# ABOUT THE AUTHOR

## Kaiser Qureshy, MD, FRCSC

Dr. Qureshy received his medical degree from McMaster University. He subsequently completed his training in otolaryngology/ head and neck surgery at the University of Manitoba. Dr. Qureshy specializes in all areas of adult and pediatric otolaryngology. He has particular interests in sinonasal disease and the surgical management of sleep-disordered breathing and obstructive sleep apnea.

# 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.

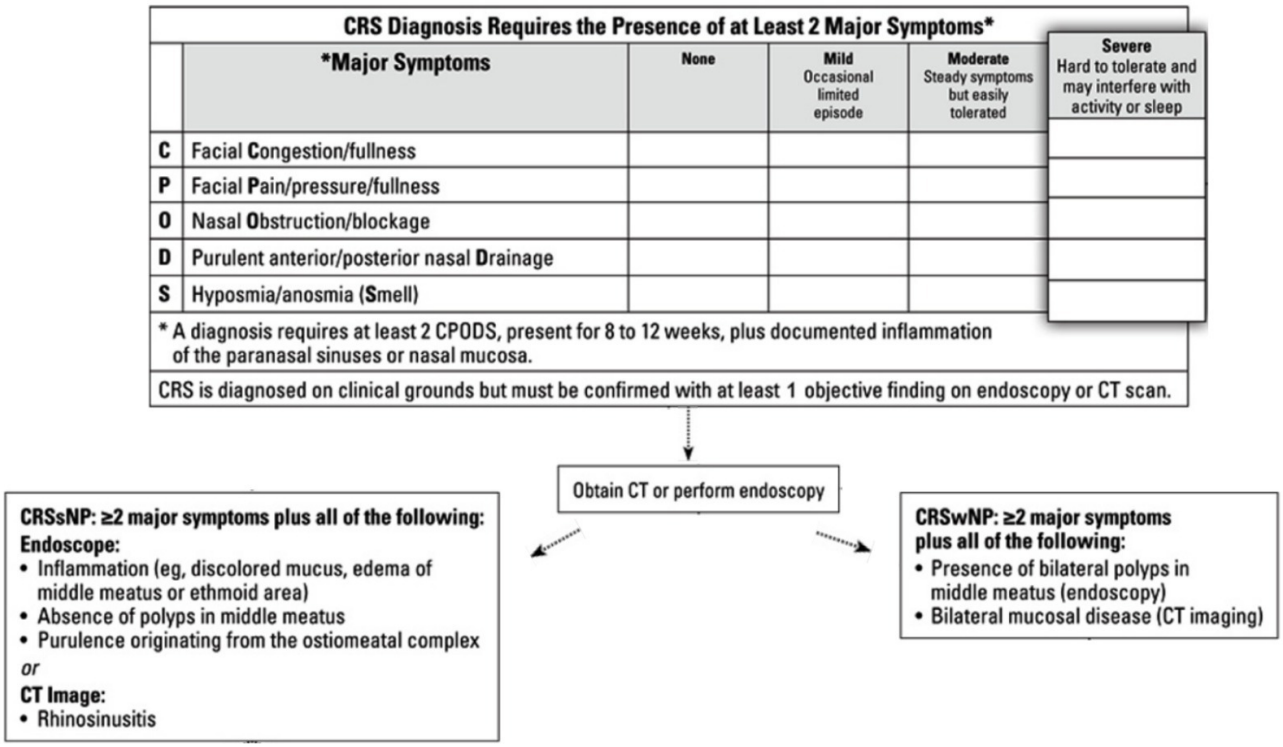


*Figure 1. CRSwNP and CRSsNP diagnostic criteria. Figure adapted from the Canadian Clinical Practise Guidelines for Acute and Chronic Rhinosinusitis (Desrosiers et al., 2011).[2]*

### 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

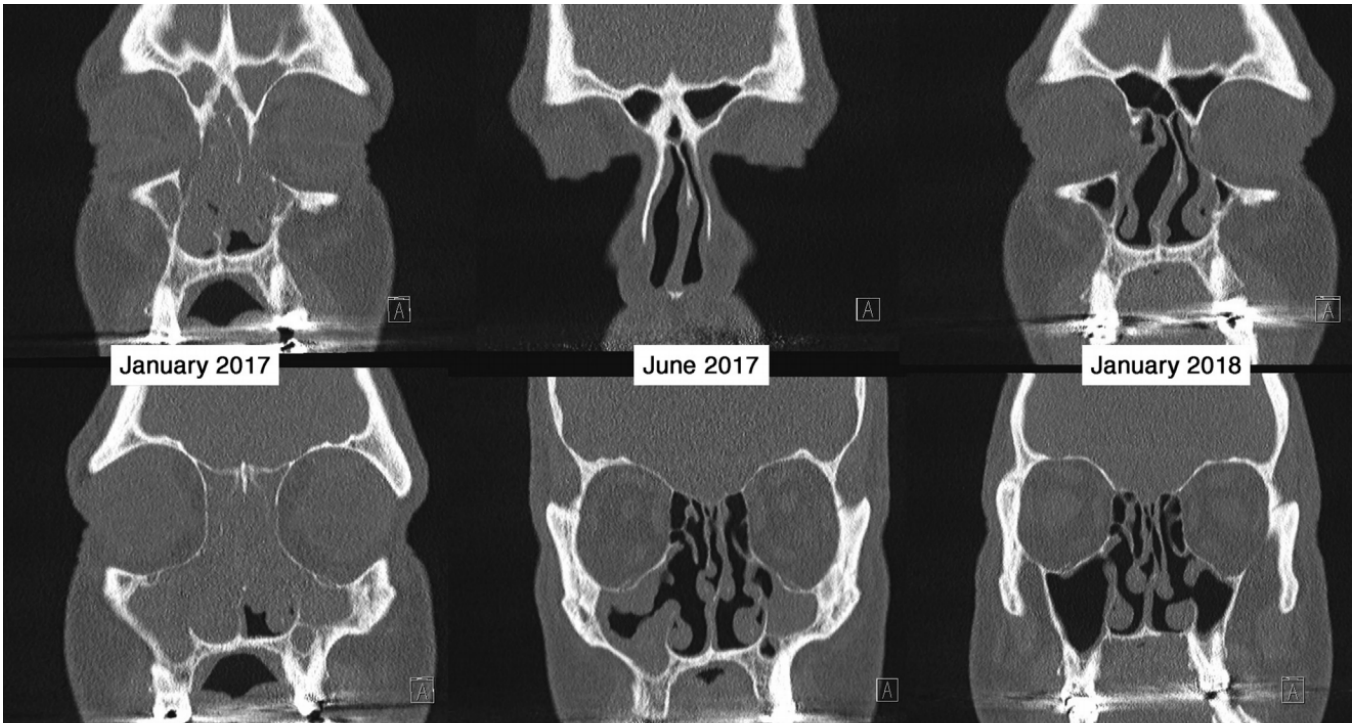


*Figure 2. CT scans over the course of a year in CRSwNP patients taking dupilumab. Image adapted from Bachert et al., 2020.*[38]

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.

## ACKNOWLEDGMENT

The author wishes to acknowledge **Akasham Rajagopaul**, Bachelor of Medical Sciences (BMSc), University of Western Ontario for his role in helping with the literature review and writing of this manuscript.

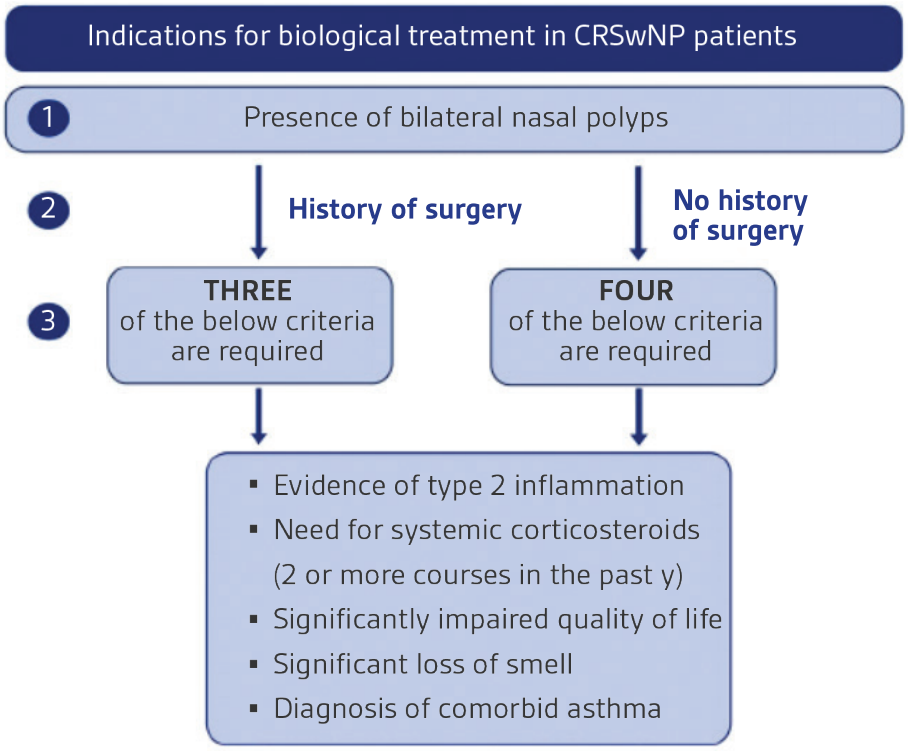


*Figure 3. Indications for biological treatment in CRSwNP patients. Image adapted from Fokkens et al., 2019.*[41]


*References:*

*1. Ahern S, Cervin A. Inflammation and endotyping in chronic rhinosinusitis—a paradigm shift. Medicina. 2019;55(4):95.*

*2. Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, Ciavarella A, Doyle PW, Javer AR, Leith ES, Mukherji A. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy Asthma Clin Immunol. 2011;7(1):1-38.*

*3. Rudmik L. Economics of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2017;17(4):20.*

*4. Stevens WW, Schleimer RP, Kern RC. Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2016;4(4):565-72.*

*5. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and risk factors of chronic rhinosinusitus, allergic rhinitis, and nasal septal deviation: results of the Korean National Health and Nutrition Survey 2008–2012. JAMA Otolaryngol Head Neck Surg. 2016;142(2):162–167.*

*6. Kim DH, Han K, Kim SW. Effect of chronic rhinosinusitis with or without nasal polyp on quality of life in South Korea: 5th Korea National Health and Nutrition Examination Survey Korean. Clin Exp Otorhinolaryngol. 2016;9(2):150–156.*

*7. Macdonald KI, McNally JD, Massoud E. The health and resource utilization of Canadians with chronic rhinosinusitis. Laryngoscope. 2009;119(1):184-189.*

*8. Tan NC, Psaltis AJ. Latest developments on topical therapies in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2020;28(1):25-30.*

*9. Rudmik L, Hoy M, Schlosser RJ, Harvey RJ, Welch KC, Lund V, Smith TL. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2013;3:281–298.*

*10. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal Saline for Chronic Sinonasal Symptoms: A Randomized Controlled Trial. Arch Otolaryngol Head Neck Surg. 2007;133(11):1115–1120.*

*11. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev 2007:CD00639*

*12. Fowler J, Rotenberg BW, Sowerby LJ. The subtle nuances of intranasal corticosteroids. J Otolaryngol Head Neck Surg. 2021;50(1):1-6.*

*13. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev 2016;4:CD011993-CD011993.*

*14. Kang TW, Chung JH, Cho SH, Lee SH, Kim KR, Jeong JH. The effectiveness of budesonide nasal irrigation after endoscopic sinus surgery in chronic rhinosinusitis with asthma. Clin Exp Otorhinolaryngol. 2017;10(1):91.*

*15. Neubauer PD, Schwam ZG, Manes RP. Comparison of intranasal fluticasone spray, budesonide atomizer, and budesonide respules in patients with chronic rhinosinusitis with polyposis after endoscopic sinus surgery. Int Forum Allergy Rhinol. 2016;6(3):233–7.*

*16. Bhalla RK, Payton K, Wright ED. Safety of budesonide in saline sinonasal irrigations in the management of chronic rhinosinusitis with polyposis: lack of significant adrenal suppression. J Otolaryngol Head Neck Surg. 2008;37(6):821 –5.*

*17. Welch KC, Thaler ER, Doghramji LL, Palmer JN, Chiu AG. The effects of serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24(1):26–8*

*18. Smith KA, French G, Mechor B, Rudmik L. Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(3):228–32*

*19. Soudry E, Wang J, Vaezeafshar R, Katznelson L, Hwang PH. Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. Int Forum Allergy Rhinol. 2016;6(6):568 –72.*

*20. Seiberling KA, Chang DF, Nyirady J, Park F, Church CA. Effect of intranasal budesonide irrigations on intraocular pressure. Int Forum Allergy Rhinol. 2013;3(9):704–707.*

*21. Schlosser RJ, Soler ZM. Evidence-based treatment of chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy. 2013;27(6):461-466.*

*22. Poetker DM, Jakubowski LA, Lal D, Hwang PH, Wright ED, Smith TL. Oral corticosteroids in the management of adult chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2013;3:104–20.*

*23. Hox V, Lourijsen E, Jordens A, Aasbjerg K, Agache I, Alobid I, Bachert C, Boussery K, Campo P, Fokkens W, Hellings P. Benefits and harm of systemic steroids for short-and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. Clin Transl Allergy. 2020;10(1):1-27.*

*24. Mostafa BE, Hay HA, Mohammed HE, Yamani M. Role of leukotriene inhibitors in the postoperative management of nasal polyps. Orl. 2005;67(3):148-53.*

*25. Van Gerven L, Langdon C, Cordero A, Cardelús S, Mullol J, Alobid I. Lack of long-term add-on effect by montelukast in postoperative chronic rhinosinusitis patients with nasal polyps. Laryngoscope. 2018;128(8):1743-51.*

*26. Pauli C, Fintelmann R, Klemens C, et al. Polyposis nasi–improvement in quality of life by the influence of leukotriene receptor antagonists. Laryngorhinootologie 2007;86:282–286.*

*27. Schäper C, Noga O, Koch B, Ewert R, Felix SB, Gläser S, Kunkel G, Gustavus B. 8 Anti-inflammatory Properties of Montelukast, a Leukotriene Receptor Antagonist in Patients With Asthma and Nasal Polyposis. J Investig Allergol Clin Immunol. 2011;21(1):51.*

*28. Haye R, Aanesen JP, Burtin B, Donnelly F, Duby C. The effect of cetirizine on symptoms and signs of nasal polyposis. J Laryngol Otol. 1998;112(11):1042-6.*

*29. Head K, Chong LY, Piromchai P, Hopkins C, Philpott C, Schilder AG, Burton MJ. Systemic and topical antibiotics for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;4:CD011994.*

*30. Blaiss MS. Chronic rhinosinusitis with nasal polyps management in the age of biologics. Allergy Asthma Proc. 2020;41(6).*

*31. Iqbal IZ, Kao SS, Ooi EH. The role of biologics in chronic rhinosinusitis: a systematic review. Int Forum Allergy Rhinol. 2020;10(2):165-174.*

*32. Thamboo A, Kilty S, Witterick I, Chan Y, Chin CJ, Janjua A, Javer A, Lee J, Monterio E, Rotenberg B, Scott J. Canadian Rhinology Working Group consensus statement: biologic therapies for chronic rhinosinusitis. J Otolaryngol Head Neck Surg. 2020;50(1):1-9*

*33. Sanofi-aventis Canada. (2020). DUPIXENT® Canada Product Monograph.*

*34. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131(1):110–6.*

*35. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous Dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA. 2016;315(5):469–79.*

*36. Han JK, Bachert C, Desrosiers M, Laidlaw TM, Hopkins C, Fokkens WJ, Paggiaro P, Cho SH, Olze H, Greos LS, Zhang M. Efficacy and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyps: results from the randomized phase 3 sinus-24 study. J Allergy Clin Immunol. 2019;143:S1A-S4A.*

*37. Bachert C, Desrosiers M, Mullol J, Hellings P, Cervin A, Sher L, Bosso JV, Lee SE, Maspero JF, Fujieda S, Matsune S. A randomized phase 3 study, sinus-52, evaluating the efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2019;143(2):AB433.*

*38. Bachert C, Zinreich SJ, Hellings PW, Mullol J, Hamilos DL, Gevaert P, Naclerio RM, Amin N, Joish VN, Fan C, Zhang D, Staudinger H, Pirozzi G, Graham NMH, Khan A, Mannent LP. Dupilumab reduces opacification across all sinuses and related symptoms in patients with CRSwNP. Rhinology. 2020;58(1):10–7.*

*39. Smith KA, Pulsipher A, Gabrielsen DA, Alt JA. Biologics in chronic rhinosinusitis: an update and thoughts for future directions. Am J Rhinol Allergy. 2018;32(5):412-23.*

*40. Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2020;145(3):725-39.*

*41. Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, Canonica GW, Deneyer L, Desrosiers M, Diamant Z, Han J, Heffler E, Hopkins C, Jankowski R, Joos G, Knill A, Lee J, Lee SE, Mariën G, Pugin B, Senior B, Seys SF, Hellings PW. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019;74(12):2312-2319. doi: 10.1111/all.13875.*