

Role of Medical Therapy in the Management of Nasal Polyps

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Abstract Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease of the nasal and paranasal sinus mucosa that, despite differing hypotheses regarding its cause, remains poorly understood. Major symptoms are nasal congestion or blockage, loss of smell, rhinorrhea, postnasal drip, and facial pain or pressure. Among the objectives of CRSwNP management are to eradicate nasal polyps from nasal and sinus cavities, eliminate symptoms, and prevent recurrences. Corticosteroids are the mainstay of treatment and are the most effective drugs for treating CRSwNP. Other potential treatments are nasal saline irrigation and antihistamines (in allergic conditions). Endoscopic sinus surgery is recommended when medical treatment fails. After surgery, medical treatment, including nasal and oral corticosteroids, is recommended.

Keywords Chronic rhinosinusitis · Antibiotics · Antihistamines · Antibiotics · Anti-IL-5 · Antileukotrienes · Corticosteroids · Macrolides · Nasal decongestants · Nasal douching · Omalizumab · Nasal polyps · Medical therapy · Management

Introduction

Chronic rhinosinusitis (CRS), with or without nasal polyps, affects 11% of the European population [1], while CRS with nasal polyps (CRSwNP) is an inflammatory condition of

unknown etiology that is present in 2% to 4% of the European adult population [2]. CRSwNP is often associated with asthma and other respiratory diseases, such as cystic fibrosis, primary ciliary dyskinesia, aspirin sensitivity, and idiopathic bronchiectasis [3, 4]. Although CRSwNP is not a life-threatening disease, it can significantly decrease an individual's quality of life [5–8]. CRSwNP appears as grape-like structures in the upper nasal cavity, originating from the ethmoid sinus. They consist of loose connective tissue, edema inflammatory cells, along with some glands and capillaries. They are covered with varying types of epithelium, mostly respiratory pseudostratified epithelium with ciliated cells and goblet cells. Eosinophils are the most common inflammatory cells in nasal polyps, but neutrophils, mast cells, plasma cells, lymphocytes, and monocytes are also present, as well as fibroblasts. Interleukin (IL)-5 is the predominant cytokine in CRSwNP, inducing the activation and prolonged survival of eosinophils [2, 9].

In the international rhinosinusitis guidelines (EPOS) [2], CRSwNP has been defined as inflammation of the sinonasal mucosa with nasal congestion in combination with nasal discharge and/or facial pain/pressure and/or reduction or loss of smell for more than 12 weeks; and endoscopic signs of polyps and/or edema/mucosal obstruction in middle meatus; and/or CT changes within the ostiomeatal complex and/or sinuses. Several mechanisms have been proposed for the development of CRSwNP, but the common mechanism seems to be an integrated process involving the mucosal epithelium, extracellular matrix, and inflammatory cells and mediators. In a postulated, cell-mediated immune reaction in the pathogenesis of nasal polyp formation, steroids would act on the immune system by inhibiting cytokine production from a number of cells, such as T cells, eosinophils, or epithelial cells [10, 11]. In addition to T-cell activation, several studies have demonstrated leukotriene release as well as other arachidonic acid metabolites in nasal

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polyps from patients with CRSwNP, asthma, and aspirin sensitivity [12–14].

The treatment of CRSwNP has been a major subject of various studies resulting from respective consensus groups and task forces in the United States [15] and Europe [2]. The objectives of CRSwNP management are to eradicate nasal polyps from nasal and sinusal cavities, eliminate symptoms, and prevent recurrences. Although the effect of corticosteroids is potent, their use in CRSwNP has been a subject of discussion for many decades. Many patients undergo extensive medical management and multiple surgeries and still experience continuous relapses. Most authors agree on the fact that management of NP should be based primarily on a medical approach to be addressed by surgical procedures only in the case of drug failure [16–19].

Medical Treatment of Chronic Rhinosinusitis with Nasal Polyps

The introduction of topically administered corticosteroids has improved the treatment of upper and lower airway inflammatory disease. The clinical efficacy of corticosteroids may depend in part on their ability to reduce airway eosinophil infiltration by preventing their increased viability and activation. Both topical and systemic corticosteroids may affect the eosinophil function by both directly reducing eosinophil viability and activation [20–22] and indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells [23]. The potency of these effects is lower in nasal mucosa than in nasal mucosa tissue, suggesting an induced inflammatory resistance to steroid treatment in nasal polyps [24, 25].

Topical Corticosteroids

Mygind et al. [26] showed that beclomethasone dipropionate administered daily for 3 weeks reduced nasal symptoms in patients with CRSwNP compared with a control group of patients treated with placebo. In another study with beclomethasone dipropionate administered daily for 4 weeks (double-blind, crossover), Deuschl and Drettner [27] found a significant improvement in the symptoms of blockage and nasal patency measured with rhinomanometry. A difference in size of polyps was not observed. In a randomized, double-blind, parallel, placebo-controlled study with budesonide for 4 months, Holopainen et al. [28] showed total mean score and peak nasal inspiratory flow (PNIF) in favor of budesonide. Polyps also decreased in size in the budesonide group. Tos et al. [29] also showed that budesonide in spray and powder were significantly more effective than placebo with regard to reduction of polyp size, improvement in sense of smell, and reduction of symptom score. Vendelo Johansen et

al. [30] tested budesonide compared with placebo for 3 months in a multicenter, randomized, double-blind study among patients with small and medium-sized nasal polyps. Polyps decreased in the budesonide group, while an increase was seen in the placebo group. Both nasal symptoms and PNIF improved in the budesonide group. Lildholt et al. [31] compared budesonide, 400 or 800 µg/d, with placebo for 4 weeks. Symptom relief was significant in both budesonide groups compared with placebo, but there was no significant difference in polyp size between the groups as measured by the investigators. PNIF was significantly improved in the budesonide group and increased during the study; however, no difference was noted for sense of smell. Holmberg et al. [32] used fluticasone propionate, budesonide, and placebo for 26 weeks in a double-blind, parallel group in which patients with polyps, grades 1 and 2, were investigated. There was a significant improvement in symptoms and PNIF for both steroid groups compared with placebo.

Keith et al. [33] compared fluticasone propionate nasal drops with placebo in a placebo-controlled, parallel-group, multicenter, randomized study for 12 weeks. Although polyp reduction was not significant, nasal blockage and PNIF significantly improved in the fluticasone propionate nasal drops group. Penttila et al. [34] tried fluticasone propionate nasal drops, 400 and 800 µg, and placebo daily for 12 days in a randomized, double-blind, multicenter study for a dose-response analysis. Nasal symptoms as well as PNIF were significantly reduced in both fluticasone propionate groups. Lund et al. [35] compared fluticasone propionate, budesonide, and placebo for 12 weeks in a double-blind, randomized study. Polyp score was significantly improved in the fluticasone propionate group. Acoustic rhinometry improved in both active groups. PNIF improved in both active groups but did so faster with fluticasone propionate. Overall symptoms did not differ statistically between the groups after treatment. Aukema et al. [36] sought to investigate in a 12-week, double-blind, placebo-controlled study whether treatment with fluticasone propionate nasal drops could reduce the need for surgery in 54 patients with severe CRSwNP who were on the waiting list for functional endoscopic sinus surgery. It was found that surgery was no longer required in 13 of 27 patients treated with fluticasone propionate nasal drops, compared with 6 of 27 in the placebo group. Six patients from the placebo group dropped out, in contrast to only one from the fluticasone propionate nasal drops group. Nasal symptoms were reduced in the fluticasone propionate group and PNIF increased significantly.

Small et al. [37] reported on 354 individuals who were divided into 3 groups and received mometasone furoate once or twice daily or placebo for 4 months. In both mometasone furoate groups, significant polyp reduction was seen in addition to improvement in loss of smell, rhinorrhea, and nasal congestion. Regarding congestion/obstruction, twice-

daily was superior to once-daily administration, while both doses significantly increased PNIF. A comparable study was performed by Stjärne et al. [38] using twice-daily mometasone furoate, which had a significant effect in reducing polyp size, whereas once-daily administration was not statistically effective compared with placebo. Both mometasone furoate doses significantly improved congestion/obstruction as well as PNIF; however, no improvement in sense of smell was seen after 4 months. A third study, also by Stjärne et al. [39], in 298 individuals with mild to moderate nasal polyps compared the treatment with nasal mometasone furoate once daily with placebo during 16 weeks. They found a significant decrease in nasal congestion and polyp size, together with improvement in sense of smell, PNIF, and quality of life. Vlckova et al. [40] demonstrated that fluticasone propionate, 400 µg twice daily, administered using OptiNose's breath actuated bidirectional delivery device, was an effective and well-tolerated treatment of mild to moderate CRSwNP. Hansen et al. [41] also demonstrated that the OptiNose administering fluticasone propionate, 400 µg twice daily, is an effective and well-tolerated treatment. A recent Cochrane review suggested that topical steroids for CRSwNP in patients with cystic fibrosis have no demonstrable effect on subjective nasal symptom scores. They have some effect in reducing polyp size, but due to the small sample size, poor study completion rates, and lack of follow-up, the study is at high risk of bias and evidence for efficacy is limited. Overall, no clear evidence exists for using topical steroids in cystic fibrosis patients with CRSwNP [42]. Topical corticosteroids have been demonstrated to be effective (Ib) and are recommended (A) in CRSwNP patients.

Oral Steroids

Corticosteroids exert their anti-inflammatory effect by acting on specific receptors present in all human cells, including nasal polyp tissue [43]. The reason why some nasal polyp phenotypes are resistant to intranasal corticosteroids, increasing the need for intermittent short courses of oral corticosteroids and finally for surgery, is not well-understood. However, some hypotheses dealing with abnormal corticosteroid receptor expression or a reduced effect of corticosteroids on nasal polyp fibroblast proliferation have been postulated [44]. Until now, only a few randomized studies have reported a beneficial effect of combined oral and intranasal glucocorticoids in CRSwNP [7, 45–49]. Benitez et al. [45] performed a randomized controlled study. After 2 weeks on oral prednisone, patients with CRSwNP continued for 10 weeks on intranasal budesonide. After 2 weeks, a significant reduction in polyp size with improvement on symptoms and nasal patency was observed compared with a control group. After 12 weeks of steroids, a

reduction in CT changes was observed. An additional study extended the follow-up to 48 weeks, showing an improvement in quality of life resulting from combined oral and intranasal corticosteroid treatment [6]. In a double-blind, randomized, placebo-controlled study, Hissaria et al. [46] compared prednisolone, 50 mg/d for 14 days, with placebo. A significant improvement was found in nasal symptoms, polyp size, and MRI, supporting the effect of oral steroids on CRSwNP. In a randomized, double-blind, placebo-controlled study, Van Zele et al. [47] showed that a short course of oral methylprednisolone (32 mg/d initially and tapered off for 20 days) also improved nasal symptoms, loss of smell, polyp size, nasal patency, and nasal and blood inflammatory markers in CRSwNP, with these effects being maximal at 14 days and lasting up to 30 (nasal congestion, smell) or 50 (polyp size) days of follow-up. In a recent randomized controlled study, patients with CRSwNP ($n=60$) were randomly allocated to oral prednisolone, 25 mg/d, or placebo for 2 weeks, followed in both groups by fluticasone propionate nasal drops, 400 µg twice daily, for 8 weeks and then fluticasone propionate nasal spray, 200 µg twice daily, for 18 weeks [48]. The authors concluded that initial oral steroid therapy followed by topical corticosteroids seems to be more effective over 6 months than topical corticosteroids alone in decreasing polyp size and improving olfaction in patients with at least moderate CRSwNP. A recent Cochrane review identified a short-term benefit of oral steroids in patients with multiple CRSwNP [50].

There is no study available on depot injection of corticosteroids or local injection into the inferior turbinate. These types of treatment are actually obsolete due to the risk of fat necrosis at the site of the injection or blindness following endonasal injection. A recent study by Becker et al. [51] studied 358 CRSwNP patients with a mean follow-up of 30 months. Intra-polyp corticosteroid injection was associated with a significantly lower rate of complications than surgical excision of polyps, which may decrease the need for further surgical intervention of polyps. Oral steroids have been demonstrated to be effective (Ia) and are recommended (A) in CRSwNP patients.

Oral Antibiotics

Short-Term Oral Antibiotics

Enterotoxins produced by *Staphylococcus aureus* can act as superantigens and thus influence the course of CRSwNP. After surgery, 23 patients who tested positive in a perioperative culture for *S. aureus* strains producing enterotoxins A to E and toxic shock syndrome toxin-1 were randomly assigned to one of two groups: group A, who in addition to standard treatment received oral antistaphylococcal antibiotics for 3 weeks, and group B, who received placebo

[52]. Both groups were compared preoperatively and at 3 and 6 months after surgery using a symptom-specific score, an endoscopic score, and the Sino-Nasal Outcome Test (SNOT)-22 quality-of-life questionnaire. Patients who received antibiotic therapy achieved slightly better results. However, the differences were not statistically significant. Regardless of postoperative treatment, approximately 30% of patients had an *S. aureus*-negative culture 6 months after surgery.

Although there was no major difference in the presence of enterotoxin genes in *S. aureus* strains derived from nasal polyp or control patients, we found an increased immune response to *S. aureus* enterotoxins in nasal polyps that resulted in a more pronounced eosinophilic inflammation and higher total IgE production in those polyps affected. We suggest that *S. aureus* superantigens amplify the inflammation in about 50% of CRSwNP cases, resulting in a strong T-helper type 2 polarization, eosinophil activation, and an overproduction of IgG₄ and IgE. These findings point to new therapeutic approaches aside from the currently used topical and systemic steroid therapy for CRSwNP. In a double-blind, placebo-controlled study, it was shown that a low dose of doxycycline treatment for 20 days had a sustained, clinically relevant effect on polyp size for more than 3 months [53]. In another double-blind, placebo-controlled study, CRSwNP patients ($n=47$) were treated with methylprednisolone in decreasing doses (32–38 mg once daily), doxycycline (200 mg on the first day, followed by 100 mg once daily), or placebo for 20 days. In this study, data showed a significant effect of oral methylprednisolone and doxycycline on polyp size, nasal symptoms, and mucosal and systemic markers of inflammation [47]. Although these studies suggest some effect on nasal polyps, there are still not enough data to recommend the use of short-term antibiotics in CRSwNP patients.

Long-Term Oral Antibiotics

In a prospective study, patients with CRS without nasal polyps (CRSsNP) or CRSwNP ($n=90$) were randomly assigned to receive medical treatment with an oral macrolide during 3 months or surgery and were observed over 1 year [54]. Outcome assessment included symptoms (visual analogue scale [VAS]), quality of life (SNOT-22 and the Medical Outcomes Survey Short Form-36 [SF-36] health survey), nasal nitric oxide, acoustic rhinometry, saccharine clearance time, and nasal endoscopy. Both medical and surgical treatments of CRS improved, with no significant improvement difference being shown between the two groups or between CRSsNP and CRSwNP (except for nasal volume, which was greater after surgery and in the CRSwNP patients). Sixty patients with CRSsNP and CRSwNP were treated with azithromycin or placebo. On

the SNOT-22, Patient Response Rating Scale, VAS scores, and SF-36, no significant differences between the azithromycin and placebo groups were demonstrated. Likewise, no relevant significant differences between the groups were shown in nasal endoscopy, PNIF, smell tests, or microbiology [55]. The currently data are not sufficient to recommend the use of long-term antibiotics in CRSwNP patients.

Nasal Decongestants

Clinical trials before and after decongestant application in patients with nasal polyps did not show any densitometry changes in the sinuses or in polyps, and only some decongestion was observed in the inferior turbinate [56]. A randomized, double-blind, placebo-controlled trial did not show any difference among placebo, epinephrine, and naphazoline with regard to polyp size [57]. Not enough existing data are available to recommend the use of nasal decongestants in CRSwNP patients.

Antihistamines

One randomized, placebo-controlled trial on antihistamines in CRSwNP patients was identified [58]. Forty-five surgically treated patients with residual or recurrent nasal polyps received cetirizine, 20 mg, or placebo for 3 months. Polyp size, nasal symptom score at follow-up visits, and nasal symptoms by daily diary cards served as outcome parameters. The number and size of polyps remained unchanged during the study period. Nasal symptom scores at follow-up visits did not significantly differ between the two treatment methods. In the daily diary cards, significantly fewer days with a symptom score of 1 or less were observed for nasal hypersecretion (weeks 1–4, 5–8, and 9–12), sneezing (weeks 1–4 and 5–8), and nasal obstruction (weeks 9–12). However, daily diary scores above 1 were rare for nasal hypersecretion and sneezing in the entire study population [58]. Based on current data, antihistamines are not recommended for the treatment of CRSwNP (D). In patients with concomitant allergic rhinitis, antihistamines may be recommended (A).

Antifungal Therapy

Ricchetti et al. [59] combined topical steroid treatment with amphotericin B in 74 patients with CRSwNP for 4 weeks and found 48% disappearance of the polyps at endoscopy in previously endoscopically operated patients. In a double-blind, randomized, placebo-controlled trial of patients with CRSwNP ($n=60$), topical amphotericin B was not shown to be superior, but rather was even worse than saline in CT and subjective scores [60]. An open randomized trial suggested that adding amphotericin B to lysine aspirin (LAS) in a

long-term topical treatment may be beneficial in terms of recurrence protection [61]. Recurrence after 20 months was found in 13 of 25 patients treated with LAS after surgery and in 15 of 25 after medical polypectomy and LAS, and 5 of 16 after surgical polypectomy and 7 of 23 after medical polypectomy protected with LAS and amphotericin B, respectively. Low fungal detection indicates that the presumed protective effect of amphotericin B added to LAS may not be due to antifungal effect [61]. A multicenter, randomized, placebo-controlled, double-blind trial conducted in 120 patients (80% with CRSwNP) using nasal lavage for 3 months confirmed no benefit with amphotericin B added to nasal lavage when compared with placebo lavage in the treatment of CRS [62]. No difference between amphotericin B and placebo was found in terms of subjective and objective improvement measures. Patients on placebo showed an improvement in postnasal drip and rhinorrhea in the non-asthma subgroup, while PNIF significantly deteriorated in patients treated with amphotericin B [62]. Topical amphotericin B had no significant effect on the level of any of the proinflammatory cytokines, chemokines, or growth factors in nasal lavage samples in patients with CRS with and without nasal polyps [63]. Gerlinger et al. [64] investigated the effect of amphotericin B nasal spray on CRSwNP-operated patients. These results led to the conclusion that amphotericin B does not give rise to a significant alteration in CT score, clinical symptoms, or quality of life. The more favorable clinical aspects observed in the amphotericin B-treated group during the endoscopic follow-up did not correspond to an improvement in symptoms. As several recent randomized clinical trials have reported important negative outcomes (Ib-), antifungal treatment is not recommended (A) in CRSwNP patients.

Antileukotrienes

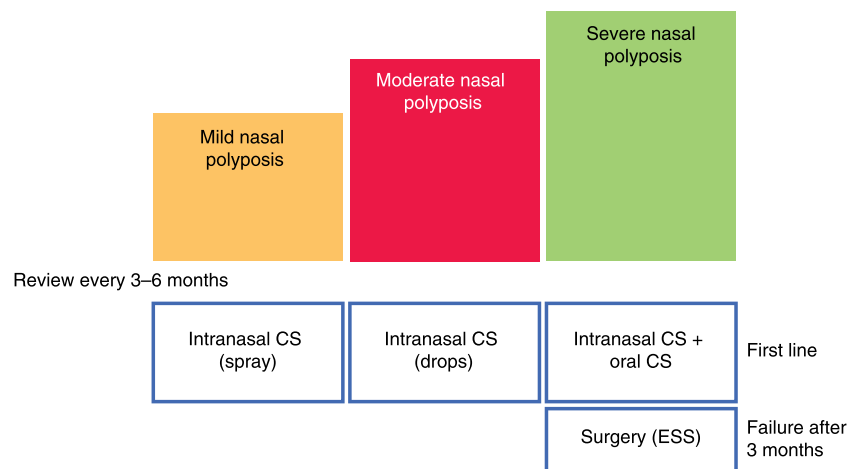
Zileuton or zafirlukast treatment in 36 patients with CRSsNP or CRSwNP added to standard treatment resulted in a significant improvement in nasal symptoms scores. Overall improvement was noted by 72% of the patients, and side effects occurred in 11% [65]. In 15 aspirin/salicylic acid triad patients, the addition of antileukotriene resulted in 9 of 15 (60%) patients showing sinusitis improvement, and an overall benefit was seen in 12 of 15 (80%) patients, confirmed by endoscopy [66]. In a group of CRSwNP patients, subjective improvement in nasal symptoms occurred in 64% of aspirin-tolerant patients and 50% of aspirin-sensitive patients. Significant improvements in PNIF only occurred in aspirin-tolerant patients [67]. A double-blind, comparative study of 40 patients compared the effects of the leukotriene receptor antagonist montelukast (10 mg/d) and beclomethasone nasal spray (400 µg) on the postoperative course of patients with CRSwNP. No significant

differences were found between these two postoperative treatments in the year following surgery [68]. In a randomized, placebo-controlled trial, 20 patients with nasal polyps were treated with montelukast, 10 mg/d, and 10 patients received placebo treatment for 4 weeks. Nasal polyp scores, eosinophilia/cationic protein levels in nasal secretions, and health-related quality of life were assessed before and after treatment. No significant changes in polyp scores and nasal eosinophilic/cationic protein levels were observed. In some health-related quality-of-life parameters, better scores were observed in the treatment group [69]. In a randomized controlled trial without allocation concealment, 38 consecutive adult patients with bilateral nasal polyps were treated with oral prednisolone for 14 days and budesonide nasal spray for 8 weeks ($n=18$). Twenty individuals received similar treatment with additional oral montelukast, 10 mg/d, for 8 weeks. Concomitant nasal allergy was more frequent among montelukast-treated patients. When compared with patients treated with steroid alone, those treated with montelukast showed a significant reduction in symptom scores at 8 weeks with respect to headache, facial pain, and sneezing. However, montelukast therapy did not have a significant effect on the overall symptom score or on symptoms of nasal blockage, hyposmia, or nasal discharge [70]. More recently, montelukast has been shown to reduce nasal polyp eosinophilic inflammation by both reducing cytokines and eosinophil viability [71]. Vuralkan et al. [72] studied the effects of montelukast and intranasal mometasone on the postoperative course of 50 patients with CRSwNP. There was a significant reduction in SNOT-22 scores in both groups throughout the study period. A significant difference was also noted in the recurrence rate between both groups, with mometasone showing a marginal advantage. Eosinophils in peripheral blood were found to be effective with regard to recurrence rate. It was concluded that both drugs seem to have a complementary action [72]. Antileukotrienes have shown a limited level of efficacy (III) and have a low degree of recommendation (C) in CRSwNP patients.

Aspirin Desensitization

Systemic aspirin desensitization or topical LAS treatment may be implicated in protection against CRSwNP recurrence. Sixty-five aspirin-sensitive asthmatics underwent aspirin challenge, followed by aspirin desensitization and daily treatment with aspirin over 1 to 6 years. There were significant reductions in numbers of sinus infections and an improvement in olfaction. Numbers of sinus/polyp operations per year and doses of nasal corticosteroids were significantly reduced. There were also reductions in hospitalizations and the use of oral steroids for asthma treatment [73]. Nucera et al. [74] followed 3 groups of

Fig. 1 Evidence-based management for adults with chronic rhinosinusitis with nasal polyps. CS corticosteroids, ESS endoscopic sinus surgery



CRSwNP patients (~50% aspirin sensitive)—the first with 76 consecutive nasal polypectomy patients who had a topical LAS afterward, the second with 49 patients with 40 mg triamcinolone retard and also further LAS, and the third with 191 control patients who only underwent polypectomy. The group treated with LAS postoperatively had a recurrence rate of 6.9% after 1 year and 65% after 6 years, whereas controls experienced recurrence in 51.3% at 1 year and 93.5% at 6 years after the operation. Systemic glucocorticoids and nasal LAS resulted in 33% with unchanged polyp size after 3 years, compared with 15% in the operated group. However, this was not statistically significant [74]. A case–control trial of treatment with LAS to one nostril and placebo to the other in 13 patients with bilateral nasal polyps resulted in delayed polyp recurrence, and 8 remained symptom free at the 15-month observation period, which was significantly better than results of the patients previously treated with steroids for recurrence prevention. Endoscopy and acoustic rhinometry indicated a lower polyp size on the aspirin-treated side [75]. One double-blind, randomized, placebo-controlled trial did not demonstrate any effect on nasal airway using 16 mg of intranasal LAS every 48 h compared with placebo treatment in aspirin-sensitive patients after 6 months of treatment [76]. Outcomes included subjective symptom scores, acoustic rhinometry, PNIF, and peak expiratory flow. A significant decrease of the Cys-LT₁ receptor in the turbinate mucosa of the patients with active treatment was found compared with the placebo group. However, the addition of intranasal LAS in doses of up to 50 mg/d to routine therapy reduced polyp size and did not adversely affect asthma [77]. Although the mechanisms by which aspirin desensitization benefits patients are not completely understood, aspirin therapy results in reduced leukotriene levels. There is currently level Ib of evidence with recommendation A to use aspirin desensitization in aspirin-sensitive patients, although the evidence and recommendation to treat CRSwNP patients are still low.

Antibodies

Anti-IgE

In several investigations, total IgE levels in nasal secretions, nasal polyp homogenisates, and blood serum were higher in patients with CRSwNP than in controls. Omalizumab, a recombinant, DNA-derived humanized IgG_{1k} monoclonal antibody that selectively binds to human IgE, reduces serum and tissue IgE levels. Omalizumab is approved for patients with moderate to severe allergic asthma. Two anecdotal reports [78, 79] and one pilot study in eight patients [80] showed beneficial effects of omalizumab in CRSwNP. Pinto et al. [81] conducted a randomized, double-blind, placebo-controlled trial of anti-IgE for CRS in 14 patients (12 of 14 with CRSwNP) refractory to standard treatment, including sinus surgery. All patients received omalizumab, 0.016 mg/kg per IU, total serum IgE/mL subcutaneously, or placebo injections every 4 weeks for 6 months. The main outcome parameter was pretreatment and post-treatment sinus opacity in coronal CT scans. The median change in sinus opacity in omalizumab-treated patients was 11.9%, compared with

Table 1 Summary of treatment evidence and recommendations for adults with chronic rhinosinusitis with nasal polyps

Treatment ^a	Evidence level/ recommendation	Relevance?
Topical corticosteroids	Ib, A	Yes
Oral steroids	Ia, A	Yes
Nasal douching	Ib, A	Yes (symptomatic)
Oral antihistamines (only in allergic patients)	Ib, A	Yes

^a Not enough data are available on efficacy for a variety of medications: antileukotrienes (III, C), topical antibiotics, short- and long-term oral antibiotics, antimycotics, nasal decongestants, aspirin desensitization, antibodies (anti-IgE, anti-interleukin-5), mucolytics, phytopreparations, immunomodulators, capsaicin, or proton pump inhibitors

5.9% in placebo-treated patients ($P<0.391$). No significant differences were found in various secondary outcome parameters, including SNOT-20, olfactory test, endoscopy, eosinophils, and PNIF. Vennera et al. [82] recently evaluated the evolution of 19 patients who were treated with omalizumab for severe asthma and who also had CRSwNP. Polyp size was significantly reduced at the end of follow-up (3 months) compared with baseline. None of the patients needed additional surgery during omalizumab treatment. Furthermore, there was a clear reduction in the proportion of patients using intranasal corticosteroids between baseline and the end of the follow-up period (95% vs 42%; $P<0.002$). Based on current data, the evidence for efficacy of omalizumab is very low, and more studies are needed in order to recommend its use in the treatment of CRSwNP patients (D).

Anti-Interleukin-5

Interleukin-5 is a key activator in eosinophil growth, recruitment, and activation. High amounts of IL-5 were detected in polyp homogenates, nasal secretions, and blood serum of patients with nasal polyps. Mepolizumab and reslizumab are humanized anti-IL-5 monoclonal antibodies that reduce the number of eosinophils in blood and tissues [83]. Individuals with bilateral nasal polyps ($n=24$) were randomly assigned to receive reslizumab or placebo. At no individual time point, a significant improvement in symptoms and PNIF was observed in both treatment groups compared with placebo. The total nasal polyp score was significantly decreased in the 1-mg/kg group at week 12 when compared with baseline values; however, this was not the case when compared with the control group. Blood eosinophil counts dropped significantly in both active groups, followed by a steep increase above baseline values 8 to 19 weeks postinjection, suggesting a rebound hypereosinophilia. Patients with nasal secretion IL-5 levels greater than 40 pg/mL were more likely to reveal a reduction of at least one polyp score on an eight-point scale when treated with anti-IL-5 [84]. In a further randomized, double-blind, placebo-controlled study, CRSwNP patients received mepolizumab ($n=20$) or placebo ($n=10$). Twelve of 20 patients receiving mepolizumab had a significantly improved polyp size and sinus opacity, compared with 1 of 10 patients receiving placebo at week 8 versus baseline. The authors concluded that IL-5 inhibition is a potential novel therapeutic approach in patients with severe eosinophilic nasal polyps [85]. Currently, anti-IL-5 antibodies are still not recommended in the treatment of CRSwNP.

Immunosuppressants

In steroid-dependent asthma, immunosuppressants, including methotrexate, may help reduce the steroid dosage. Two anecdotal reports indicate that CRSwNP may substantially

improve when methotrexate is given in steroid-dependent asthma or malignant conditions with concomitant CRSwNP [86, 87]. Based on current data, the use of immunosuppressants is not recommended in CRSwNP patients.

Saline Douching

Several controlled studies have assessed the effect of isotonic and hypertonic saline in CRS [2]. Freeman et al. [88] recently investigated the effect of saline douching of one side of the nasal cavity for 6 weeks in patients with CRSwNP and CRSsNP after endoscopic sinus surgery. The authors concluded that saline douching reduces nasal discharge and may improve edema during the healing phase following endoscopic sinus surgery, suggesting a potential anti-inflammatory role. No long-term effect was found. Nasal douching has a high level of evidence (Ib) and is recommended (A) in the treatment of CRSwNP.

Conclusions

Intranasal corticosteroids and, occasionally, short courses of oral steroids are the most effective drugs for treating CRSwNP and constitute the first line of treatment (Fig. 1). Other effective treatments are nasal saline irrigation and antihistamines (in allergic conditions) (Table 1). Although some products have not shown real efficacy (antibiotics, antifungals, nasal decongestants, proton pump inhibitors), others have some efficacy but need more investigation to receive full recommendation (antileukotrienes, aspirin desensitization, antibodies [anti-IgE, anti-IL-5], and immunosuppressants). Finally, endoscopic sinus surgery is recommended when medical treatment fails, and after surgery, follow-up and medical treatment, including nasal and oral corticosteroids, are recommended.

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