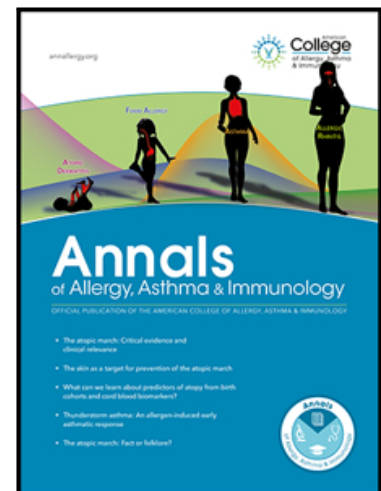


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MEDICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS—YARDSTICK

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ANNALS of ALLERGY, ASTHMA, and IMMUNOLOGY YARDSTICK SERIES**Title:**

MEDICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS – YARDSTICK

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Abbreviations

AERD = Aspirin exacerbated respiratory disease

AFRS = Allergic fungal rhinosinusitis

ATAD = Aspirin therapy after desensitization

BS = Baby shampoo

CI = Confidence interval

COX-1 = Cyclooxygenase-1

CRS = Chronic rhinosinusitis

CRSwNP = Chronic rhinosinusitis with nasal polyps

CRSSNP = Chronic rhinosinusitis without nasal polyps

ECRSwNP = Eosinophilic chronic rhinosinusitis with nasal polyps

EDS-FLU = Exhalation delivery system with fluticasone

EGPA = Eosinophilic granulomatosis with polyangiitis
 FDA = Food and Drug Administration
 FESS = Functional endoscopic sinus surgery
 HS = Hypertonic saline
 INCS = Intranasal corticosteroids
 IL = Interleukin
 IS = Isotonic saline
 LS = Least squares
 NCS = Nasal congestion score
 NOS = Nasal obstruction score
 NP = Nasal polyp
 NPS = Nasal polyp score
 OCS = Oral corticosteroids
 PAMP = Pathogen-associated molecular patterns
 PROM = Patient reported outcome measures
 NECRSwNP = Non-eosinophilic chronic rhinosinusitis with nasal polyps
 NI = Nasal irrigation
 NSI = Nasal saline irrigation
 SA = Staphylococcus aureus
 SCIT = Subcutaneous immunotherapy
 SE = Standard error
 SLIT = Sublingual immunotherapy
 SNOT22 = Sino-Nasal Outcome Test 22
 Th = T helper
 VAS = Visual analog scale

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Chronic rhinosinusitis (CRS) is an inflammatory condition of the paranasal sinuses defined by classic symptoms, imaging findings, and/or endoscopic findings. There are a growing number of emerging pharmacologic therapies being evaluated to treat patients with CRS, some of which have gained indication status in the United States. There have not been updated treatment guidelines published in the United States however since 2014. This document is meant to serve as an updated expert consensus document for the pharmacologic management of patients with CRS. We review available data focusing on prospective clinical trials on oral and intranasal corticosteroids, nasal irrigation, biologics, antibiotics, and allergy immunotherapy for CRS both with and without nasal polyposis, as well as specific therapies for aspirin exacerbated respiratory disease associated CRS and allergic fungal CRS. There are multiple options to treat CRS, and clinicians should be knowledgeable about the efficacy and risks of these available therapies. Allergists/Immunologists now have various therapies available to treat patients with CRS.

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition of the paranasal sinuses defined by classic symptoms, imaging findings, and/or endoscopic findings. The majority of societies require both symptoms and either classic findings on CT and/or endoscopy and define the chronicity as lasting 12 weeks or longer.^{1, 2} There is little agreement on best practices for treatment from varying societies.¹ In the United States, there has not been an updated consensus statement or practice parameter since 2014.² Due to this and the advent of newly approved therapies for this condition, this yardstick is meant to provide up to date information on various treatment modalities and their efficacy for CRS.

There will be an updated United States Practice Parameter on CRS available soon. This yardstick will not be as rigorous as the updated practice parameter and will not utilize a systematic review or GRADE format for guidance. Rather, it will attempt to provide a synopsis on available non-surgical therapies and where these therapies may fit into patient treatment.

The text reviews various treatment modalities dividing CRS into CRS with nasal polyps (CRSwNP) including aspirin exacerbated respiratory disease (AERD), CRS without nasal polyps (CRSsNP), and allergic fungal rhinosinusitis (AFRS). However, studies may not always separate out these phenotypes and endotypes, and thus at times, the sections will discuss mixed types.

Finally, one cannot discuss pharmacologic therapy for CRS in a vacuum without considering surgical therapy. While detailed discussion of surgical therapy is beyond the scope of this manuscript, surgical intervention clearly has a place alongside medical management of this disease. In most cases, the authors suggest functional endoscopic sinus surgery (FESS) with removal of all polyps and opening up the sinus ostia prior to or concomitantly with medical management, especially in the case of AFRS, where debulking of the fungal disease load is a prerequisite to successful medical therapy.

An overall treatment algorithm including the discussed therapies is presented in Figure 1.

INTRANASAL CORTICOSTEROIDS (INCS)

SPRAYS AND DROPS

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)

There is a significant body of literature that supports the efficacy of intranasal corticosteroids in the treatment of CRSwNP. It is well summarized in various exhaustive recent publications.³⁻⁵

Focusing on double-blind, placebo-controlled studies after 1990 yielded 28 trials in patients with CRSwNP with or without previous sinus surgery.⁶⁻³³ The trials included patients at different stages of disease ranging from unoperated polyposis to previously operated polyposis to postoperative therapy. Routes of administration varied between nasal sprays, dry powder, drops and nebulized particles. Agents used included fluticasone furoate, fluticasone propionate, mometasone furoate, budesonide, beclomethasone dipropionate, and triamcinolone acetonide. Based on the body of evidence and the risk to benefit assessment with these medications, INCS should be considered as first-line therapy for CRSwNP. In the authors' opinions, no single agent in this category is superior to another, but patients should be educated on proper use for optimal efficacy

CHRONIC RHINOSINUSITIS WITHOUT NASAL POLYPS (CRSsNP)

Many of the trials using INCSs in CRSsNP are summarized in a Cochrane review which included 10 studies.³⁴ The studies were heterogeneous in design, patient selection, duration of treatment, type of INCS used, presence of a placebo arm, and prior surgery. The corticosteroids were all applied intranasally and in two studies were applied directly into the operated sinus cavity via a special device.^{35, 36} Most of the patients were characterized as having CRSsNP and two studies had mixed populations of CRSsNP and CRSwNP.^{7, 15} Duration of therapy ranged from 11 days to 52 weeks and the agents used were Tixocortol³⁷, Fluticasone propionate^{7, 38},

betamethasone³⁵, beclomethasone³⁹, mometasone¹⁵, budesonide^{36, 40, 41}, and dexamethasone⁴². Eight studies had a placebo arm and the other two studies compared two active therapies and four were conducted in postoperative patients. When symptom scores were examined, five studies had data amenable to meta-analysis and the pooled results significantly favored the INCS group over placebo.^{15, 35, 36, 38, 41} Another four trials had data on the proportion of patients responding to treatment and the meta-analysis of the pooled results significantly favored the INCS group over placebo.^{36, 40-42} The two studies not amenable to meta-analysis both showed significant improvement in nasal symptoms and nasal patency compared to baseline with the INCSs.^{37, 39} Two more recent studies have evaluated the impact of INCSs in patients with CRSsNP, one compared to placebo⁴³ and the other to clarithromycin.⁴⁴ In the study with the placebo arm, mometasone led to a reduction of total nasal symptom scores that was numerically superior to placebo but not statistically significant after 16 weeks of treatment.⁴³ In the same study, endoscopic scores were significantly superior to placebo and patients were more satisfied with their therapy in the active agent group. Zeng and colleagues evaluated mometasone furoate nasal spray or clarithromycin for 12 weeks in patients with CRSsNP and showed a significant reduction in symptom scores and endoscopic appearance in both groups compared to baseline.⁴⁴ The above efficacy data, although heterogeneous, as well as the established safety record of INCSs support their positioning as part of the medical therapy for patients with CRSsNP.

CORTICOSTEROID DELIVERY VIA LARGE VOLUME IRRIGATION

Large volume corticosteroid nasal irrigation has become common practice in patients with CRS. A recent review evaluated publications related to this modality of treatment between 2013-2018 and summarized findings in 11 studies.⁴⁵ Of the six studies evaluating comparative efficacy, five

were performed in postoperative patients and most of the studies had mixed populations of CRSwNP and CRSsNP. Harvey et al. compared equivalent doses of mometasone delivered either as spray or irrigation and found that the irrigation group was significantly superior for improving nasal obstruction, CT scores and endoscopic appearance.⁴⁶ In two studies evaluating budesonide irrigation for 12-24 weeks post-nasal polypectomy, investigators reported improvements in SNOT 22 score, endoscopic score and, in one study, a decreased requirement for oral corticosteroids (OCS) after treatment compared to baseline.^{47, 48} In the one study where around 70% of the patients had not undergone sinus surgery of any kind, budesonide nasal irrigations administered for 30 days resulted in numerical but not statistically significant improvements in SNOT-22 and endoscopic scores compared to a saline irrigation group.⁴⁹ Another study comparing budesonide irrigation to saline in subjects after surgery showed improvements in quality of life measures compared to pretreatment in both groups but failed to show statistical superiority of the budesonide group.⁵⁰ Finally, one study examined only patients with CRSsNP who had not undergone surgery, randomizing patients to either nasal saline irrigation plus mometasone furoate nasal spray (200 mcg daily) or mometasone nasal irrigation (2.4 mg in 8oz saline) plus nasal saline spray for 8 weeks.⁵¹ Both groups had significant improvements in SNOT22 scores compared to baseline. The nasal irrigation treatment was superior to the spray therapy and the difference almost approached statistical significance.

Five studies evaluated safety by various measures (cosyntropin stimulation, intraocular pressure, serum and salivary cortisol, and urinary free cortisol) after budesonide, fluticasone propionate or betamethasone cream irrigations for up to 3 years and showed subclinical alteration of cortisol levels but no obvious adrenal suppression.⁵²⁻⁵⁶ There were no observed changes to intraocular pressure with either budesonide or fluticasone. Of note, these studies evaluated small numbers

of subjects (range 12-61) and, although high volume nasal irrigations seem safe and effective for postoperative management, more research with larger studies is needed.

EXHALATION DELIVERY SYSTEM

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)

A newer mode of administering INCS is the exhalation delivery system with fluticasone (EDS-FLU) which has a flexible mouthpiece and a nosepiece that utilizes a closed palate mechanism to allow medication delivery past the head of the inferior turbinate and deeper into the superior/posterior regions of the nasal passages including the osteomeatal complex.⁵⁷ Two pivotal randomized, double blind, EDS-placebo controlled multicenter trials in patients with CRSwNP evaluated EDS-FLU at 3 doses (93, 186 and 372 mcg twice daily) administered for 16 weeks with an 8 week single arm extension using only the highest dose.^{58, 59} Both studies showed a significant improvement in the primary outcome measures (congestion score and polyp grade) with all doses compared to placebo. Adverse events were generally local and mild except for three previously operated subjects on active therapy who developed septal perforations.^{58, 59} In a post-hoc sensitivity analysis of the two pivotal trials above,^{58, 59} EDS-FLU was equally efficacious in patients who were symptomatic despite regular use of INCS or INCS naïve subjects, suggesting it may work in INCS treatment failure patients.⁶⁰ However, there is no head-to-head trial of EDS-FLU with other delivery systems, and therefore, at present, it is not possible to recommend this device over other INCS preparations.

CHRONIC RHINOSINUSITIS WITHOUT NASAL POLYPS (CRSsNP)

A small, early, placebo controlled trial using the bi-directional device with fluticasone (400 mcg twice daily for 12 weeks) showed significant improvements in endoscopy scores, nasal flow,

symptom scores and sense of smell compared to placebo in patients with CRSsNP.⁶¹ Two more recent large trials were performed using the EDS-FLU in patients with mixed populations of patients with CRSwNP and CRSsNP.^{62, 63} In both trials, there were more patients with CRSsNP and patient outcomes were reported separately for both CRS phenotypes allowing an appreciation of the benefit of this new administration modality in patients with CRSsNP.

Clearly, INCS are the mainstay therapy for patients with CRSwNP and can be used in several forms. Currently, the authors do not recommend any specific delivery method over another. Cost of therapy and patient preference should be considered when selecting a therapy.

ORAL CORTICOSTEROIDS (OCS)

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)

Short courses of OCS have been used in patients with CRSwNP with success and can be considered the medical equivalent of a surgical polypectomy (“medical polypectomy”). Two recent documents have reviewed these studies and performed meta-analyses on the findings when feasible.^{3, 64} Randomized controlled studies were reviewed and the control arms included either placebo or other therapies. The agents used were either prednisone or prednisolone and the duration of therapy varied from 7-21 days. Many of the studies included intranasal corticosteroid therapy either concomitantly with or initiated after cessation of the OCSs. When data were available, meta-analysis was performed, and uniformly showed significant efficacy of OCS in reducing nasal symptoms and nasal polyp scores 2-3 weeks after start of therapy.⁶⁵⁻⁶⁹ When the same parameters were evaluated 10-12 weeks after start of therapy, the reduction in polyp score was still significant in the OCS group but the reduction in symptom scores was

not.⁶⁶⁻⁶⁸ Many of these studies also showed significant improvements in nasal flow measurements as well as the sense of smell after OCS.⁶⁵⁻⁶⁹ Serious adverse effects such as peptic ulcers or osteonecrosis of the femoral head were not reported but there was an increase in insomnia, gastrointestinal disturbances and dyspepsia noted in participants treated with prednisone compared to controls.^{66, 69}

Two recent studies evaluated the utility of postoperative OCS. Arancibia and colleagues performed surgery on a group of patients with CRSwNP and then randomized them to a tapering course of prednisone or placebo for 4 weeks accompanied by nasal saline douching.⁷⁰ Both groups had significant improvements in symptoms, endoscopic scores, smell and quality of life 4 weeks after surgery irrespective of OCS intake. Shen and colleagues also randomized patients postoperatively to oral prednisone or placebo for 2 weeks after surgery.⁷¹ Both groups had high volume saline irrigations and intranasal mometasone postoperatively. There were improvements in visual analog symptom scales, Sino-Nasal Outcome Test 22 (SNOT22) scores and Lund Kennedy nasal endoscopy scores up to 6 months after surgery in all patients, with no added benefit in the group on OCS treatment. When subjects were stratified based on tissue eosinophilic content, OCS treatment tended to be more effective in improving endoscopy scores 3 and 6 months after surgery in the non-eosinophilic group.

In summary, treatment of CRSwNP with OCS is beneficial, but the reduction in polyp size is unlikely to be maintained without the addition of an intranasal corticosteroid. Because of concerns with potential side effects, this modality cannot be used very frequently. If used, a longer course (2-3 weeks with taper) rather than a shorter course (3-5 days) is often necessary to produce an effective outcome, with starting doses in the range of 40-60 mg of daily prednisone equivalent with taper. Long-term OCS, beyond this time course are not recommended.

CHRONIC RHINOSINUSITIS WITHOUT NASAL POLYPS (CRSsNP)

There is a paucity of studies evaluating the effect of OCS on symptoms in patients with CRSsNP. In 3 studies, various regimens including OCS were used to treat patients with CRSsNP.⁷²⁻⁷⁴ Concomitant medications (antibiotics, INCS, SI) were used along with OCS and there were significant improvements compared to baseline after therapy in a sizeable proportion of subjects. Because multiple therapies were used, it is impossible to draw any conclusions on the benefit of OCS alone. A small study in nonallergic patients with symptoms of CRSsNP demonstrated benefit of a 2-week course of prednisone on smell recognition and detection compared to baseline.⁷⁵ Considering the lack of good evidence supporting the use of OCS in CRSsNP, and their significant potential adverse events, these agents should be used judiciously.

NASAL IRRIGATION (NON-STEROID)

Nasal irrigation (NI) is considered an adjunctive therapy for CRSwNP or CRSsNP as it has been found in many studies to be effective at clearing secretions and inflammatory mediators from the nasal cavity while improving mucociliary function. As a result, international consensus statements from 2016 and 2020 have strongly recommended (Grade A evidence) high volume (>200ml) nasal saline irrigation (NSI) for CRSwNP and CRSsNP.^{4, 76} A European position paper from 2012 also strongly recommended NSI for only CRSsNP (Grade A evidence).⁷⁷ However, a Cochrane review on saline irrigation from 2016 strongly recommended NSI for CRS as a low-risk treatment with potential benefit but based this recommendation on low quality of evidence.⁷⁸ Infectious agent transmission using tap water versus sterilized water has been primarily presented as case summaries. Experts concur that tap or well water should not be used

for NI without prior boiling to kill any bacteria or other organisms, and proper hygiene (e.g. sterilizing devices and replacing per manufacturers recommendations) should be used.⁷⁹

TPYES OF NASAL IRRIGATION

Studies have investigated isotonic saline (IS), hypertonic saline (HS) and lactate ringer solution, non-dilute isotonic seawater, additives such as saccharides and surfactants and modes of delivery (position, squeeze bottle, powered nasal irrigation).⁷⁹ One recent study used a computational fluid dynamics model to demonstrate that delivery of NI is more effective using greater volumes of solution to flood the ostia rather than using direct jet entry irrigation.⁸⁰

META ANALYSES AND SYSTEMATIC REVIEWS

One meta-analyses and systematic review included 11 studies evaluating 663 patients with either CRSwNP or CRSsNP.⁸¹ Eight of these studies compared different saline solutions and three compared different delivery devices.⁸¹ Other interventions evaluated included thermal water and oligo-elements found in seawater which appeared more effective than IS. However, because these studies were conducted on relatively small patient numbers, over different treatment time periods and using different clinical endpoints, clinical evidence supporting their use was weak.⁸¹

A more recent systematic review and meta-analysis included seven randomized controlled trials comparing HS verses IS in 454 patients with CRS with and without NPs.⁸² They assessed nasal secretion, nasal congestion, headache, smell, and overall symptomatic relief. Two studies evaluated radiologic scores and two assessed mucociliary clearance.⁸² All studies favored HS over IS but HS was associated with a higher risk of adverse effects (most commonly nasal irritation and burning sensation; as well as tearing, nosebleeds, and headache). These adverse

effects caused decreased adherence in the studies. They recommended HS as being more effective but were unable to provide any guidance regarding NI methods, devices, doses, or frequency of use.⁸²

NI WITH SALINE SOLUTIONS POST FESS:

Studies have reported subjective and objective improvement in CRSwNP patients treated post-FESS with IS and hypertonic sea water (2.3%) NI.^{83, 84} One larger prospective open label study investigated normal IS versus a mineral-rich IS solution in CRSwNP post-complete ethmoidectomy and found that adding minerals to the IS solution improved endoscopic and QOL scores in older patients, patients with an initial poor QOL or higher symptom scores and in smokers.⁸⁵

Finally, a recent study compared NI with buffered HS to physiological seawater in CRSwNP patients post-FESS but further characterized them as eosinophilic (ECRSwNP) and non-eosinophilic (NECRSwNP) phenotypes.⁸⁶ They found that as a group there were significant subjective and objective improvements with NI irrespective of the solution used however, when patients were stratified based on ECRSwNP and NECRSwNP, the latter group treated with buffered HS experienced a greater improvement in mucosal edema and crusting immediately post-operatively and significant objective improvement in Lund-Kennedy endoscopic scores and saccharine clearance times.⁸⁶

NI WITH ADDITIVES:

A systematic analysis of alternative therapies reviewed using additives to NI such as baby shampoo (BS), thyme honey, bromelain additives and echinacea.⁸⁷ Although they showed clinical effectiveness, the scientific evidence was too weak to provide any clinical recommendations for their routine use.⁸⁷

There are a few RCTs focused on NI additives like baby shampoo (BS) and xylitol in patients with CRS post-FESS. One study investigated using 1% BS and normal saline for NI in CRS patients irrespective of NP status post-FESS (n=18).⁸⁸ The 1% baby shampoo concentration was previously determined to disrupt preformed bacterial biofilms and inhibit additional biofilm formation.⁸⁸ Symptomatic CRS patients despite surgery and medications were treated post-operatively with NI using 1% BS twice daily for 4 weeks; 60% noted improvement in thickened mucus and post-nasal drainage and approximately 47% noted overall subjective symptom improvement although there was no effect on altering biofilm formation.⁸⁸ A recent study enrolled 77 CRSwNP subjects to receive NSI versus BS and found that the latter was significantly more effective at reducing crusting, nasal discharge and synechia formation as well as improving SNOT 22 scores.⁸⁹ One potential complication of using BS or other surfactants in the nasal irrigation is loss of smell or complete anosmia which can occur in up to 40% of patients.^{90, 91}

A more recent study enrolled 52 CRS patients with and without NPs still symptomatic despite aggressive medical treatment who received NI with IS versus xylitol before and after FESS.⁹² Both groups had improvement in subjective patient reported outcome measures (PROM) including visual analogue scores for pain, nasal obstruction symptom scores and SNOT22 scores but the xylitol group had statistically significant better effect compared to the IS group.⁹² There

were several limitations to this study including sample size, lack of objective measurements and not stratifying patients based on CRSwNP and CRSsNP status.⁹²

One RCT investigated hyaluronic acid versus IS by nasal nebulizer twice daily for 30 days in patients with CRSsNP.⁹³ No significant objective or subjective differences were found between treatment groups. However, NI irrespective of solution type used, was found to improve PROMs for SNOT22, VAS for nasal congestion and hyposmia/hypogeusia scores.⁹³ However, no objective differences in nasal endoscopy, anterior rhinomanometry, peak nasal inspiratory flow rate or nasal cytology were noted to substantiate these subjective findings.⁹³

One study investigated NI with hyaluronic acid compared to IS specifically in CRSsNP post-FESS and found patients benefited both subjectively or objectively from this treatment.⁹⁴ Another study compared improvement in olfaction in CRSsNP patients treated with NSI versus INCS and found that neither treatment was beneficial.⁹⁵

In summary, NI is a recommended therapy for CRS and use of hypertonic solutions or additives may be of benefit in some patients, however normal saline irrigation is reasonable for most patients.

ANTIBIOTICS

In the absence of immune deficiency, cystic fibrosis, primary ciliary dyskinesia, odontogenic disease, and other underlying disorders, CRS with or without NPs is not a primary infectious disorder. As such, eradication of a putative pathogenic infection is not the mainstay of treatment, but rather consists of addressing the underlying inflammation. Although not a primary infectious process, these disorders are associated with the development of a rich bacterial microbiome and

the combination of inflammation driven both by microinvasive disease as well as a secondary inflammatory process in response to bacterial-derived pathogen-associated molecular patterns (PAMPs) and bacterial toxins contribute to the persistence and severity of disease. As such, the role of antimicrobial therapy as an adjunctive treatment of CRS is plausible. In addition, certain antimicrobials, especially the macrolide antibiotics and tetracyclines, have anti-inflammatory properties and may contribute to modulation of CRS through non-antimicrobial mechanisms.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRS_wNP)

Many of the recommendations regarding antibiotic use apply to both CRS_wNP and CRS_sNP as many of the studies have not vigorously distinguished the two conditions. As noted, CRS_wNP in most individuals is a type 2 inflammatory disorder. One of the surprising biologic effects of interleukin (IL)-13 is its capacity to down-regulate expression of antimicrobial peptides, in particular, β -defensins and cathelicidins, peptides that are particularly important in preventing infection with staphylococcal aureus (SA). Indeed, over 60% of patients with NPs and 80% with AERD demonstrate SA in sinus cultures.⁹⁶

In addition to the worsening symptoms driven by this infection, SA is likely to contribute to the severity of the type 2 state through its tendency to act as a source of both antigens and superantigens that will drive type 2 cytokine expression. Thus, it is reasonable to speculate that antibiotics are likely to have some benefit in treating these disorders. However, there are surprisingly few well performed trials to justify their use in the treatment of CRS_wNP. One study utilized doxycycline 200 mg x 1 dose followed by 100 mg daily for 20 days, and demonstrated a significant reduction in polyp size, although no significant differences in symptoms, peak nasal inspiratory flow, rhinorrhea, or hyposmia were observed.⁶⁸ It is unclear

whether this efficacy was related to an antimicrobial effect or the association of doxycycline with an anti-inflammatory profile.⁹⁷ Furthermore, these results could not be reproduced in a more recent follow-up study.⁹⁸

Given their potential for producing GI symptoms, rash/hypersensitivity reactions, *Clostridia difficile* outgrowth, and especially the promotion of antibiotic resistance, current guidelines do not support the use of antibiotics in CRSwNP in the absence of an acute bacterial-mediated exacerbation.⁷⁶ In several studies, macrolide use was associated with reduction in nasal polyp size. However, the current understanding of their anti-inflammatory profile suggests that macrolides may be particularly effective in attenuating Type 1 inflammation. For example, in the lower airway, benefits are more likely to be observed in subjects with lower IgE and without eosinophilia.⁹⁹ Overall, there is less evidence of efficacy of macrolides in CRSwNPs compared to CRSsNPs.^{97, 99-101} The current data therefore do not support the routine use of antibiotics in patients with CRSwNP.

CHRONIC RHINOSINUSITIS WITHOUT NASAL POLYPS (CRSsNP)

As with CRSwNP, CRSsNP not an infectious disease and there is little basis to support the utilization of short courses of antibiotics (<3 weeks).

In contrast to their use as antimicrobials however, macrolide antibiotics have been proposed as a therapeutic agent in CRSsNP based upon their anti-inflammatory profile.^{97, 99, 102} These effects have been reported to include inhibition of IL-8 and TNF- α expression, mucin gene expression, down-regulation of NF- κ B signaling pathways, disruption of neutrophil function, and the inhibition of fibroblast proliferation and collagen production. Given these mechanistic properties, macrolide antibiotics have been proven effective and are recommended for lower

airway inflammatory disorders including COPD and non-type 2 asthma.¹⁰³ Several randomized control trials with well-designed outcomes have found evidence supporting their use manifested as significant improvements in SNOT-20 and endoscopy scores. A 2013 review of 17 studies supported the use of macrolides in CRSsNPs¹⁰⁴ and, similarly, evidence supporting their benefit was concluded in a systematic review performed in 2019.¹⁰² However, in contrast, a 2016 Cochrane review argued against there being sufficient evidence to support their use.¹⁰⁵ It should also be noted that, as stated above, macrolide antibiotics are associated with frequent GI complaints including diarrhea, abdominal discomfort, and nausea/vomiting. They also have the potential risk of cardiac toxicity including arrhythmias associated with QTc prolongation alone or secondary to drug-drug interactions resulting in an FDA advisory in patients with cardiovascular risk factors. Of note, these risks may extend at least a year beyond the initial antibiotic exposure.¹⁰⁶ At present the use of macrolide antibiotics as an adjunctive therapy in CRSsNP is supported by the literature, however their use must be weighed against the risks stated above. It needs to be noted that there are currently no solid recommendations regarding the appropriate duration of their use and current guidelines do not support use of long-term (or short-term) antibiotics.⁷⁶

An alternative consideration has been the utilization of topical antibiotics, arguing for possible increased efficacy associated with the ability to attain higher local concentrations along with decrease in risks associated with systemic absorption. This use would require well-performed ESS to permit penetration into the sinuses. Several randomized controlled trials including those with bacitracin, neomycin, tobramycin, and mupirocin have failed to demonstrate striking benefit and a Cochrane review was unable to make any recommendation as no trial was felt to meet the

inclusion criteria. Thus, at present there is insufficient evidence to support the routine use of topical antibiotics in CRS.^{76, 107}

BIOLOGICS

Nasal polyps (NPs) are most often characterized by pronounced tissue eosinophilia and a predominant type 2 inflammatory infiltrate comprised of mast cells, type 2 innate lymphoid cells (ILC2s), T helper type 2 (Th2) cells, and basophils.¹⁰⁸ These immune cells are capable of producing a variety of type 2 pro-inflammatory mediators such as IL-4, IL-5, IL-13, and IgE that can perpetuate the ongoing inflammatory response observed in NPs.¹⁰⁸⁻¹¹² Thus, therapies aimed at targeting type 2 inflammation have been investigated for challenging CRSwNP cases. Here we discuss the biologics that have completed phase three clinical trials for the treatment of CRSwNP (Summarized in Table 1)

Dupilumab is a monoclonal antibody that blocks IL-4 receptor alpha, the shared receptor for IL-4 and IL-13 signaling, and thus prevents downstream type 2 inflammation. In June 2019, dupilumab was approved by the Food and Drug Administration (FDA) to treat inadequately controlled CRSwNP. It is also FDA-approved to treat atopic dermatitis and moderate to severe refractory eosinophilic or OCS-dependent asthma. Two phase-three trials, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52, demonstrated clinical efficacy of dupilumab as adjuvant therapy to topical INCS for patients with nasal polyps.¹¹³ In both studies, dupilumab met its primary endpoints: change from baseline in nasal polyp score (NPS) and nasal congestion severity at week 24. Dupilumab reduced the nasal polyp size and nasal congestion severity significantly from baseline compared to placebo in both Sinus-24 and Sinus-52 (Table 1). Furthermore, the secondary outcomes, including symptoms, quality of life, and sense of smell

improved with dupilumab. There was a 74% and 83% reduction in time to OCS use and surgery, respectively, compared to the placebo group. Notably, in SINUS-24, the treatment effects diminished after the drug discontinuation, whereas in SINUS-52, sustained improvement was seen at week 52, highlighting an apparent need for continued therapy for disease control. The adverse effects included injection site reaction, transient eosinophilia, eosinophilic granulomatosis with polyangiitis (EGPA) (2 cases and 1 case reported in the dupilumab and placebo arms, respectively), and conjunctivitis (7 in the dupilumab, 1 in the placebo group).

Omalizumab is an anti-IgE monoclonal antibody that binds to circulating IgE and was FDA approved in December 2020 for the treatment of nasal polyps that are inadequately controlled with INCS. It is also approved for uncontrolled moderate to severe persistent allergic asthma and chronic spontaneous urticaria. Two phase-three studies (POLYP-1 and POLYP-2) were published in 2020 and showed clinical efficacy of omalizumab in treating nasal polyposis.¹¹⁴ In both studies, patients were randomized (1:1) into weight and IgE-level based dose of omalizumab or placebo as an adjunct to mometasone nasal spray for 24 weeks. Both studies significantly met the coprimary endpoints of change from baseline in NPS and daily nasal congestion at 24 weeks for the omalizumab arms compared to placebo (Table 1). Pooled analysis showed substantial improvement of SNOT-22 (by 23.1 points in omalizumab vs. by 7.7 in placebo), total nasal symptom scores, and sense of smell with omalizumab. In addition, the proportion of patients meeting criteria for surgery at 24 weeks was less in the omalizumab group compared to placebo. Omalizumab was well tolerated and the most common adverse effects for omalizumab which had been previously reported included headache, injection site reactions,

arthralgia, dizziness, and upper abdominal pain. Of note, hypersensitivity reactions were uncommon.

Mepolizumab is a monoclonal anti-IL-5 antibody that binds to free IL-5, thereby preventing the IL-5 signaling cascade that promotes eosinophil activation and recruitment. It is FDA approved for the treatment of severe refractory eosinophilic asthma and EGPA. A phase 3 study (SYNAPSE) has recently been published, showing efficacy of mepolizumab over placebo.¹¹⁵ In this study, 414 adult subjects with history of polyp surgery were randomized to receive mepolizumab (100 mg subcutaneous every four weeks) or placebo for 52 weeks. Mepolizumab met its primary endpoints with improvement in endoscopic nasal polyp score (adjusted difference in medians -0.73, 95% CI -1.11 to -0.34; $p<0.0001$) and nasal obstruction VAS score (-3.14, -4.09 to -2.18; $p<0.0001$) at 52 weeks. Based on the SYNAPSE study, mepolizumab was approved as an add on therapy for use in adults with CRSwNP in July 2021

Benralizumab is a monoclonal anti-IL-5 receptor antibody approved for use in severe eosinophilic asthma. A phase three study (NCT03401229, OSTRO III) has not been published. However, a recent press release states that the study coprimary endpoints were met, and patients with CRSwNP treated with benralizumab had a significant decrease in polyp size and nasal obstruction scores compared to placebo.¹¹⁶

As more biologics are expected to be available for therapeutic use in CRSwNP, one must decide when to consider biologics to treat patients with CRSwNP. Clinicians must consider patient preference, cost of therapy, and efficacy of therapy when selecting a treatment plan. Since

biologics target type 2 inflammation, they are most appropriate in CRS patients with type 2 inflammation. Loss of smell, asthma, eosinophilic inflammation, elevated IgE, and/or allergen sensitization may be considered surrogate markers of type 2 inflammation in this population.¹¹⁷
¹¹⁸ Thus, patients with difficult-to-treat CRSwNP, especially in association with other type 2 diseases, including moderate to severe asthma are good candidates for biologics.^{117, 118} Additionally, patients with risk of polyp recurrence, including patients with AERD, AFRS, asthma, and prior sinus surgery, may be appropriate candidates for biologics.¹¹⁹ However, the role of biologics in CRSwNP in patients without moderate to severe asthma or their use as an alternative to surgical therapy in patients who have not failed prior FESS is still unclear based on our current understanding. Similarly, the appropriate duration of use of biologics is unknown.

To date, no type 2 biomarker has been identified that specifically predicts treatment success with one biologic versus another and there are no head-to-head direct comparisons among the different biologics. Thus, at this time, one biologic cannot be recommended over another, but future studies are needed to better understand the use of individual biologics in CRSwNP and help guide clinical care.

ALLERGEN IMMUNOTHERAPY

A systematic review of subcutaneous immunotherapy (SCIT) to aeroallergens for CRS identified four studies conducted between 1983 to 2004 discussed below.¹²⁰ Two were prospective trials that included CRSwNP and CRSsNP patients post-FESS^{121, 122} and one included children with CRS without prior surgery and no mention of polyp status.¹²³ In the pediatric study, patients treated with sublingual immunotherapy (SLIT) (n=20) compared to control (n=17) experienced fewer rhinitis symptoms, less turbinate swelling and improved radiologic findings.¹²³

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)

One CRSwNP adult study (n=72; 66 on SCIT and 6 controls) conducted in 1994 was inconclusive regarding its therapeutic benefit.¹²¹ In contrast, an earlier CRSwNP SCIT study conducted in 1983 (n=31) reported improved symptom scores for those receiving SCIT (n=15) at 4 months and after long-term follow-up associated with improved radiologic outcome scores compared to controls (n=16).¹²² It should be mentioned that this study permitted adjunctive systemic and INCS during the trial.¹²² It is unclear from these IT studies performed how much of the observed benefit was derived from improvement in the concomitant AR as opposed to how much improvement was derived by improving the sinus disease. There have been no studies of SLIT in patients with CRSwNP.

CHRONIC RHINOSINUSITIS WITHOUT NASAL POLYPS

One retrospective, uncontrolled case series of 114 CRSsNP patients treated with SCIT reported improvement in modified rhinitis outcome questionnaire scores with decreased sinus pain, discolored mucus discharge and nasal congestion along with a 54% reduction in sinus surgeries.¹²⁴ Given the minimal data and limitations to available data, there is little justification to support the use of SCIT for CRSsNP.

There have been no studies of SLIT in patients with CRSsNP.

ASPIRIN EXACERBATED RESPIRATORY DISEASE (AERD)

A subset of patients with CRSwNP also have comorbid asthma and an intolerance to medications that inhibit the cyclo-oxygenase-1 (COX-1) enzyme. These patients historically have been

referred to as having Samter's triad but now are commonly referred to as having AERD. Within minutes to hours of ingesting a COX-1 inhibitor, such as aspirin or ibuprofen, patients with AERD develop significant upper and lower respiratory symptoms including rhinorrhea, congestion, shortness of breath, wheeze, and cough.

Treatment of patients with AERD can follow the same algorithm as for treatment of patients with CRSwNP, however, there is an additional unique treatment option for these patients as outlined below.

ASPIRIN THERAPY AFTER DESENSITIZATION

Paradoxically, while COX-1 inhibitors can lead to enhanced respiratory symptoms, daily aspirin therapy after desensitization (ATAD) has been shown to be a unique treatment option in patients with AERD. Large retrospective cohort studies and smaller double-blind placebo-controlled clinical trials have shown that patients with AERD may clinically benefit from daily ATAD.¹²⁵ In these studies, AERD patients on ATAD reported increased quality of life, improvement in upper and lower respiratory symptoms, delayed nasal polyp regrowth, and reduced need for repeated sinus surgery.¹²⁶⁻¹²⁹ The mechanisms by which aspirin elicits symptoms acutely but provides extended clinical benefit following desensitization are still not fully understood.

AERD patients should be considered for ATAD if they have a history of rapidly recurring nasal polyps following sinus surgery, uncontrolled sinus symptoms despite medical management, and have required frequent bursts of OCSs to control their upper or lower respiratory symptoms. An exhaustive guide to performing and managing aspirin desensitization is outside the scope of this report but is summarized elsewhere.¹³⁰ Most aspirin desensitization protocols can be safely

performed in an outpatient setting that is capable of managing severe allergic reactions. As lysine aspirin is not available in the US, protocols utilizing oral aspirin or a combination of intranasal ketorolac followed by oral aspirin are traditionally used.^{131, 132} It is expected that AERD patients will develop symptoms at some point during the desensitization. As such, patients should be monitored and objective measurements including pulmonary function and vital signs should be repeatedly assessed. If the patient becomes symptomatic, they should be medically treated (i.e., given albuterol for wheeze, oxymetazoline for nasal congestion). Following symptom resolution, the inciting aspirin dose should be re-administered prior to escalating to larger doses.

The target dose of a desensitization is 325 mg of Aspirin after which, the patient is discharged to continue taking aspirin at home. While a uniform consensus is lacking as to the exact dose of aspirin patients should continue, 1,300 mg daily is typically recommended, if tolerated. However, some patients may still experience clinical benefit with a reduced dose of 650 mg daily.¹³³ Doses lower than 325 mg, while cardio-protective, are not thought to maintain desensitization in the setting of AERD. It is critical that patients take their aspirin daily to remain desensitized. If greater than 48 hours elapses between doses, patients should be evaluated by their physician prior to resuming as a repeat desensitization may be needed.

ATAD is not without limitations. In a recent study of AERD patients who were desensitized for at least 10 years, 38% of survey responders had to discontinue their daily aspirin regimen.¹²⁸ Adverse reactions to aspirin, lack of clinical benefit, and need to undergo surgery were cited as the reason for discontinuation in 37%, 26%, and 23% of these patients, respectively.¹²⁸ As such, patients with a history of gastrointestinal or bleeding disorders are not appropriate candidates for

ATAD. Other contraindications to ATAD include patients with severe uncontrolled asthma ($FEV_1 < 70\%$ predicted), pregnancy (or attempting to become pregnant), and a history of medication non-compliance. It is also recommended that AERD patients undergo sinus surgery or an aggressive course of OCS (medical polypectomy) prior to their desensitization. This reduces nasal polyp burden and has been shown to reduce the severity of symptoms elicited during the desensitization itself.¹³⁴ In summary, ATAD can be an effective lower-cost treatment option in patients with AERD but the risks and benefits of the procedure and subsequent therapy as well as the use of alternative therapies (including biologics) should be discussed with patients before initiating. Additionally, ATAD is not recommended for patients with CRSwNP who are tolerant of COX-1 inhibitors as studies have shown it is not effective in patients without AERD.

LEUKOTRIENE MODIFYING AGENTS

Leukotriene receptor antagonists (e.g., montelukast, zafirlukast) and 5-lipoxygenase inhibitors (e.g., zileuton) are currently not approved for the treatment of CRSwNP. Furthermore, although there are small clinical trials that may support their efficacy, which may be better for 5-lipoxygenase inhibitors vs leukotriene receptor antagonists,¹³⁵ the level of evidence for recommending these agents as a treatment of CRSwNP is very weak. However, leukotriene modifying agents may be beneficial in treating comorbid asthma, which is observed in over half of patients with CRSwNP. Leukotriene modifying agents may play a more prominent role when managing patients with AERD, a condition characterized by enhanced levels of cysteinyl leukotrienes.¹³⁶ Additionally, when taken prior to an aspirin desensitization, leukotriene modifying agents can reduce the severity of lower airway symptom reactions elicited.^{136, 137} However, even in AERD, these agents are not recommended as a monotherapy.

ALLERGIC FUNGAL RHINOSINUSITIS (AFRS)

As discussed in the introduction and in the treatment algorithm, surgical intervention is more a requirement in AFRS as compared to other phenotypes/endotypes of CRS, and thus the pharmacologic agents below should be used in conjunction with surgical intervention.

INTRANASAL CORTICOSTEROIDS

The use of INCS after surgery in patients with AFRS is recommended based, in large part, on the fact that these agents have shown benefit in the treatment of CRSwNP. Large trials examining efficacy of INCS in AFRS are lacking.¹³⁸ Dai and colleagues performed a randomized study in 30 patients with AFRS and evaluated the benefit of budesonide intranasal nebulization or budesonide nasal spray in postoperative patients.¹³⁹ None of the patients in the nebulization group had recurrent disease at a median follow up of 18 months whereas 26.7% of patients treated with spray did, suggesting a possible superiority of nebulized administration.

ORAL CORTICOSTEROIDS

There are multiple trials utilizing OCSs for variable lengths of time in patients with AFRS after surgical therapy.¹³⁸⁻¹⁴¹ The duration of treatment varied from weeks to months postoperatively and most studies utilized a taper regimen. All studies showed a lower likelihood of recurrence of disease postoperatively in the patients treated with OCS compared to the control groups. Limitations of the studies include retrospective design in most, small numbers of participants, and concomitant therapy with other agents (INCSs and in some cases antifungal therapy).

ANTIFUNGALS

There are three arguments for the use of anti-fungal agents in AFRS. Most compelling is that AFRS is a potent inflammatory disorder specifically induced by the fungus and it seems self-evident that reduction or eradication of the fungal load should produce clinical benefit. In addition, there is evidence that these agents can be beneficial when used in the closely related disorder, allergic bronchopulmonary aspergillosis. Finally, azoles, like macrolides, have anti-inflammatory effects and seem particularly beneficial in targeting type 2 inflammation. Despite these arguments, there is a surprising lack of evidence for a benefit for antifungals in AFRS.^{76, 138} In part, this may reflect the absence of well performed, appropriately powered, well-controlled studies and, in particular, the failure to enroll patients who assiduously meet the diagnostic criteria for AFRS. One recent study suggesting the potential for efficacy of antifungals in AFRS demonstrated significantly better symptoms (SNOT-20) and sinus CT scores when itraconazole was given for one month preoperatively in comparison to an untreated cohort.¹⁴⁰ However, at present there is insufficient evidence to support the use of antifungals in AFRS.

ALLERGEN IMMUNOTHERAPY

Three studies investigating SCIT in AFRS have been reported.¹⁴¹⁻¹⁴³ Two were cross-sectional studies (n=22 and n=17) of a prospective study protocol and one was a retrospective chart review (n=60).¹⁴¹⁻¹⁴³ All evaluated patient responses post-operatively, and all included SCIT to fungal antigens (one included other aeroallergens to which the patients were sensitized).¹⁴¹⁻¹⁴³ These studies had small sample sizes and had conflicting results regarding efficacy. Only one case series of 10 AFRS patients treated with SLIT based on the patient's fungal sensitization pattern

has been reported which revealed decreased subjective complaints, physical findings, Lund-McKay scores, and serum IgE levels without adverse effects.¹⁴⁴ Based on the above, SCIT could perhaps be considered in some AFRS patients. There is lack of compelling evidence for the use of SLIT in AFRS.

CONCLUSIONS

There are multiple possible management options for patients with CRS. The clinician should first attempt to phenotype/endotype these patients based on history, laboratory evaluation, endoscopic findings, histology, as proper identification can aid in selection of the most appropriate therapy. Intranasal corticosteroids (no matter the method of delivery) and nasal irrigation are appropriate first steps in management. In the setting of AFRS, surgery is required as a first step in management. Add on therapies for treatment failure should be based on phenotype/endotype and should take into account efficacy, safety, cost effectiveness, and shared decision making with the patient as there is no single best “next step” in therapy.

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Table 1. Anti-Type 2 biologics approved or undergoing phase-three studies for therapeutic treatment of CRSwNP

Biologic/ Clinical Trials	Pharmacology	Recommended dose	Main outcomes	Secondary outcomes (Significant improvement vs placebo at Week 24 for dupilumab and omalizumab, at Week 52 for mepolizumab)	Adverse reaction
Dupilumab/ LIBERTY NP SINUS 24 and 52¹¹³	Anti-IL-4R alpha; targets IL4 and IL-13	300 mg every 2 weeks subcutaneously	LS mean change from baseline (SE) and LS mean difference vs placebo (95% CI; p value) <i>Sinus 24:</i> - NPS (scale 0-8): -1.89 (0.14), and vs placebo: - 2.06 (-2.43 to -1.69; p<0.0001) - NCS (scale 0-3): -1.34 (0.07), and vs placebo: - 0.89 (-1.07 to -0.71; p<0.0001) <i>Sinus 52:</i> - NPS (scale 0-8): -1.71 (0.11), and vs placebo: - 1.80 (-2.10 to -1.51; p<0.0001) - NCS (scale 0-3): -1.25 (0.06), and vs placebo: - 0.87 (-1.03 to -0.71; p<0.0001)	- Quality of life (SNOT-22) - Sense of smell - Total nasal symptom score - Radiographic assessment (Lund-Mackay score) - Increased time to oral corticosteroids or surgery	Injection site reaction, transient eosinophilia, EGPA, conjunctivitis
Omalizumab/ POLYP 1 and POLYP 2¹¹⁴	Anti-IgE	Weight and IgE level based every 2 weeks or 4 weeks subcutaneously	Mean change from baseline (SE) and vs placebo (95% CI; p value) <i>Polyp 1:</i> - NPS (scale 0-8): -1.08 (0.16), and vs placebo: -1.14 (-1.59 to -0.69; p<0.0001) - NCS (scale 0-3): -0.89 (0.10), and vs placebo: -0.55 (-0.84 to -0.25; p=0.0004) <i>Polyp 2:</i> - NPS (scale 0-8): -0.90 (0.17), and vs placebo: -0.59 (-1.05 to -0.12; p=0.0140) - NCS (scale 0-3): -0.70 (0.11), and vs placebo: -0.50 (-0.80 to -0.19; p=0.0017)	- Quality of life (SNOT-22) - Sense of smell - Total nasal symptom scores Trend to reduced need for surgery and rescue therapy*	Headache, injection site reaction, arthralgia, upper abdominal pain
Mepolizumab/ SYNAPSE¹¹⁵	Anti-IL-5	100 mg every 4 weeks subcutaneously	Median change from baseline and treatment effect (95% CI; p value) NPS (scale 0-8): - 1.00, and vs placebo -0.73 (-	- Improved overall symptom VAS - Quality of life	No different than placebo Nasopharyngitis

			1.11 to -0.34; $p < 0.001$) • NOS VAS score (scale 0-10): -4.41, and vs placebo -3.14 (-4.09 to -2.18; $p < 0.0001$)	(SNOT-22) • Loss of smell • Reduced need for surgery and oral corticosteroids	
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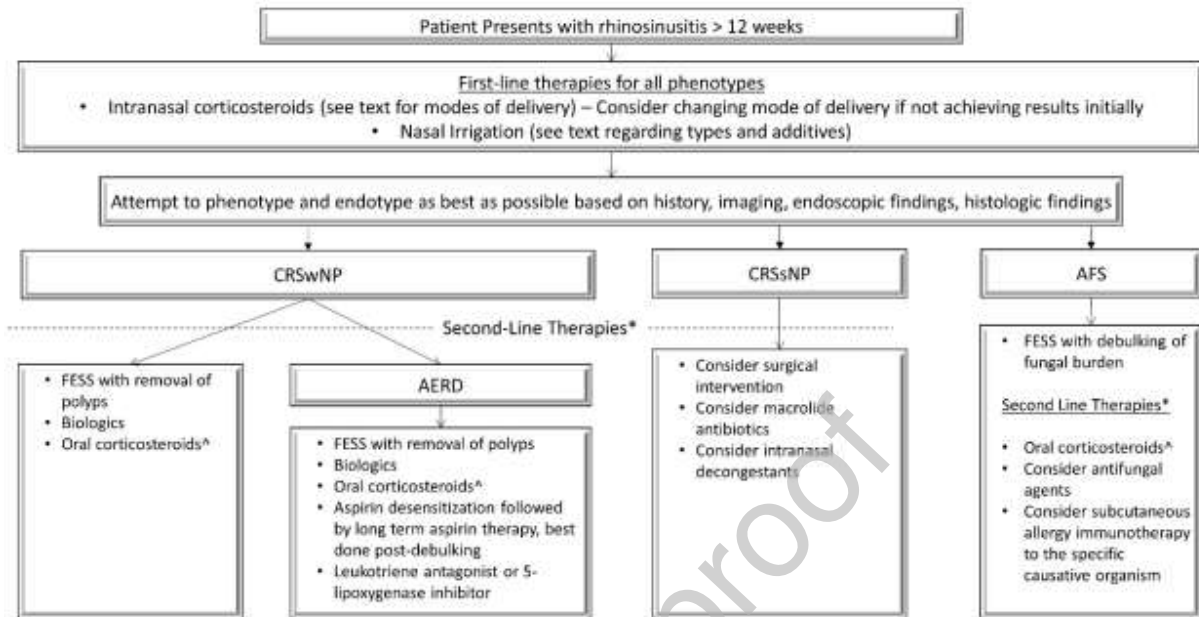
*There was reduced proportion of patients requiring corticosteroids and surgery, that was not statistically significant.

R- receptor LS - Least Squares; SE – Standard error; NPS- nasal polyp score; NCS- nasal congestion score; NOS- nasal obstruction CI –confidence interval.

EGPA – Eosinophilic granulomatosis with polyangiitis; VAS – visual analogue scale

Data from phase III evaluating benralizumab (“OSTRO III”) were not available at the time of writing.

Figure 1. Proposed algorithm for the management of chronic sinusitis



*Second Line therapies are not listed in order of recommendation or preference

[^]Oral steroids should be limited in use and not as chronic therapy