

Evidence-Based Management of Nasal Polyposis by Intranasal Corticosteroids: From the Cause to the Clinic

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Key Words

Eosinophils • Inflammation • Intranasal corticosteroids • Nasal polyposis

Abstract

Background: Nasal polyposis is an inflammatory disorder involving the mucosa of the nose and paranasal sinuses and affecting approximately 2–4% of the general population. **Methods:** A literature search of Medline and Embase was conducted to obtain an overview of the epidemiology, pathophysiology, and current treatment of nasal polyposis, focusing on evidence-based efficacy of intranasal corticosteroids (INSs) as primary and postoperative therapy. Recent research on INSs in nasal polyp treatment, along with notable historic findings, was reviewed. **Results:** Nasal polyps are mostly characterized by eosinophil infiltration, a complex inflammation of nasal mucosa, and possibly production of polyclonal IgE. Current treatment modalities include INSs, oral corticosteroids, and surgery; surgery is generally limited to those with an insufficient response to medical treatment. Because of their effects on eosinophil-dominated inflammation, INSs and oral corticosteroids are the primary medical treatment strategies. The very low ($\leq 1\%$) systemic bioavailability of newer INSs minimizes the systemic adverse effects

seen with oral corticosteroids. **Conclusion:** Based on randomized, controlled trials, guidelines recommend INSs as first-line therapy for nasal polyps and for care after polypectomy. Clinical data suggest INSs are effective in reducing polyp size and relieving nasal symptoms. INS treatment has also reduced nasal polyp recurrence in patients undergoing functional endoscopic sinus surgery. Treatment with these mainstay options has been found to improve quality of life, which, along with symptom improvement, is a key factor in disease treatment.

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Introduction

Nasal polyposis (NP) is an inflammatory disorder involving the mucosa of the nose and paranasal sinuses [1, 2]. Approximately 2–4% of the general population are affected by NP, and the prevalence tends to increase with age [3–5]. NP is approximately twice as common in males as females, possibly because of the greater degree of smoking and exposure to occupational dusts and chemicals in males than in females [4, 6]. Results of a survey of more than 1,000 patients with NP revealed that men were 2.3 times more likely to be smokers and 2.5 times more like-

ly to have been exposed to occupational dusts and chemicals than were women [7]. NP may also have a genetic component. The disorder has been found in several members of the same family, although studies on monozygotic twins have not always identified NP in both siblings [8]. The incidence is also higher in patients with airway diseases than in the general population. For example, NP has been found in 36–96% of aspirin-intolerant people, 7% of adults with asthma, 10% of children and 50% of adults with cystic fibrosis, 66–100% of people with allergic fungal sinusitis, and 40% of those with primary ciliary dyskinesia [8–11].

Characteristic symptoms of NP include nasal obstruction, congestion, discharge, and occasionally purulence, with more than 75% of patients experiencing impairment or loss of sense of smell [12–14]. Consequently, NP can have a marked, detrimental effect on quality of life (QoL), including physical and social functioning and mental health [15, 16]. Improvement in QoL has become an increasingly important factor in the management of NP [8, 15, 16]. The disease is also associated with significant treatment-related costs. A retrospective study ($n = 2,652$) in patients with NP found annual per patient costs of USD 2,757 for nasal polyp surgery and an additional USD 3,979 per patient for postsurgical visits and procedures. Costs for prescription drugs averaged from USD 550 to 700 per patient per year [1].

The goals of treatment are to eliminate polyps or reduce their size and number, open the nasal airway, improve or restore the sense of smell, prevent recurrence after surgery, and improve QoL [17, 18]. Management of nasal polyps focuses on drug treatment approaches, with first-line options being oral and intranasal corticosteroids (INs), reserving surgery for patients who do not respond to medical treatment [8].

This paper aims to provide a useful summary of the epidemiology and inflammatory pathophysiology of NP and of the evidence-based efficacy of oral and IN treatment and surgical intervention. The review also briefly discusses future perspectives of nasal polyp treatment.

Methods

Literature searches of Medline and Embase were conducted from January 1980 through February 2008, a period of continuing clinical research into the use of corticosteroids in the treatment of NP. Additionally, Medline was searched for relevant clinical studies conducted and published until September 2009. The search sought to identify primary and review articles about the epidemiology, inflammatory pathophysiology, and current medi-

cal and surgical treatment modalities of NP. Search terms utilized included 'nasal polyps (polyposis)', 'corticosteroids', 'intranasal corticosteroids', 'nasal polyposis and surgery', 'functional endoscopic sinus surgery', and 'inflammation in nasal polyposis'. Searches were also conducted using the names of INs currently available, by both generic names [budesonide, flunisolide, beclomethasone dipropionate, triamcinolone acetonide, fluticasone propionate (FP), mometasone furoate nasal spray (MFNS), and fluticasone furoate] and brand names [Rhinocort Aqua, Nasarel, Beconase, Nasacort AQ, Flonase, Nasonex, and Veramyst, respectively. Ciclesonide, and its brand names Omnaris and Omniair, were included in searches, but no literature was found evaluating this drug in the treatment of nasal polyps]. This electronic search was supplemented by manual searches of the reference lists of identified relevant articles. References in the retrieved articles were reviewed to identify additional potentially relevant studies that the search strategy might have missed.

The search was restricted to English-language publications. In reviewing evidence for the efficacy of a surgical or medical treatment for NP, preference was given to clinical studies that were randomized, placebo or active comparator controlled, and double blinded. Further assessment of publication bias was not undertaken. Level-of-evidence classification is provided in the tables. Several classification systems have been developed to rate quality of evidence in the literature and inform treatment recommendations, including Strength of Recommendation and Taxonomy [19]; Oxford Centre for Evidence-Based Medicine; US Preventive Services Task Force; and Grading of Recommendations Assessment, Development and Evaluation [20]. This review is based on the evidence classification published in the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EP3OS) [8].

Results and Discussion

Pathophysiology

Nasal polyps originate in the sinuses and the osteomeatal complex and appear as grape-like structures in the upper nasal cavity. They consist of loose connective tissue, edema, inflammatory cells, glands and capillaries, and are covered primarily with respiratory pseudostratified epithelium with ciliated cells and goblet cells [8].

While it is not known why some people develop polypoid ballooning of the nasal mucosa [8], underlying inflammatory changes in NP have been well documented. Nasal polyps are characterized by eosinophil infiltration (in up to 90% of cases), inflammation of the nasal mucosa, and production of polyclonal IgE [12, 21–23]. Eosinophilia is a hallmark of NP, particularly among Caucasians, and older data suggested no major histological difference in NP among African, Chinese, and Caucasian patients [24]. However, using markers of activation for eosinophil and neutrophil granulocytes such as eosinophil cationic protein and myeloperoxidase, it was recent-

ly shown that the amount of activated eosinophils is significantly lower among Chinese patients [25, 26]. Compared with controls and patients with chronic rhinosinusitis without nasal polyps, patients with nasal polyps also demonstrate increased numbers of plasma cells, greater numbers and activation of T cells, and a deficit in T-regulatory cell function [27, 28]. Other inflammatory cells present in NP include neutrophils, mast cells, monocytes and fibroblasts [8]. Mast cells are more often IgE positive (especially in asthmatics) and have a greater degree of degranulation [29, 30]. The density of mast cells in nasal polyps appears to correlate with the expression of mRNA for stem cell factor, a cytokine with chemotactic and survival activity for mast cells [31].

Interleukin (IL)-5 is significantly ($p < 0.0001$) increased in nasal polyps compared with healthy tissue, is the predominant inflammatory cytokine present, and is a key protein in the pathologic activation of eosinophils [32]. Eosinophils are a major source of IL-5, which suggests an autocrine role resulting in persistent eosinophilia [32]. Other inflammatory mediators present at increased levels in nasal polyps are IL-1 β , -3, and -13; granulocyte-macrophage colony-stimulating factor; the mRNA of RANTES (regulated on activation, T-cell expressed and secreted); and in some cases, interferon- γ , all of which inhibit eosinophil apoptosis [12, 33]. However, antagonizing IL-5 alone in an ex vivo polyp model induced eosinophil apoptosis [34].

RANTES protein and eotaxin are eosinophil chemoattractants involved in the chemotaxis and migration of eosinophils in NP [12, 35, 36]. In addition, the interactions between the adhesion molecules very late antigen-4, which are located on eosinophils, and vascular cell adhesion molecule-1, which is upregulated on endothelial cells in polyp vasculature, may have an important role in the extravasation of eosinophils into nasal polyps [9, 37]. The deposition of albumin and the decrease in extracellular matrix protein formation, partially regulated by eosinophilic inflammation, may have a pathogenic effect on polyp formation and growth [35].

NP is a multifactorial disease that often occurs in the setting of chronic rhinosinusitis and other respiratory diseases, such as asthma, cystic fibrosis, and aspirin sensitivity [38]. Several hypotheses have been studied to clarify the trigger for eosinophilic influx in nasal polyps, but none has been validated. Current knowledge about the pathophysiology of nasal polyp formation does not support a causal relation between allergic rhinitis and nasal polyps, although both disorders are characterized by mast cell degranulation, high local levels of IgE and cyto-

kine-driven, eosinophil-dominated inflammation [9]. Other purported mechanisms include viral or bacterial infection [39] and allergic fungal sinusitis in which the eosinophilic inflammatory response that is mounted may be targeted at fungi in the nasal mucosa [40]. Since the differential diagnosis can include tumors, inverted papillomas, and other serious conditions, patients with unilateral nasal obstruction, nasal bleeding, or bleeding polyps should be referred to an ear, nose, and throat specialist for endoscopy.

One hypothesis generating increasing evidence involves the implication of enterotoxins derived from *Staphylococcus aureus* as disease-modifying agents in the pathophysiology of NP [22, 41–43]. Colonization of the middle meatus with *S. aureus* is present in more than 60% of patients with polyps; this is a greater incidence than in controls [44]. *S. aureus* secretes several toxins [*S. aureus* enterotoxins (SAEs)] that have superantigen activity, specifically, the ability to cross-link the class II major histocompatibility complex of antigen-presenting cells and the T cell receptor β -chain variable region [45]. This results in activation of T cells and subsequent production of interleukins (IL-4, IL-5, IL-13) and eotaxin that may lead to eosinophilic inflammation and local IgE production [45]. In about 30–50% of nasal polyp patients, colonization of the middle meatus with *S. aureus* is associated with the presence of IgE antibodies to SAEs [44]. Nasal polyps with specific IgE to SAEs have significantly higher concentrations of IgG and IgE, as well as a shift in IgG subclass (higher IgG4 and lower IgG2), than polyps without specific IgE production [46]. Eicosanoid synthesis (e.g. cysteinyl leukotrienes) is also upregulated in nasal polyp tissue of patients with IgE antibodies to SAE to a greater degree than in those without detectable IgE antibodies. This upregulation appears to be related to the inflammatory reaction induced by the enterotoxins [47]. A recent investigation of cytokine and mediator production after stimulation with *S. aureus*-derived proteins (enterotoxin B, protein A, and lipoteichoic acid) revealed greater mast cell degranulation (with protein A) and increased cytokine release (with enterotoxin B) in nasal polyps than in control tissue [45].

Current Treatment Modalities for NP

Surgery

Based on the published evidence, sinus surgery should be reserved for patients who do not satisfactorily respond to medical treatment [8]. Two randomized, controlled tri-

als evaluated treatment with oral and topical corticosteroids with or without surgery for NP and found that medical treatment alone is adequate to treat the majority of symptoms in these patients in the short to medium term [16, 48].

In most patients, surgery followed by INS therapy is necessary for durable improvement in symptoms, polyp size, and olfactory thresholds [49]. Sinus surgery without oral or topical corticosteroid treatment is associated with a high rate of polyp recurrence and does not address the underlying inflammation; surgical overtreatment and its sequelae should be avoided [18]. The effect of INSs on preventing/reducing postoperative polyp recurrence is well documented [8]. When surgery is indicated, extensive postoperative care and follow-up are required to preserve postoperative results and prevent polyp regrowth. Success with surgery may depend on the surgical technique, the type/cause of polyps, or other, as yet unidentified factors. A systematic review of functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis with nasal polyps identified symptomatic improvement after FESS in 78–88% of patients in 3 randomized controlled trials and 4 nonrandomized comparative studies, as well as in 40–98% (median, 88%) of patients from 35 case series studies [50]. Other comparative procedures had improvement rates between 43 and 84% [50].

Long-term success of surgery has been variable based on published studies [51–53]. A prospective cohort study in the UK in 3,128 patients showed that revision surgery was conducted in 11.4% of patients within 3 years [51]. In a case series of 118 patients with severe polyposis, followed for 12–168 months after surgery, 60% developed recurrent polyposis. Of those patients, 47% were advised to undergo revision surgery, which 27% subsequently did [52]. Moreover, a follow-up study in 41 patients who had undergone surgery for nasal polyps 20 years earlier found that 85% (35/41) had polyps [53]. Nearly 20% (8/41) had undergone 11 or more surgical operations during the 20-year period. Most of these patients (7/8) had aspirin sensitivity [53]. None of the aspirin-sensitive patients were polyp-free at the time of the study, indicating that aspirin sensitivity may predict a risk of polyp recurrence [53].

Corticosteroids

Rationale for Treatment with Corticosteroids

The multiple anti-inflammatory effects of corticosteroids on nasal polyps include the reduction of infiltration and activation of eosinophils in the airways [8, 54, 55] and a decrease in the secretion of chemotactic cytokines by

the nasal mucosa and polyp epithelial cells [8, 56]. A histological study revealed significant decreases in eosinophil cationic protein and albumin concentrations, as well as reductions in eotaxin and fibronectin levels, in tissue homogenates from patients with NP treated with oral corticosteroids [35]. Corticosteroids have been shown to inhibit mRNA expression in nasal polyps of the chemokines eotaxin, eotaxin-2 and monocyte-chemotactic protein-4 [57]. Corticosteroids may also upregulate anti-inflammatory genes such as transforming growth factor- β and uteroglobin [58]. Given the central role of eosinophil-dominated inflammation in the pathophysiology of NP, and the inhibitory effect of corticosteroids on that inflammation, corticosteroids have become a mainstay of therapy for NP [9, 18].

Oral Corticosteroids

Oral corticosteroids have traditionally been used for NP based on the observed clinical effect, despite the absence of supporting evidence from large, double-blind, randomized, placebo-controlled studies [8, 59]. Two randomized placebo-controlled trials demonstrated the efficacy of a 2-week oral prednisolone treatment (30 mg/day for 4 days followed by a 2-day reduction of 5 mg/day [59] or 50 mg/day [60]) in improving nasal symptoms and significantly reducing polyp size. Patients experienced significantly improved scores for nasal obstruction, loss of sense of smell, rhinorrhea, and sneezing [59]. Polyp size was shown to be significantly reduced, based on nasendoscopy and MRI ($p < 0.001$ for both) [60]. QoL parameters were not assessed in either study; however, a study by Alobid et al. [61] concluded that a 2-week short course of oral corticosteroids improved mental and physical QoL parameters in patients with severe NP. Short courses (2–3 weeks) of oral glucocorticosteroids may be effective for rapid control of symptoms; however, eosinophil concentrations have been shown to rebound after an average of 8 weeks in some patients [62].

The use of oral corticosteroids is typically limited to short courses because of the risk of systemic adverse effects [8]. In one study of 46 patients receiving oral glucocorticosteroids for at least 21 days/year, 10.9% were found to have osteoporosis of the lumbar spine, 43.5% had osteopenia of the lumbar spine, and 48.8% (20/41) had asymptomatic adrenal insufficiency [63]. Oral corticosteroids are contraindicated in patients with acute infections, peptic ulcers, psychoses and osteoporosis. These limitations and risks for systemic adverse effects have driven the need for alternative treatments for polyposis, such as topical corticosteroids.

Table 1. Treatment with nasal corticosteroids in chronic sinusitis with NP

Study ¹	Drug (vs. placebo)	n	Duration weeks	Effect on nasal symptoms ¹	Objective measures ²	Effect on polyp size	Level of evidence ³
Mygind et al. [64] (1975)	BDP	35	3	total symptom score		NS	Ib
Deuschl et al. [65] (1977)	BDP	20	2 × 4 (crossover)	blockage	rhinomanometry	NS	Ib
Holopainen et al. [66] (1982)	BUD	19	16	total symptom score	nasal peak flow eosinophilia	yes	Ib
Vendelbo Johansen et al. [67] (1993)	BUD	91	12	blockage sneezing secretion sense of smell (NS)	PNIF	yes	Ib
Lildholt et al. [68] (1995)	BUD	116	4	blockage sneezing secretion sense of smell (NS)	PNIF	yes	Ib
Holmberg et al. [69] (1997)	FPNS/BDP	55	26	overall assessment	PNIF	yes BDP	Ib
Tos et al. [70] (1998)	BUD	138	6	total symptom score sense of smell		yes	Ib
Lund et al. [71] (1998)	FPNS/BDP	29	12	blockage rhinitis (NS) sense of smell (NS)	PNIF acoustic rhinometry	yes FP	Ib
Keith et al. [72] (2000)	FPND	104	12	blockage rhinitis sense of smell (NS)	PNIF olfactory test (NS)	NS	Ib
Penttilä et al. [73] (2000)	FPND	142	12	blockage rhinitis sense of smell (NS)	PNIF olfactory test	yes	Ib
Hadfield et al. [74] (2000)	BETND	46	6	subjective nasal symptom score (NS)		yes	Ib
Aukema et al. [78] (2005)	FPND	54	12	nasal obstruction rhinorrhea post-nasal drip loss of smell	PNIF CT scan (NS)	yes	Ib
Small et al. [13] (2005)	MFNS ⁴	354	16	obstruction loss of smell rhinorrhea	PNIF	yes	Ib
Stjärne et al. [75] (2006)	MFNS	310	16	obstruction loss of smell (NS) rhinorrhea	PNIF	200 mg q.d. no 200 mg b.i.d. yes	Ib
Stjärne et al. [76] (2006)	MFNS	298	16	obstruction loss of smell rhinorrhea QoL	PNIF	yes	Ib

BDP = Beclomethasone dipropionate; BETND = betamethasone nasal drops; BUD = budesonide; FPND = fluticasone propionate nasal drops; FPNS = fluticasone propionate nasal spray; MFNS = mometasone furoate nasal spray; NS = not significant; QoL = quality of life.

¹ Randomized, placebo-controlled trials.

² All results statistically significant vs. placebo except where noted not statistically significant (NS).

³ Classification based on the categories utilized in EP3OS [8].

⁴ MFNS has been approved for this indication in the United States following confirmation of its efficacy in 3 large randomized, controlled trials [13, 75, 76]. Adapted with permission from Fokkens et al. [8].

Intranasal Corticosteroids

INNs are indicated as first-line therapy for nasal polyps and postoperative care after polypectomy, according to the EP3OS guidelines [8]. Several randomized clinical trials have shown these medications to be effective treatments for NP (table 1) [8, 13, 64–76]. There are few or no randomized, controlled published trials that evaluate the effectiveness of the INNs flunisolide, triamcinolone, or beclomethasone in polyposis [77]. Two studies with beclomethasone from the 1970s showed significant symptom improvement, but they were likely too short in duration (3 and 4 weeks) to show effects on polyp size [64, 65].

Recently randomized, controlled trials have been published evaluating budesonide, FP, and mometasone furoate nasal sprays and drops for the treatment of nasal polyps. These were shown to be effective in reducing nasal symptoms (nasal blockage, secretion, sneezing, and rhinitis) and improving peak nasal inspiratory flow (PNIF) over study periods ranging from 3 to 16 weeks [13, 14, 68–73, 75, 76, 78].

In recent literature, treatment for NP has been directed at improvements in 4 key areas: reduction/elimination of polyp size, airway congestion, improvement of sense of smell, and prevention of recurrence. Three topical corticosteroids have been evaluated in adequately designed published studies: FP, budesonide and MFNS.

Trials with FP (200 µg twice daily nasal spray [69, 71] and 400 µg once daily nasal drops [72, 73, 78]) demonstrated its effectiveness versus placebo in reducing symptoms associated with polyposis, i.e. nasal congestion/obstruction and improving PNIF. Data for reducing polyp size are less robust. Lund et al. [71] demonstrated a significant improvement versus placebo in polyp score by 12 weeks. However, some studies, also 12 weeks in duration, did not present baseline data [73, 78] or showed a difference that was numerically superior but not statistically significant versus placebo [68, 72]. It is difficult to assess whether study design or limitations in objective measures of polyp size contributed to these results.

Similarly, budesonide aqueous suspension spray and/or topical powder has been associated with significant improvement in symptoms of congestion/obstruction at 4 weeks [68], 6 weeks [70], and 12 weeks [66, 67], with dosages of 200/400 µg twice daily, 128 µg twice daily, and 200 µg twice daily, respectively. Study design and results for polyp size and/or number varied among studies. Polyp size or number was improved in the budesonide treatment group compared with placebo in all studies [66–68, 70]; improvement was statistically significant in 3 of the

studies that assessed small [66] and moderate to severe bilateral polyps [68–70].

In 2 similarly designed 16-week trials, subjects with large bilateral NP receiving MFNS 200 µg once or twice daily [13, 77] showed statistically significant improvements in congestion/obstruction and PNIF [13, 77], and, in 1 study, sense of smell [13]. In both studies, nasal polyp size was significantly reduced in the MFNS twice-daily dosing groups [13, 77], and in 1 study, significant reduction was seen with MFNS 200 µg once daily [13]. A retrospective analysis of pooled data from these studies concluded that MFNS 200 µg twice daily provided significant relief of anterior rhinorrhea and PNIF by day 2, nasal congestion by day 3, postnasal drip by day 5, and improvement of sense of smell by day 13 [14].

In a 16-week study of subjects with mild to moderate bilateral NP, MFNS 200 µg once daily also demonstrated significant advantages versus placebo in improving 3 of 4 QoL parameters: nose breathing, interference with daily activities, sleep disturbance, and taste and smell. Assessment was based on a 3-point investigator-administered scale [79]. Congestion, PNIF, and polyp size were also significantly improved in this patient population [76].

Data presented regarding congestion/obstruction reduction with INNs as a class tend to be more conclusive than data supporting the improvement of sense of smell and reduction in polyp size. The data for sense of smell and reduction of polyp size are more variable across studies, even among those with similar study design. There is a dearth of QoL data, however, because randomized, controlled trials of INNs have not included QoL outcomes in study protocols [16]. Two studies utilized the SF-36 validated questionnaire to assess effect of NP treatment on QoL [15, 16]. Medical (oral and intranasal corticosteroid) and surgical treatment in patients with large polyps resulted in significant improvement in all health domains [16], while INNs alone or after surgery resulted in significant improvement in 5 of 8 health domains [15].

The EP3OS guidelines recommend INNs as first-line treatment for moderate to severe disease [8]. In the absence of endoscopic examination, if no improvement is seen after 4 weeks of treatment, then referral to an ear, nose and throat specialist for consideration for surgery is recommended. Short-course oral corticosteroids [8] are recommended as adjunctive therapy to long-term INS therapy only for patients with severe disease, and progress should be evaluated by a specialist after 1 month of treatment [8].

Table 2. Nasal corticosteroids in the postoperative treatment of persistent rhinosinusitis to prevent recurrences of nasal polyps

Study	Drug	n	Treatment time, weeks	Effect on nasal symptoms ²	Effect on polyp recurrence – method of test	Level of evidence ³
Virolainen et al. [79] (1980) ¹	BDP	40	52	blockage (statistical analysis not reported)	yes – posterior rhinomanometry	IV
Drettner et al. [81] (1982) ¹	FLSD	22	12	total nasal score (blockage secretion, sneezing)	NS – posterior rhinomanometry	Ib
Karlsson et al. [80] (1982)	BDP	40	120	not described	yes – physical examination	IIa
Dingsør et al. [82] (1985) ¹	FLSD	41	52	blockage	yes – anterior rhinoscopy	Ib
Hartwig et al. [83] (1988) ¹	BUD	73	26	blockage (NS)	yes – anterior and posterior rhinoscopy	Ib
Dijkstra et al. [84] (2004) ¹	FPNS	162	52	NS	NS – nasal endoscopy	Ib
Rowe-Jones et al. [85] (2005) ¹	FPNS	109	5 years	overall visual analogue score	yes – endoscopic polyp score and total nasal volume	Ib
Stjärne et al. [76] (2009) ¹	MFNS	162	24	rhinorrhea other symptoms (NS)	yes – nasal endoscopy	Ib Ib

Adapted with permission from Fokkens et al. [8]. BDP = Beclomethasone dipropionate; BUD = budesonide; FLSD = flunisolide; FPNS = fluticasone propionate nasal spray; MFNS = mometasone furoate nasal spray; NS = not significant.

¹ Randomized, placebo-controlled trials.

² Results statistically significant vs. placebo except where otherwise noted.

³ Classification based on the categories utilized in EP3OS [8].

Postoperative Treatment with INSs

There is much evidence supporting the efficacy of INSs in reducing recurrence of nasal polyps after sinus surgery, including simple polypectomy and radical ethmoidectomy (table 2) [8, 72, 79–85]. Several small ($n \leq 43$), well-controlled trials have demonstrated that treatment with beclomethasone dipropionate [79, 80], flunisolide [81, 82], or budesonide [83] may reduce polyp recurrence and/or improve the nasal symptoms of congestion and sneezing.

Two randomized, double-blind, placebo-controlled trials with larger patient populations yielded conflicting results regarding postoperative FP in preventing nasal polyp recurrence [84, 85]. In one, Dijkstra et al. [84] randomly assigned 162 patients to FP nasal spray 400 μg twice daily, 800 μg twice daily, or placebo for 1 year after FESS combined with perioperative systemic corticosteroids (a 2-week course of prednisone). After 1 year, 46 patients had been withdrawn for recurrent disease and 32 patients were withdrawn for persistent symptoms [84]. No significant difference was detected between the FP and placebo groups with respect to polyp recurrence as seen by endoscopy or in the number of subjects who withdrew due to recurrent or persistent disease.

Rowe-Jones et al. [85] published results that conflicted with those found by Dijkstra et al. [84] in a 5-year follow-up study in patients requiring FESS ($n = 109$). Following a 3-week course of oral prednisolone after FESS, subjects were randomized to placebo or FP nasal spray 200 μg

twice daily, beginning 6 weeks after FESS. Mean overall polyp scores were 2 points at baseline and 0.2 points at 6 weeks after FESS. After 1 year, polyp scores were significantly more improved from the 6-week post-FESS measurement in the FP group compared to the placebo, with a 0.1-point improvement in the FP group and a slight 0.2-point worsening in the placebo [last observation carried forward (LOCF); $p < 0.027$]. At 5 years, the difference was greater between the 2 groups; a 0.2-point increase in polyp score from post-FESS in the FP group, compared with a 0.7-point increase in the placebo group (LOCF; $p < 0.023$). The changes in total nasal volumes were also significantly better in the FP group than in the placebo group at both 1 and 5 years' follow-up (LOCF); nasal mucociliary clearance time was also significantly better with FP [85]. All other outcome value differences between groups at 5 years were not statistically significant [85]. Failure, defined as having 2 consecutive months requiring systemic prednisolone, occurred in 11% (12/109) of patients [81]. Two of these patients were receiving FP and 10 were receiving placebo ($p = 0.06$) [85].

These apparently conflicting results are difficult to assess, primarily due to study design differences. The recurrence/failure rates were very different between the 2 studies, with the study by Dijkstra et al. [84] having relatively higher recurrence rates (48%) than the low failure rate (11%) seen in the study by Rowe-Jones et al. [85]. The patient populations may have also been different; for example, Dijkstra et al. [84] excluded patients with sinus

Table 3. Other medical management for chronic rhinosinusitis with nasal polyps [105–115]

Treatment	Study	Evidence ¹	Clinical importance
Antihistamine	1 RCT allergic	Ib	yes (in allergy only)
Antileukotriene	3 cohort	III	no
Lysine aspirin desensitization	1 RCT; 2 CT	Ib	yes
Furosemide	1 RCT; 1 CT	Ib (–) ²	yes
Capsaicin	1 RCT	Ib	no
Anti-IL-5	1 RCT	Ib (effective in subgroup of patients)	no
Nasal amphotericin B	3 RCT	Ib (–) ²	no

Adapted with permission from Fokkens et al. [8]. CT = Clinical trial; RCT = randomized, controlled trial.

¹ Classification based on the categories utilized in EP3OS [8].

² Ib (–) = Study with a negative outcome.

surgery in the previous 6 weeks and Rowe-Jones et al. [85] excluded those having had sinus surgery within the previous 12 months.

Since the approval of MFNS in the US, a large, randomized, placebo-controlled double-blind multicenter trial found that MFNS prevented or prolonged the time to nasal polyp recurrence [86]. In this study, subjects who had undergone FESS to treat endoscopically verified bilateral NP were treated with MFNS 200 µg once daily or placebo. MFNS significantly increased time to nasal polyp recurrence compared with placebo. In the intent-to-treat population (n = 159), median time to recurrence was 125 days in the placebo group and >175 days in the MFNS group (p = 0.049) [86]. Median time to nasal polyp recurrence could not be precisely calculated in the MFNS-treated group because less than half the subjects experienced recurrence before the end of the study [86].

The mechanism for reduction in recurrent polyposis by INSs may be related to wound healing following FESS. In a recent pilot study conducted by Jorissen and Bachert [87] in patients with NP after FESS, a combination score of inflammation, edema and polyps was significantly reduced after 6 months [median score, 2.0 points with MFNS compared to 4.0 points with placebo (p = 0.03)].

Safety of Corticosteroids

The use of systemic corticosteroids for NP is significantly limited by their association with serious adverse effects, particularly after long-term use [8, 63, 88]. These adverse events include an increase in intraocular pressure, reduction in bone mineral density, and thinning of the skin. In contrast, the low systemic bioavailability and

high first-pass metabolism of MFNS, FP and budesonide considerably minimize the risk of systemic adverse events [89–92]. While a 1-year study of the older INS beclomethasone dipropionate in children with allergic rhinitis demonstrated a reduced growth rate (average growth, 5 cm over 1 year compared with 5.9 cm receiving placebo; p < 0.01), no effects on growth have been found with the newer INSs [93–98]. Although not relevant to an adult population, these data reflect the low bioavailability of newer topical corticosteroids. No other adverse effects of systemic corticosteroid therapy have been associated with the use of an INS [99, 100].

INSs are generally well tolerated; local adverse effects (e.g. nose and throat irritation, transient dryness, and epistaxis) are typically mild and self-limiting and do not lead to discontinuation of therapy [89, 100]. The proportion of patients reporting adverse events in clinical trials of MFNS, budesonide, and FP for NP treatment is similar to the incidences observed in studies of these INSs in allergic rhinitis or acute rhinosinusitis [13, 72, 75, 76, 101–103]. Counseling patients on the correct use of topical corticosteroids is advised to increase appropriate deposition [104].

Other Treatment Options and Potential Future Therapies for NP

For patients who do not respond adequately to treatment with a corticosteroid nasal spray, corticosteroid nasal drops may be an option [8]. However, surgery followed by postoperative nasal douching and treatment with an INS are frequently warranted, with the possible addition

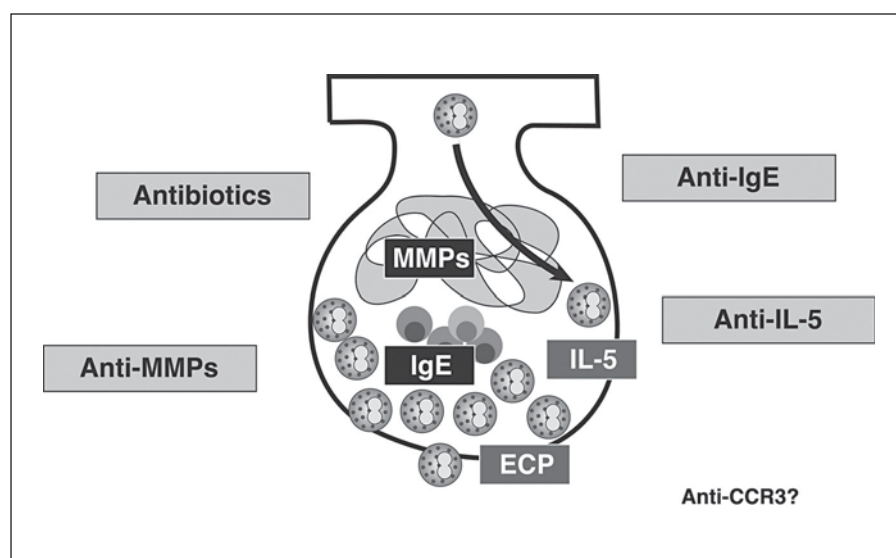


Fig. 1. Future approaches to the treatment of NP. CCR3 = CC chemokine receptor 3; ECP = eosinophil cationic protein; MMPs = matrix metalloproteinases.

of short courses of systemic corticosteroids and/or long-term antibiotics [8, 49].

Several other therapies and delivery methods have been investigated for nasal polyps (e.g. antihistamines, intranasal amphotericin B, capsaicin, furosemide, anti-leukotrienes, lysine aspirin desensitization, and anti-IL-5 and anti-IgE antibodies, mucosal atomization device), but substantial evidence of their benefit in a large number of patients is currently lacking (table 3) [8, 105–115]. Among therapies investigated, anti-IL-5 antibodies warrant further study based on promising results from a small ($n = 24$), randomized, double-blind single-injection study in patients with bilateral nasal polyps. This study evaluated treatment with reslizumab, an anti-IL-5 monoclonal antibody (mAb). At 4 weeks after dosing, patients were sorted into ‘responders’ and ‘non-responders’; 8 of 16 patients who received active treatment showed improved polyp scores [109]. Nasal secretions with elevated IL-5 protein were associated with success of reslizumab; elevated IL-5 protein levels in nasal secretions were proposed to be predictive of response to treatment [109]. Another anti-IL-5 mAb, mepolizumab, which is dosed in repeated injections, is currently under investigation for treatment of nasal polyp disease [116].

Furthermore, based on the significant local production of IgE antibodies in nasal polyps and its correlation with disease severity [18, 22], anti-IgE mAbs may provide a valid treatment approach; omalizumab is an anti-IgE antibody with clinical indication in severe allergic asthma,

and has been proposed for use in nasal polyp disease [117]. Omalizumab reduces serum IgE levels and down-regulates IgE receptors on mast cells and basophils, leading to disruption of mast cell activation and degranulation [117]. In a preliminary open-label study of omalizumab in 4 patients with allergic asthma and recurrent nasal polyps, a mean shrinkage in polyp size of approximately 20% has been reported [118]. It remains unclear how IgE and mast cell degranulation may contribute to polyposis [117].

Other potential targets for future therapeutic approaches include other components of the inflammatory response involved in NP (fig. 1). For example, the antagonism of matrix metalloproteinases (MMPs), concentrations of which are increased in polyps compared to controls (specifically MMP-9 and MMP-7), that are able to degrade extracellular matrix proteins, is a potential therapeutic target [18, 119]. A placebo-controlled, randomized study in chronic rhinosinusitis patients after surgery used doxycycline [120], an agent capable of inhibiting MMP synthesis and activity, and also inhibiting the growth of *S. aureus* [18].

Several other potential future therapies have shown promise in *in vitro* studies, but studies in nasal polyps have not yet been reported. These therapies include CC chemokine receptor 3 antagonists; anti-chemokine (eotaxin) antibodies [121, 122]; antagonists against the Th2 cytokines IL-4 and IL-13, which play important roles in the development of airway inflammation [123], and immune-suppressive agents [18].

Conclusions

The symptoms of nasal polyps are associated with a substantial economic burden and negative impact on patients' QoL. Given the key role of inflammation in the pathophysiology of NP and the chronic nature of the disorder, INSs are recommended as first-line therapy; a short-term course of oral corticosteroids may be needed in patients with severe disease. Furthermore, because surgery for refractory NP does not address the underlying pathophysiology, recurrences are common, warranting postoperative maintenance treatment with INSs to prevent or delay recurrence. Mainstay treatment that reduces polyp size and number and improves nasal symp-

toms of the disease has been found to improve QoL [15, 16]. New therapeutic options are emerging for a subgroup of patients with severe INS-resistant diseases, including mAbs against IL-5 and IgE. Individualized management of NP may control patients' symptoms and improve QoL for years.

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