1. Normal motile cilia (9 + 2) configuration; adapted from Knowles, M. R.,et al, 2013

Epidemiology

The true incidence and prevalence of PCD is unclear owing to the difficulty in establishing a firm diagnosis. Surveys in Norway and Japan have estimated an incidence of 1 per 10,000-20,000 live births[1]. There are also areas of higher incidence due to the genetic characteristics of the population. For instance, in Bradford, United Kingdom, which has a predominantly South Asian population with less genetic variation, incidence rates of about 1 per 2265 have been identified[2]. The true incidence/prevalence rates can also depend on how PCD is diagnosed: up to 70% of patients with likely PCD will have an identifiable genetic mutation while 10-20% of patients with PCD are reported to have normal ciliary ultrastructure on electron microscopy[3].

Clinical Features

PCD can be missed for many years, as children will present with chronic, intermittently acute, symptoms that require a high index of suspicion from a clinician to connect and form the whole clinical picture (**Table 1**). In retrospect, neonatal distress is present in over 80% of children with PCD, even when born at term, and is often diagnosed as transient tachypnea of the newborn (TTN) or sometimes neonatal pneumonia[4].

These infants will then suffer from chronic nasal congestion and discharge, with almost 100% developing a persistent, daily wet cough. Through their early childhood years, they will frequently get recurrent acute-on-chronic otitis media, each episode often treated individually without clinicians realizing there may be a connection between them. They will also begin to present with repeated respiratory infections/exacerbations, treated as asthma and/or pneumonias, again in discrete episodes that may not be connected. These patients may have normal or non-specific findings on chest x-rays, even between illnesses. In one study, children without a laterality defect had a median age of diagnosis of 6 years of age.[9] This means that school age children can present with nasal congestion, cough, sinus issues, etc. and potentially have an underlying diagnosis of PCD that needs to be considered. Sinus issues are also common but with variable onset, as each set of sinuses develop at different ages in young children, leading to chronic sinusitis. By the time these patients reach late adolescence/adulthood, they invariably will have bronchiectasis if not diagnosed early and provided preventative care. It is important to ensure cystic fibrosis (CF) is excluded as an alternative condition causing chronic cough and recurrent respiratory exacerbations in children. In addition to these features, laterality defects are common in patients with PCD (situs inversus or ambiguuus). In adults, infertility may be a presenting symptom, with some patients being diagnosed after they or their partner have struggled to conceive.

Diagnosis

Controversy exists over the gold-standard method of diagnosis in PCD. Previously, electron microscopy or high-speed video microscopy were considered the diagnostic test of choice. More recently, as the many genetic mutations for PCD have been increasingly elucidated, many guidelines now suggest using a multi-gene panel as the initial diagnostic step. While the microscopic investigation of cilia does not leave one at risk of missing an undescribed/untested mutation, it requires a skilled operator to collect the nasal ciliary biopsy, a capable technician to prepare the sample, advanced equipment, and a knowledgeable pathologist to analyze the sample. Suitable samples for electron microscopy are reported to be collected approximately 60-80% of the time but still with the possibility of false positives/negatives, while genetic testing is thought to now have more than 80% sensitivity. Furthermore, there are debates over the advantages

When to Suspect PCD (at least 2 of 4 of the following features):
• Unexplained neonatal respiratory distress, especially in term infants
• Year-round daily cough starting before 6 months of age
• Year-round daily nasal congestion beginning before 6 months of age
• Organ laterality defect

Table 1. Symptoms that may be indicative of PCD; Adapted from Shapiro et al, 2018

and disadvantages between the microscopy methods: some structural defects can be absent or hard to identify on electron microscopy, but high-speed video microscopy will show impaired function. Conversely, the moving image on high-speed video microscopy can be difficult to interpret conclusively, while electron microscopy produces static images more easily reviewed. All forms of diagnostic testing can lead to false negatives, making definitive diagnosis challenging (**Figure 2**).

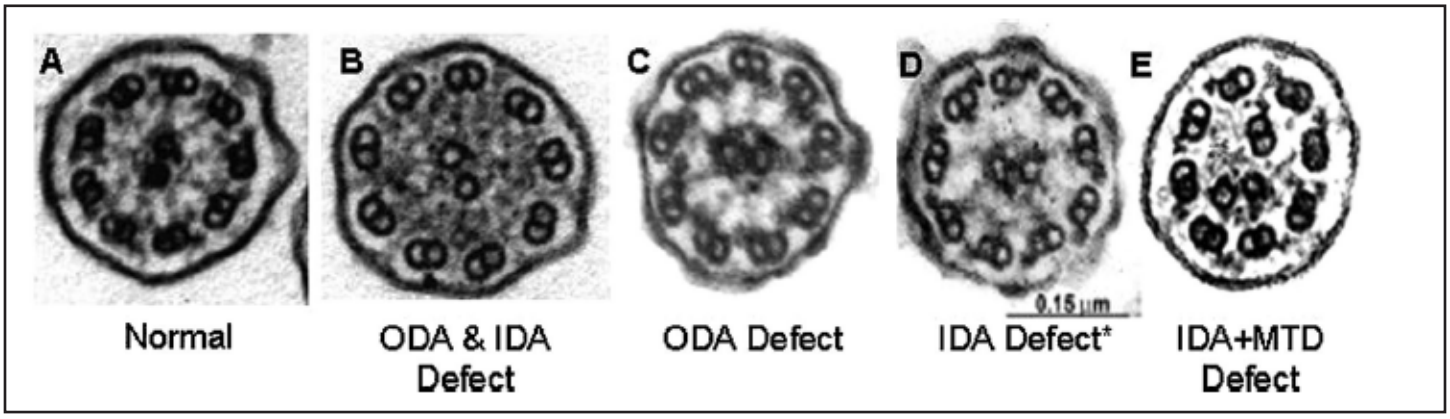


Figure 2. Electron microscopy findings in primary ciliary dyskinesia Shapiro, A. J.et al, 2015

There are other tools that can aid in the diagnosis of PCD. For children who are able to perform pulmonary function, nasal nitric oxide may be used as a screening tool, with a level below 77 nl/min showing a sensitivity of about 98% and specificity of 99% for PCD. This method has the advantages of being quick, returning results immediately, and being non-invasive. However, it is not typically used for a definitive diagnosis, with either microscopy and/or genetic testing being subsequently utilized to confirm the diagnosis of PCD. Nasal nitric oxide differs from exhaled nitric oxide. It requires a specific device and a cooperative child (usually having the same criteria as needed for the performance of spirometry). There is some controversy over the best technique, but most well-accepted techniques require the patient to exhale forcefully via the mouth against resistance for several seconds while a tube secured in the nose is connected to the measurement device; some will measure during tidal breathing or breath holding as well. (**Figure 3**). The key is to achieve soft palate closure so nitric oxide concentration from the lungs does not affect that of the nasal cavity/sinuses, which is what is being measured.



Figure 3. Pediatric patient using nasal nitric oxide; Davis, Stephanie D., Ernst Eber, and Anastassios C. Koumbourlis, eds. Diagnostic tests in pediatric pulmonology: Applications and Interpretation. Springer, 2014.

In older children and adults, a sputum culture is also sometimes utilized as a partially useful screening tool. While non-specific, the presence of certain bacteria like *Pseudomonas aeruginosa* is unusual in a patient without impaired muco-ciliary clearance issues or immunodeficiency, and so it can help to raise the suspicion of PCD, among other potential conditions. More commonly, sputum cultures in children with PCD are found to have *Hemophilus influenzae*, *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. Mycobacterial cultures showing the presence of non-tuberculous mycobacterium can also point towards an underlying diagnosis (**Figure 4**).

AMERICAN THORACIC SOCIETY DOCUMENTS

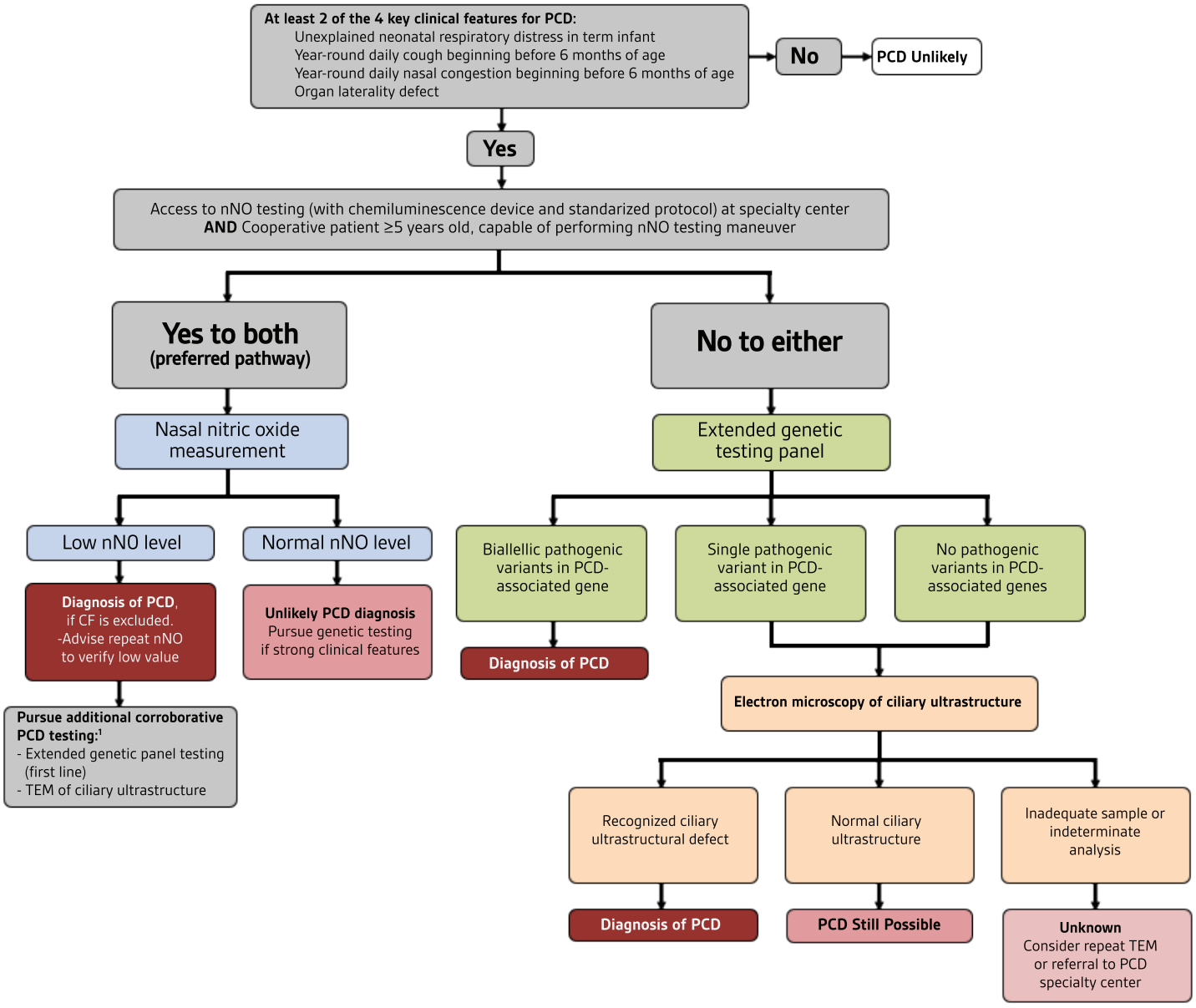


Figure 4. Suggested diagnostic algorithm for evaluating the patient with suspected primary ciliary dyskinesia ; adapted from Shapiro, A. J. et al, 2018

Management

The approach to patients with PCD focuses significantly on **preventative** care. Many of the treatments utilized extrapolate evidence from other muco-ciliary clearance disorders, primarily cystic fibrosis. First and foremost, patients should be monitored on a regular basis: this includes clinical review, throat swab (infants) or sputum (older, capable children) surveillance cultures, and pulmonary function (in those able to perform); mycobacterial cultures are also collected at regular intervals given the higher incidence of non-tuberculous mycobacteria in patients with PCD and the possibility of this affecting isolation status and treatment. A key indicator for current health status and risk of progression is the forced expiratory volume in one second (FEV1), which is typically done at every visit; these children will generally have an established baseline FEV1 with deviations from this leading to investigations and treatments as clinically indicated. If measured early in the disease process, the FEV1 and spirometry is often normal, as it is well known that FEV1 is not a very sensitive measure for early disease and/or damage.[10] A new test, the multiple breath washout (MBW) test, is showing promise at being more sensitive for early change but is not widely available, as it is mainly a research tool currently. The most common abnormality, if present, is a reduced FEV1 with an obstructive pattern, like that seen in asthma (which is why it can sometimes be misdiagnosed as asthma). As the data continues to emerge it is thought that these patients start with similar spirometry as their peers early in life and deteriorate faster (than natural age-related loss), but this can be somewhat mitigated with early diagnosis and management.[11] Added emphasis is given to immunizations in these children, especially influenza and pneumococcal vaccines. Mucolytic (e.g. inhaled dornase-alpha) and osmotic agents (e.g. inhaled hypertonic saline) are also frequently employed in preventative care for children with PCD, determined by their severity and progress. Daily chest physiotherapy is also recommended to aid mucus clearance: infants are often started on percussion chest physiotherapy with progression to airway-based techniques appropriate to the child's developmental age, eventually utilizing positive expiratory pressure devices. Patients demonstrating exacerbations should be treated promptly and effectively to minimize airway damage and risk of bronchiectasis; specific antibiotics are usually started based on the patient's known microbiology from their surveillance cultures while awaiting results from a culture taken at the time of the exacerbation, and adjusted, if necessary. Patients with PCD are prone to develop respiratory bacteria with antibiotic resistance, which greatly impacts antibiotic choice. Depending on the severity of the exacerbation, the majority are treated with oral antibiotics as outpatients, while a proportion of these children will require admission and intravenous antibiotics for more significant illness. They may also be prescribed inhaled antibiotics on a routine basis, using the same guidelines as children with cystic fibrosis, to reduce exacerbations from pathogenic bacteria that have colonized the airway. Additionally, there is a role for anti-inflammatory therapies, such as macrolide antibiotics, in preventative care for some children with PCD, with evidence similar to that of cystic fibrosis emerging in people with non-CF bronchiectasis.[5]

In those having more significant disease, chest computerized tomography (CT) scans may be required to characterize degree of lung disease/bronchiectasis and guide the intensity of therapy; there is generally no recommendation for routine CT scanning in all patients with PCD. In children, it is advisable that these CT scans take place in a centre with pediatric expertise to ensure: the most appropriate CT protocols are used (to gather the correct sequences, minimize radiation exposure, etc.), access to safe sedation if required, and suitable radiologist interpretation. Those with severe disease may be candidates for partial lung resection (localized disease) or lung transplantation (end-stage diffuse disease).

Given the complex and chronic nature of care for these patients, it is recommended that they are seen in a centre with appropriate expertise and multidisciplinary care. The healthcare team for these children may include physicians of many sub-specialties, nurses, nurse practitioners, respiratory therapists, physiotherapists, dietitians, social workers, and others to ensure a holistic approach to the child with PCD.

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ALLERGEN IMMUNOTHERAPY FOR THE CONTROL OF ALLERGIC RHINOCONJUNCTIVITIS

Allergen immunotherapy (AIT) has been available for over 100 years as a unique method of treating various allergic conditions, most efficaciously allergic rhinitis/rhinoconjunctivitis, allergic asthma and venom allergy. First developed by Noon et al in 1911, this therapy is an attractive option for patients suffering from these chronic conditions due to its potential for disease-modification.[1] As opposed to avoidance measures and other pharmacotherapies, patients on immunotherapy can, in some cases, achieve long-term benefits after 3-5 years of treatment due to the induction of allergen tolerance.[2, 3] This article will focus primarily on patients with allergic rhinitis/rhinoconjunctivitis.

AIT is currently available in 2 forms to treat allergic rhinitis: sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT). Both therapies provide specific advantages and disadvantages, and clinicians and patients should choose which approach is best through shared decision-making. AIT is indicated in any patient (usually ≥ age 5) who has IgE-mediated rhinoconjunctivitis which is not adequately controlled with avoidance measures and pharmacotherapy, or in those who are intolerant to these therapies due to adverse events.[4-7] In general, immunotherapy is contraindicated in patients with severe or unstable asthma (FEV1 <70% in adults, FEV1 <80% in children), patients on beta-blockers (ACE inhibitors are a relative contraindication), pregnant patients (de novo AIT; if on maintenance they can continue) and those with open lesions of the oral mucosa or eosinophilic esophagitis (SLIT only).[5, 8-12]

BASIC IMMUNOLOGY AND BIOMARKERS

The immunological changes with immunotherapy have been well-documented. With chronic use, there is a decrease in IgE-dependent activation of mast cells, reduction in tissue eosinophilia and a shift to the T-regulatory and Th1 immune pathways.[13-21] These changes result in a reduction in the number of antigen-specific T cells and an increase of serum specific IgG4, IgG and IgA antibodies which prevent Th2 activation, IgE-complex formation and mast cell degranulation.[7, 22-24] IL-10-producing regulatory B cells and the associated neutralizing antibodies likely contribute to the long-term benefit seen with this therapy.[25-29] Finally, the innate immune system also plays a role, with Th2 dendritic cells and innate lymphoid cells regulated by thymic stromal lymphopoietin and IL-33 activated in these patients.[30]

Biomarkers can be used to predict response to AIT. Many biomarkers have been studied, with the more commonly examined biomarkers being serum-specific IgE and the serum-specific IgE: total IgE ratio, IgG4 antibodies and T cells (both Th2 and T regulatory).[16-19, 30-38] The effects that AIT has on these biomarkers are summarized in **Table 1**.[7] Antibodies are the easiest to measure as most labs offer enzyme-linked immunosorbent assays (ELISA).

Biomarker	Effect of AIT
Serum specific IgE	Transient increase followed by blunting of seasonal increase[30-34]
Serum specific IgE: total IgE ratio	A cut-off of 16.2% predicted benefit of AIT[35,36]
Serum specific IgG1 and IgG4	10-100 fold increase reported. IgG4 correlated with outcome[37,38]
T regulatory cells	Increased following AIT[16,17,19]

Table 1. Change in biomarkers associated with AIT.[7]

SUBCUTANEOUS IMMUNOTHERAPY AND SHORT-TERM BENEFITS

SCIT is a well-established treatment option for patients with allergic rhinitis. Allergists have the option of offering pre-seasonal (alum-based) immunotherapy for pollen sensitized patients vs. perennial immunotherapy which is available for many allergens (i.e. moulds, dust mites, pollens, animals). SCIT is usually given as weekly (or twice-weekly) injections for the 'build-up' phase and then dosed every 2-4 weeks for the maintenance phase of therapy. The short-term effectiveness of SCIT has been well-documented in a meta-analysis[39] based on 51 studies, in which it was found to be moderately effective at reducing allergy symptoms in the short-term with improvement in both seasonal allergy sufferers and perennial allergy sufferers. This effect was demonstrated in both children and adults. For medication scores, a similar benefit was noted based on an analysis of 46 studies. Both pre-/co-seasonal pollen regimens versus continuous treatment for pollens, SCIT improved symptom and medication scores.[39] Pre/co seasonal pollen regimens refer to the initiation of SLIT for grass, birch and ragweed pollen for the period involving a few months before the pollen season with continuation of therapy until the end of the pollen season. The standard mean differences (SMD) are summarized in **Table 2** with values further from 0 indicating a greater reduction and effect size. Significant values not crossing a 0 confidence interval are highlighted in red.

	Overall (Seasonal and Perennial allergens)	Seasonal Allergens	Perennial Allergens	Pre/co-seasonal pollen regimes	Continuous treatment for pollens
SMD Symptom Scores	-0.65 (95% CI -0.86, -0.43)- 51 studies	-0.49 (95% CI -0.72, -0.27)	– 1.59 (95% CI -2.44, -0.74) – **based on only one study**	−0.51 (95% CI −0.63, −0.38)	−0.69 (95% CI −1.09, −0.29)
SMD Medication Scores	−0.52 (95% CI −0.75, −0.29	−0.77 (95% CI−1.28, −0.25)	−0.27 (95% CI −1.01, 0.48) – **based on only one study**	−0.40 (95% CI −0.56,−0.25)	−1.23 (95% CI −2.34, −0.12)

Table 2. SMD in symptom and medication scores for seasonal versus perennial allergens and continuous vs. pre/co-seasonal pollen regimes with SCIT.[39]

SUBLINGUAL IMMUNOTHERAPY AND SHORT-TERM BENEFITS

SLIT is the newest form of therapy, having been approved in Canada in 2012 in the form of grass pollen tablets. Currently, SLIT tablets are available to treat patients sensitized to birch tree pollen, grass pollen, ragweed pollen and dust mites (**Table 3**). SLIT drops are also utilized by some allergists but these have less robust evidence and no long-term or sustained efficacy data.[40] Pollen tablets are usually given pre and co-seasonally and dust mite SLIT is administered perennially (on a daily basis for both). The benefits of SLIT vs. SCIT include convenience of dosing (at-home dosing other than the first administration in office), a lower likelihood of systemic reactions than SCIT and sublingual administration, which can be a boon for needle-phobic patients. The primary downside of SLIT is that currently it is only approved for a limited number of allergens.

SLIT Options in Canada	Grastek	Oralair	Ragwitek	Acarizax	Itulatek
Target Allergen	Grass pollen	Grass pollen	Ragweed pollen	Dust mite	Birch pollen
Administration	8 weeks prior to grass pollen season and maintain throughout the season	12 weeks prior to grass pollen season and maintain throughout the season	16 weeks prior to tree season and maintain throughout the season	Perennial	12 weeks prior to birch pollen season and maintain throughout the season
Age Indication	5-65	5-65	5-65	18-65	18-65
Strength	12-SQ Bet		2800 BAU Timothy grass	12 SQ-HDM (6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*	

Table 3. Different options currently available in Canada for SLIT-tablets. Outlines timing of administration, age indication and strength of tablet.[8-12]

From the same meta-analysis that analyzed SCIT, 52 studies showed that SLIT improved short-term symptom scores, with benefit observed in those with both seasonal and perennial sensitizations.[39] Based on 52 SLIT trials, SMD medication scores demonstrated statistically significant reductions with both seasonal and perennial treatments. Similarly to the data on SCIT, both pre/co-seasonal pollen regimes and continuous SLIT treatment for pollens have been shown to be effective at reducing symptoms. However, only pre/co-seasonal treatment showed a benefit between these two approaches for reduction in medication scores. These results are summarized in **Table 4**.

	Overall (Seasonal and Perennial allergens)	Seasonal Allergens	Perennial Allergens	Pre/co-seasonal pollen regimes	Continuous treatment for pollens
SMD Symptom Scores	-0.48 (95% CI -0.61, -0.36)	−0.35 (95% CI −0.45, −0.26)	−0.81 (95% CI −1.41, −0.20)	−0.40 (95% CI −0.48, −0.32)	−0.55 (95% CI −0.98, −0.11)
SMD Medication Scores	−0.31 (95% CI −0.44, −0.18)	−0.24 (95% CI −0.38, −0.10)	−0.72 (95% CI −1.30, −0.13)	−0.30 (95% CI −0.42, −0.18)	0.00 (95% CI −0.32, 0.33) – non-significant

Table 4. SMD in symptom and medication scores for seasonal versus perennial allergens and continuous vs. pre/co-seasonal pollen regimes with SLIT.[39]

Overall, the short-term efficacy of both SLIT and SCIT combined was moderately in favour of AIT (SMD −0.53 (95% CI −0.63, −0.42)) for symptom scores and a small-to-medium effect was observed in favour of AIT for medication scores −0.38 (95% CI −0.49, −0.26).[39] The effects of SCIT and SLIT (pooled) based on the type of allergen are summarized in **Table 5**. All categories of allergen demonstrated efficacy other than mould where the effect size was quite variable for both symptom and medication scores.[39]

LONG-TERM BENEFITS

The long-term benefit of AIT, referring to the ongoing benefit after therapy discontinuation, is one of its most novel aspects. Typically, this benefit is measured at 12 and/or 24 months post-discontinuation of therapy. Studies looking at both SCIT and SLIT have shown disease-modification after 3 years of therapy with durability of response lasting as long as 12 years post-treatment (studied with grass pollen SCIT).[1-2, 5, 39-46] Specifically, these studies have found persistent reduction of symptoms, reduction in the need for medications, reduced responses to allergen challenges and improved quality of life following discontinuation of AIT. A study looking at 2 years of treatment did not confer long-term benefit hence supporting the recommendation of a minimum of three years of therapy.[47] AIT may be as close an immuno-modulatory intervention to a "cure" for moderated-to-severe allergic rhino-conjunctivitis (ARC) but has not qualified to a definite cure at this time. Regarding the issue of prevention, there is a high degree of heterogeneity among AIT prevention studies, making strong conclusions difficult to elucidate.[46]

Allergen	House dust mite (HDM)	Grass Pollen	Tree Pollen	Weed pollen	Moulds
SMD Symptom Scores	−0.73 (95% CI −1.37, −0.10)	−0.45 (95% CI −0.54, −0.36	−0.57 (95% CI −0.92, −0.21)	−0.68 (95% CI −1.06, −0.30)	−0.56 (95% CI −2.29, 1.18)
SMD Medication Scores	−0.63 (95% CI −1.12, −0.15)	−0.32 (95% CI −0.46, −0.18)	−0.40 (95% CI −0.59, −0.20)	−0.44 (95% CI −0.80, −0.09)	0.34 (95% CI −0.41, 1.09) – based on 1 study

Table 5. Different allergens studied for AIT (both SLIT and SCIT) and their respective short-term efficacy based on symptom and medication scores.[39]

A systematic review published in 2017 concluded that AIT (both SLIT and SCIT) significantly reduced the risk of onset of asthma in children older than preschool age who were the participants of the study.[45] Of note, this systematic review is limited due to the inclusion of smaller, heterogenous studies. The effect of AIT is best seen in the PAT study where grass pollen sensitized patients showed odds ratios of 2.5 and 2.7 for the prevention of asthma (95% CI 1.1-5.9) at the 5- and 10-year follow up mark.[46, 48-50] In another study, 812 children (5-12 years), with grass pollen allergic rhinoconjunctivitis and no history of asthma were included in the GAP trial, a randomized, double-blind, placebo-controlled study comprising 3 years of treatment with grass SLIT and 2 years of follow-up. Results demonstrated that asthma symptoms and asthma medication use was significantly lower in those subjects on SLIT compared with the placebo group (OR 0.66, p=0.036) but that there was no change in the time to the onset of an asthma diagnosis.[51]

Another benefit of AIT is its potential ability to inhibit future sensitization and atopic disease. A 2017 systematic review found that 10/18 studies analyzed (1,049 children and 10,057 adults) reported a reduction in the onset of new allergen sensitizations with AIT vs placebo, however the low quality evidence and high risk for bias in these studies is of concern in drawing firm conclusions.[52] Of note, dust mite immunotherapy was not shown to prevent new sensitizations.[46]

SAFETY

The side effects of SLIT and SCIT consist of both local and systemic reactions. Overall, the incidence of systemic reactions has been reported to be low at about 2% of SCIT patients and 1% of SLIT patients, with local reactions occurring much more frequently (50% of SCIT patients and 40-75% of SLIT patients).[5, 53-57] SCIT local reactions typically consist of injection site erythema, warmth and pain whereas SLIT local reactions most commonly include mouth, tongue and throat pruritis and/or swelling. A recent Canadian study found that the incidence rate of epinephrine use after SCIT to be about 1 per 1,047 injection visits with almost all of these reactions occurring within the first 30 minutes following the injection.[58] Severe systemic reactions are much less common in SLIT with some patients experiencing symptoms suggestive of GERD including abdominal discomfort or burning or ear/facial itching. Asthma exacerbations and anaphylaxis are extremely rare.[5] Hence, it is recommended that patients remain in the clinic for 30 minutes after a SCIT injection whereas only the 1st SLIT dose needs to be administered under supervision. The patient's asthma should be well-controlled, the patient should not exercise before or after the injection and patients should take an antihistamine prior to their injection. If reactions do occur, depending on their severity, the clinician and patient can decide if the immunotherapy should be continued and whether a dose reduction is warranted.

The advantages and disadvantages of SLIT and SCIT therapy are summarized in the EAACI guidelines (**Figure 1**).[5] It is imperative that primary care physicians are aware of patients who may benefit from AIT and make an appropriate referral to an allergist. The rhinoconjunctivitis quality of life questionnaire (RQLQ) consists of 28 questions in 7 domains (activity limitation, sleep problems, nasal symptoms, ocular symptoms, other non-nasal/ocular symptoms, practical problems and emotional function) which can be used prior to initiation of SLIT or SCIT and at 6-12 month intervals to track progress of patients. Having this objective measure of improvement should be considered a future standard of care in AIT management. Ongoing research in areas of peptide immunotherapy, recombinant allergens, biologics and novel adjuvants may shed light on potential future strategies that may be safer or less time consuming.[59]

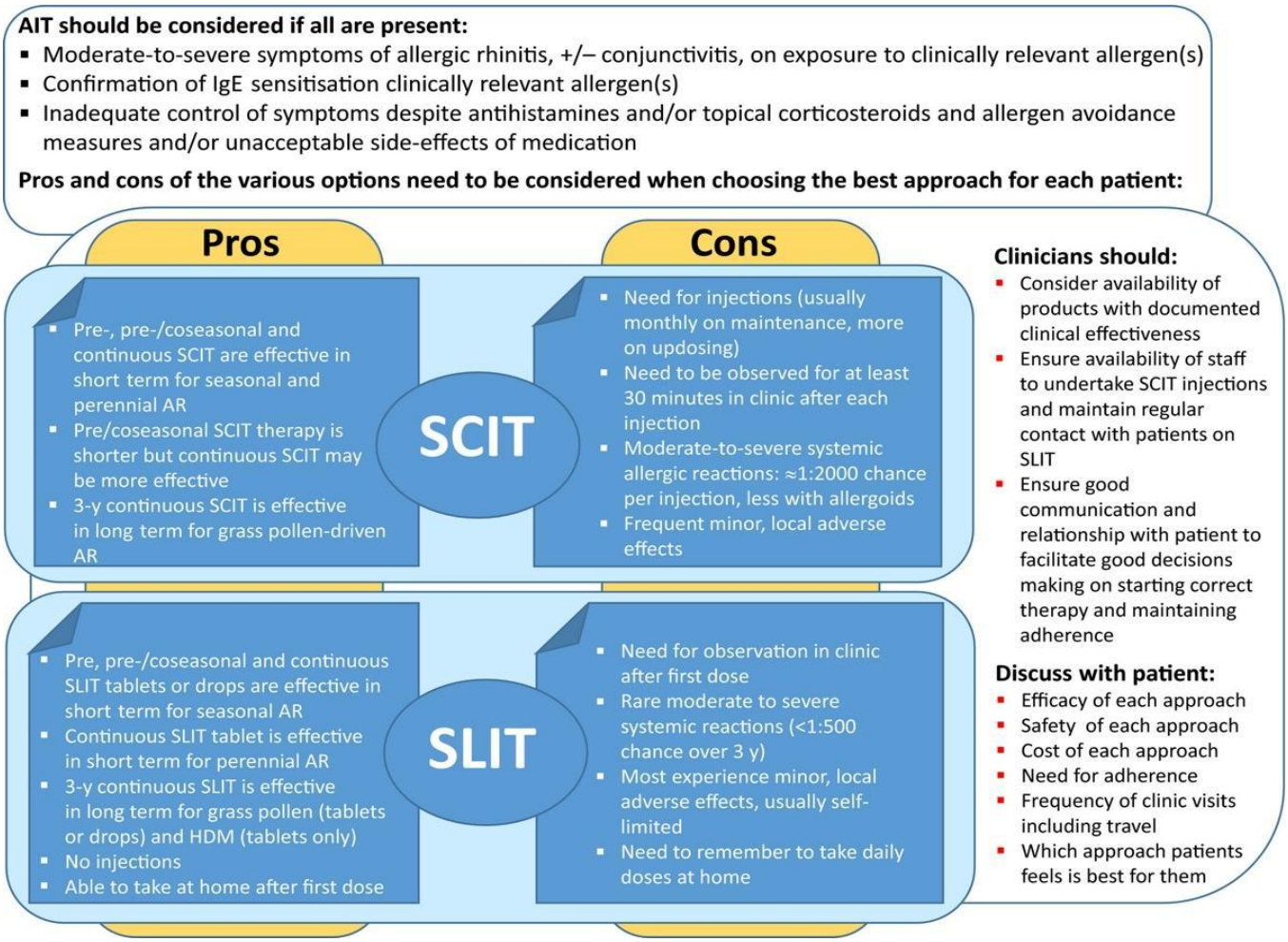


Figure 1. Advantages and disadvantages of SLIT and SCIT therapy from EAACI guidelines.

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