CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Chronic Rhinosinusitis with Nasal Polyps

Claire Hopkins, B.M., B.Ch., D.M.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 50-year-old man presents with a 5-year history of progressive nasal obstruction and reduction in his sense of smell. Symptoms were initially intermittent but have become persistent and very bothersome, with the patient rating them as severe. He reports sleep disturbance and postnasal drip and recently received a diagnosis of asthma. Alcohol consumption exacerbates his nasal congestion. Anterior rhinoscopy reveals pale, fleshy polyps filling both sides of the nasal cavity. How would you further evaluate and manage this case?

From Guy's and St. Thomas' Hospitals, London. Address reprint requests to Dr. Hopkins at the Ear, Nose, and Throat Department, Guy's Hospital, Great Maze Pond, London SE1 9RT, United Kingdom, or at claire.hopkins@gstt.nhs.uk.

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THE CLINICAL PROBLEM

Nasal polyps are benign inflammatory masses, arising from the mucosa of the nose and paranasal sinuses. They are considered to be a subgroup of chronic rhinosinusitis, and clinical diagnosis is made on the basis of the presence of sinonasal symptoms (Table 1) for more than 3 months and the visualization of polyps in the nasal cavity (Fig. 1).[1]

Symptoms substantially affect patients' quality of life.[2] Nasal obstruction and reduction in the sense of smell are the most frequent symptoms (present in 97% and 90%, respectively, of patients with polyps who present for surgical treatment[3]); sleep disturbance and nasal discharge are also common. The size of the nasal polyps correlates well with subjective nasal obstruction but does not predict the severity of other symptoms.[4]

The incidence of nasal polyps increases with age to a peak in the sixth decade.[5] The prevalence, on the basis of endoscopic examination in a Swedish population, is estimated at 2.7% of adults and is twice as high among men as among women.[6] Nasal polyps are very uncommon before the third decade of life[7]; a diagnosis of polyps in childhood should prompt investigation for cystic fibrosis. Lower rates of surgery for polyps have been reported in black and Hispanic populations than in white populations,[8] but this finding may reflect differing access to care or behavioral differences rather than lower prevalence.

Chronic rhinosinusitis includes a heterogeneous group of conditions with differing pathophysiologies. Two main subgroups are described: with and without nasal polyps. Chronic rhinosinusitis without nasal polyps may be idiopathic or odontogenic or may be caused by immunodeficiency, vasculitis, or other autoimmune conditions. The majority of cases of chronic rhinosinusitis with nasal polyps are idiopathic but may also occur as part of genetic, metabolic, or immunologic diseases (Table 2). The majority of white patients with chronic rhinosinusitis with nasal polyps

KEY CLINICAL POINTS

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

- Chronic rhinosinusitis with nasal polyps typically manifests as nasal obstruction, reduction in sense of smell, nasal discharge, and sleep disturbance, with adverse effects on quality of life.
- In patients with mild symptoms, intranasal glucocorticoids and saline irrigation should be prescribed, and patients should be educated regarding the need for long-term adherence to therapy.
- In patients with more severe symptoms, judicious short-term use of systemic glucocorticoids can ameliorate symptoms.
- Surgery to remove polyps warrants consideration in patients whose symptoms are not controlled with glucocorticoids, but rates of relapse and repeated intervention are high; intranasal glucocorticoids are continued after surgery.
- Biologic agents targeted at the inflammatory cytokines that have been shown to be involved in polyp pathophysiology are currently under study.

have a type 2 pattern of inflammation,[12,13] characterized by eosinophilia and elevated levels of interleukin-4, interleukin-5, and interleukin-13 cytokines. This finding may not apply to other racial groups, but further study is required.

Up to 60% of patients with polyps have lower airway disease, including coexisting asthma,[14,15] typically with onset in adulthood. With the exception of central compartment atopic disease, which is an IgE-mediated allergic disease triggered by inhalant allergens, the association between nasal polyps and allergic rhinitis remains unclear; nasal polyps are reported to be less common in persons with allergic rhinitis[7] and childhood-onset allergic asthma[16] than in the general population. Smoking does not seem to be a strong risk factor for chronic rhinosinusitis with nasal polyps.[17] Genetic factors are likely to play a role in the pathogenesis, and patients with this condition are more likely than controls to report having a first-degree relative with nasal polyps.[18] An increased prevalence of nasal polyps has been described among textile workers who have been exposed to occupational dust, particularly among those with longer-duration exposure.[19] A survey of persons with and those without chronic airway disease indicated that almost one third of patients with chronic rhinosinusitis with polyps, and up to 83% of those with aspirin-exacerbated respiratory disease, reported that alcohol consumption exacerbated their symptoms, such that many abstained from drinking alcohol.[20]

Table 1. Diagnostic Criteria for Chronic Rhinosinusitis with Nasal Polyps.

Inflammation of the nose and paranasal sinuses that is characterized by two or more symptoms, at least one of which should be either nasal blockage (congestion) or nasal discharge:
Nasal obstruction and congestion or nasal discharge (anterior or posterior)
With or without facial pain or pressure
With or without reduction or loss of smell
Endoscopic signs of nasal polyps or evidence of nasal polyps on computed tomography

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

The differential diagnosis includes chronic rhinosinusitis without polyps, rhinitis, structural abnormalities of the nose, and neurologic causes of hyposmia. Rhinitis is highly prevalent, affecting up to 30% of adults.[21] The resulting pale, edematous turbinates may be misdiagnosed as nasal polyps (Fig. 2). In patients with rhinitis, nasal congestion may fluctuate in severity and alternate from side to side with exaggeration of the nasal cycle (a physiologic cycle of congestion and decongestion in each nasal passage, causing alternating nasal resistance).[22] The presence of hyposmia suggests chronic rhinosinusitis with or without polyps rather than rhinitis.[23]

Nasal polyps usually occur in both nasal passages, although they may be asymmetric in size; polyps that occur in only one nasal passage should arouse suspicion for benign or malignant tumors, particularly in the presence of bloodstained nasal discharge.[24] A meningocele, either congenital or acquired after trauma, may also be mistaken for a nasal polyp.

INVESTIGATIONS

Endoscopy is usually necessary to confirm the diagnosis of nasal polyps, although anterior rhinoscopy may allow large polyps to be visualized. Computed tomographic (CT) scans are usually performed as part of surgical planning in cases that are recalcitrant to medical therapy or before biopsy. Biopsy is rarely required for diagnostic purposes unless the polyps are observed on only one side. However, histopathological examination may provide useful prognostic information; tissue eosinophilia (>10 cells per high-power field) has been associated with higher rates of recurrence.[25]

Symptom severity should be assessed routinely (Fig. 3). A systematic review[27] and a core outcome set for chronic rhinosinusitis[28] recommend the use of the 22-item Sinonasal Outcome Test (SNOT-22) in secondary care to rate the severity of symptoms. This questionnaire assesses 22 symptoms or social and emotional consequences of the condition, each on a scale from 0 to 5, with higher numbers indicating worse consequences. A simple 10-cm visual-analogue scale is also useful and reasonable in primary care for the evaluation of overall symptom severity (with scores from 0 to 3 indicating a mild condition, >3 to 7 a moderate condition, and >7 a severe condition)[29] but captures less clinical information.

Patients should also be asked about lower respiratory symptoms and whether nasal or respiratory symptoms are exacerbated by intake of salicylates (in nonsteroidal agents and dietary sources such as fresh berries and nuts). Measurement of peak expiratory flow should be considered. Further investigations are often not required unless the polyps are thought to be part of a broader condition, although a full blood count (to evaluate eosinophilia) and total IgE levels may be useful in guiding treatment and predicting prognosis. Skin-prick testing is indicated, particularly in younger patients in whom central compartment atopic disease is suspected.

TOPICAL THERAPY

In patients with mild symptoms, appropriate treatment includes intranasal glucocorticoids and saline irrigation.[1,26] Saline irrigation is recommend-

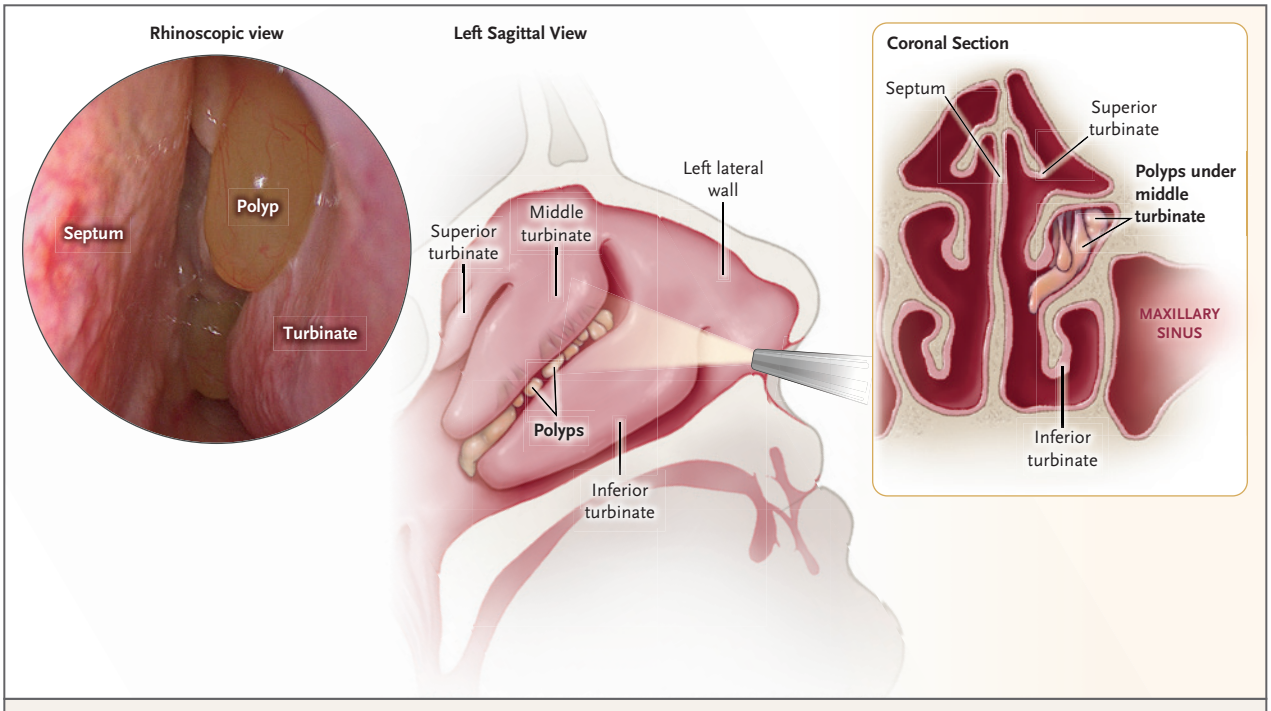

Figure 1. Nasal Polyps Seen in Left Nasal Cavity on Anterior Rhinoscopy.

Polyps can be seen in the nasal cavity, filling the space between the nasal septum and the middle and inferior turbinates on the lateral wall. Polyps may differ in color. They are often yellow, as shown, but may also appear as white or pink grapelike masses in the nose.

Table 2. Diseases Associated with Nasal Polyps.

Disease	Comments
Idiopathic nasal polyps	Men are more commonly affected than women; peak incidence occurs in sixth decade of life
Aspirin-exacerbated respiratory disease[9]	Women are more commonly affected than men; associated with onset at younger age and with more severe disease and higher rates of recurrence after surgery than idiopathic nasal polyps; asthma may be difficult to control; involves sensitivity to salicylates, in both nonsteroidal agents and dietary sources (e.g., fresh berries and nuts); 10% of patients also have reaction to acetaminophen
Allergic fungal rhinosinusitis[10]	IgE-mediated response to fungal allergens causing intense eosinophilic inflammation associated with accumulation of eosin-rich mucin; may lead to sinus expansion with proptosis and visual disturbance; wide geographic variation in prevalence, with highest reported rates in the southwestern United States
Vasculitis (e.g., eosinophilic granulomatosis with polyangiitis)	Prodromal stage of polyps and asthma that is difficult to differentiate from conditions above; high index of suspicion is needed; patients often feel systemically ill and fatigued; patients have elevated eosinophil levels (>10% of white-cell count)
Cystic fibrosis	Consider if onset of nasal polyps is before 16 yr of age; nasal polyps develop in 20% patients with cystic fibrosis; disease is characterized by neutrophilic inflammation
Central compartment atopic disease[11]	IgE-mediated allergic disease triggered by inhalant allergens (e.g., house dust mite, molds, or pollens); typically occurs in slightly younger patients than do idiopathic polyps, with allergic rhinitis often commencing in childhood; polyps arise from middle turbinates with centrally sited sinus disease; treatment focuses on management of allergy

ed by most guidelines. Although evidence from randomized trials is limited and of low quality,[30] clinical experience supports improved symptom control with nasal saline. Adverse effects are uncommon and usually mild (nasal irritation and epistaxis).

There is a large body of evidence supporting the effectiveness of intranasal glucocorticoids over placebo in terms of abatement of symptoms (nasal obstruction, rhinorrhea, and loss of sense of smell) and reduction in polyp size.[1,30] There is a low incidence of adverse events, with nasal irritation and epistaxis being the most common. Although formulations do not appear to differ in effectiveness,[30] their absorption is varied. The systemic bioavailability of second-generation compounds (mometasone and fluticasone) is less than 1%,[31] and they are safe for long-term use, without treatment breaks. They are probably underused, presumably owing to both underprescribing and poor adherence. A study involving data from an administrative database showed that only 20% of patients with chronic rhinosinusitis used topical glucocorticoids, and most at an inappropriately low dosage.[32]

For moderately or severely symptomatic nasal polyps, clinical experience suggests that intranasal delivery of glucocorticoids may be improved by the use of topical drops[1] or, in patients who have had previous sinus surgery with open cavities, by high-volume irrigations. The effectiveness of topical glucocorticoids is believed to be enhanced after surgery, probably owing to improved access.[33] A systematic review showed a greater reduction in the polyp score with topical glucocorticoids in patients who had undergone sinus surgery than in patients who had never had sinus surgery. Furthermore, the delivery of glucocorticoids by means of high-volume (240 ml) nasal irrigation has been shown to be more effective in reducing endoscopic evidence of recurrence than delivery of an equivalent dose by means of nasal spray in patients after sinus surgery.[34] Mometasone was used in this trial, but budesonide and fluticasone are commercially available in liquid formulations. Patients should be educated regarding appropriate delivery techniques (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and the need for long-term adherence to therapy.

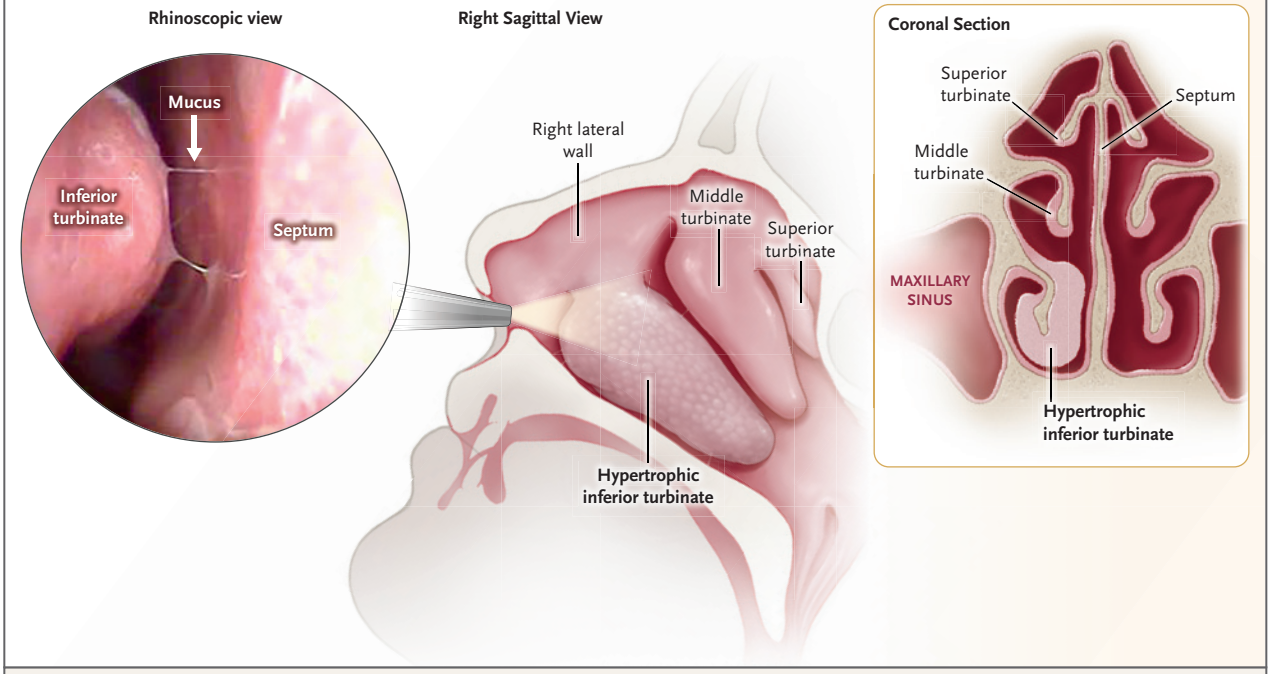

Figure 2. Image from Anterior Rhinoscopy of Right Nasal Cavity in a Patient with Allergic Rhinitis.
The mucosa of the inferior turbinate is pale and cobblestoned, with strands of mucus seen between the turbinate and septum. The hypertrophied turbinate can be seen arising from the lateral wall and can be mistakenly diagnosed as a nasal polyp.

SYSTEMIC THERAPY

Glucocorticoids

In patients with severe symptoms or in whom initial treatment has failed to achieve adequate control, a short course of oral glucocorticoids may be considered. A Cochrane review of eight randomized trials[35] showed a short-term benefit of a short course (2 to 3 weeks) of oral glucocorticoids of varying doses (generally averaging 0.5 mg per kilogram of body weight daily, with a maximum daily dose of 60 mg), as compared with placebo or no treatment. Significant improvements were noted in polyp size, nasal symptoms, or quality of life, but the data were considered to be of low quality. Gastrointestinal adverse effects and insomnia were more common with active treatment than with control. By follow-up at 3 to 6 months, there was little or no difference in symptoms between patients who were treated with oral glucocorticoids and those who were not, but all the patients were treated subsequently with maintenance nasal glucocorticoids. The potential long-term harms of repeated short courses of systemic glucocorticoids (including bone loss) must be weighed carefully against potential benefits.

Antibiotic Agents

Staphylococcus aureus may be isolated in up to 50% of patients with chronic rhinosinusitis with nasal polyps, with higher rates of positive cultures and a higher incidence of detection of *S. aureus* superantigens (which result in excessive immune activation) among patients than among controls.[36] Treatment that is aimed at reducing microbial load or eradicating pathogens from the sinuses involves an assumption that these play a role in causing or propagating chronic rhinosinusitis. However, whether sinus microbiota actually cause exacerbations or whether the changes seen are related to the inflammatory process remains unclear.

In a trial in which patients with chronic rhinosinusitis with nasal polyps were randomly assigned to receive doxycycline (3-week course), methylprednisolone, or placebo, doxycycline and methylprednisolone each significantly reduced polyp size relative to placebo.[37] Methylprednisolone appeared to have a greater benefit and faster onset of action, whereas doxycycline appeared to have a more sustained effect.[37] Another randomized trial involving patients who had undergone surgery for nasal polyps showed a lower incidence

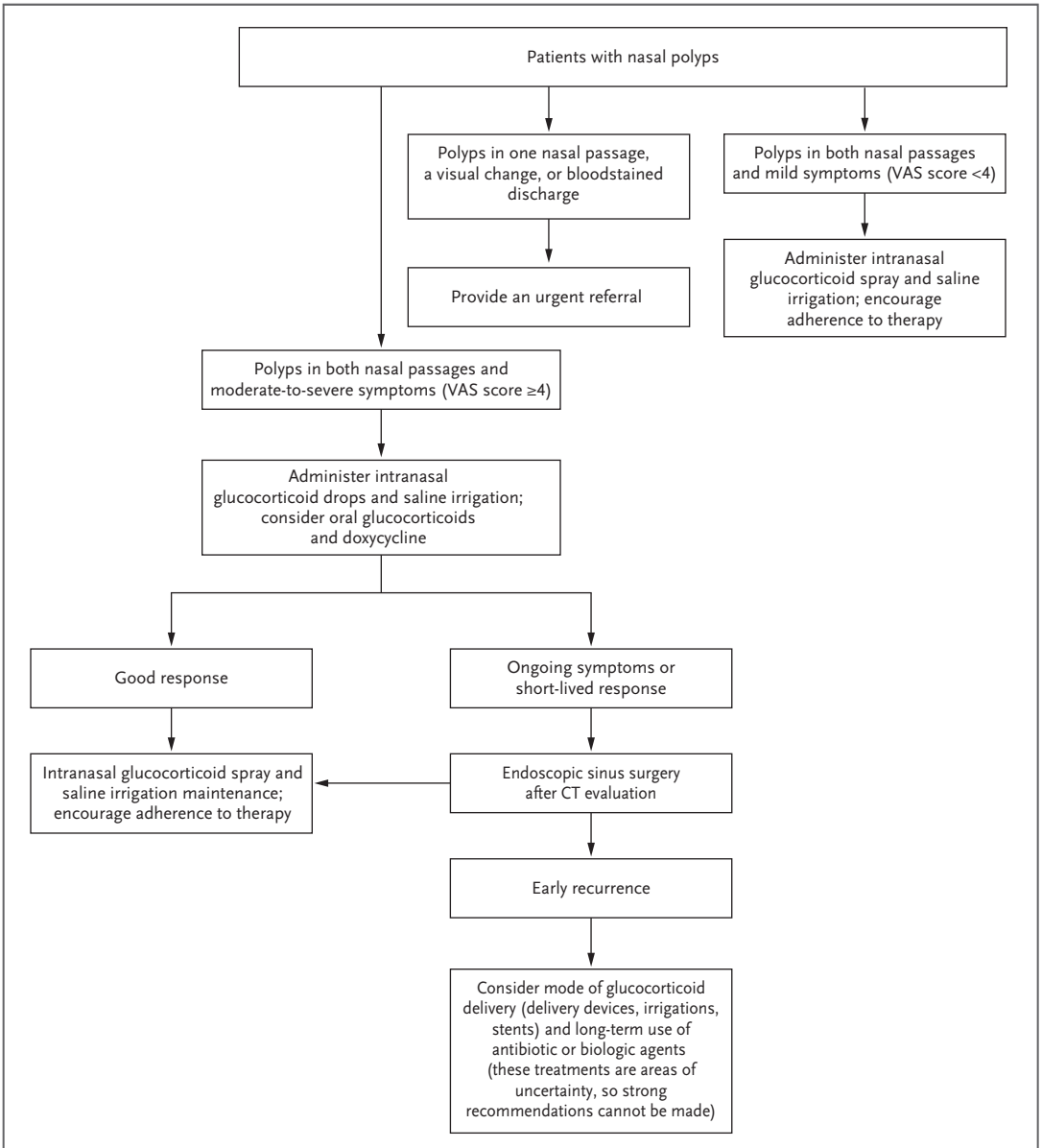

Figure 3. Algorithm for Treatment of Adults with Chronic Rhinosinusitis and Nasal Polyps.

The treatment algorithm is based on current guidelines and best available evidence.[1,26] A 10-cm visual-analogue scale (VAS) is useful and reasonable in primary care for the evaluation of overall symptom severity (with scores from 0 to 3 indicating a mild condition, >3 to 7 a moderate condition, and >7 a severe condition).

of early polyp recurrence, as assessed by endoscopy and CT, among patients given macrolides than among controls.[38] Available data suggest that long-term use of antibiotic agents may be considered as an adjunct to treatment in patients with chronic rhinosinusitis with nasal polyps, but further evaluation is needed, including evaluation of the effect on antibiotic resistance. Randomized trials have shown no benefit of antifungal therapy, either orally or topically, in patients with chronic rhinosinusitis with nasal polyps.[39]

SURGERY

Endoscopic sinus surgery is usually reserved for patients who have not had a benefit from medical therapy with regard to symptoms, patients who

have contraindications to or adverse effects from such therapy, or rarely, patients who have actual or impending complications, such as loss of vision. Surgery aims to remove polyps as well as to improve access to ongoing topical therapy; as discussed above, the effectiveness of intranasal glucocorticoids is enhanced after sinus surgery. A recent consensus to define indications for sinus surgery[40] recommended that adult patients with uncomplicated chronic rhinosinusitis with nasal polyps could be appropriately offered surgery when there was objective evidence of chronic rhinosinusitis on CT imaging, there was a minimum trial of 8 weeks of treatment with a topical intranasal glucocorticoid plus 1 to 3 weeks of systemic glucocorticoids (provided that there were no contraindications), and there was a post-treatment total SNOT-22 score of 20 or more, which is consistent with at least moderate severity.

Surgery is conventionally performed while the patient is under general anesthesia, although office-based procedures performed while the patient is awake are becoming more widespread.[41] Surgery usually involves both the removal of polyps obstructing the nasal cavity and procedures to open and extirpate polyps from the paranasal sinuses.

In a large binational cohort study, persons who underwent surgery had long-term, large improvements in health-related quality of life that were maintained over a period of 5 years.[42] However, polyp recurrence is common. Recurrent polyps have been reported on endoscopy in 40% of patients 18 months after surgery,[43] and in the large cohort study, 20% of patients underwent a revision sinus procedure within 5 years.[42] Data from randomized trials indicate that postoperative use of intranasal glucocorticoids improves symptom control and endoscopic scores and reduces the need for rescue therapy with prednisolone.[44] Ongoing medical therapy is therefore considered to be an essential part of surgical management, and patients must be counseled appropriately before and after surgery.

In patients with aspirin-exacerbated respiratory disease, postoperative aspirin desensitization (in which escalating doses are given under close medical supervision to induce tolerance) may reduce the risk of polyp recurrence.[45,46] However, gastrointestinal side effects and other adverse events contribute to low rates of continued adherence to therapy (as many as 50% of patients have withdrawn from trials). Using a lower maintenance dose may improve adherence; current regimens vary between 100 mg and 650 mg of aspirin daily, and trials comparing relative effectiveness have been limited.

AREAS OF UNCERTAINTY

A new exhalation delivery device, in which nasal delivery is driven by the patient's exhaled breath, has been shown to improve symptom control significantly, with complete polyp elimination in 25% of patients in a placebo-controlled trial, but the treatment has not undergone direct comparison with standard delivery systems.[47] Glucocorticoid-eluting stents are also being developed for use before and after sinus surgery, with the aim of higher local concentrations leading to greater control of inflammation and overcoming adherence issues. A randomized trial showed significant reductions in the incidence of surgery, in symptom scores, and in ethmoid sinus obstruction with a bioabsorbable, glucocorticoid-eluting stent, as compared with a sham procedure[48]; more data are needed to inform the cost-effectiveness and role of such stents in practice. Data are inconsistent regarding a possible benefit of the use of leukotriene inhibitors as an adjunct to glucocorticoid therapy.

Monoclonal antibodies that directly target the inflammatory pathway have been suggested as another therapy for chronic rhinosinusitis with polyps. In small, short-term, randomized trials, biologic agents that are approved for the treatment of refractory allergic asthma, including omalizumab[49] (anti-IgE), mepolizumab[50] (anti–interleukin-5), and dupilumab[51] (anti–interleukin-4 and anti–interleukin-13) significantly reduced both symptom scores and polyp size. Clinically significant reductions[52] in mean polyp scores were observed in 60% and 70% of participants in the mepolizumab and dupilumab trials, respectively, with a medium effect size in terms of reduction in the SNOT-22 score. Several ongoing phase 3 trials are further evaluating these agents in patients with nasal polyps (including mepolizumab [ClinicalTrials.gov number, NCT03085797] and dupilumab [NCT02912468]). High costs, the risk of anaphylaxis, and the use of subcutaneous injection are limiting factors in widespread application of such treatments at present. It is possible that downstream inhibition of individual cytokines

may be ineffective, given the redundancy of inflammatory pathways.

Classification of chronic rhinosinusitis into different endotypes on the basis of the inflammatory profile (e.g., on the basis of the expression of different type 2 inflammatory cytokines) has been proposed to better predict disease course and effective therapies.[53] Further work is needed to identify clinically relevant biomarkers and to determine whether treatment pathways that are based on individual endotypes are more effective than current strategies.

GUIDELINES

Guidelines endorsed by the European Rhinologic Society[1] as well as those endorsed by the American Rhinologic Society and American Academy of Otolaryngic Allergy[26] address the diagnosis and management of nasal polyps. The recommendations in this review are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has progressive nasal obstruction and hyposmia and has polyps visible on rhinoscopy in both nasal passages — findings that are consistent with a diagnosis of chronic rhinosinusitis with polyps. He presents with severe symptoms, and therefore I would recommend a trial of oral glucocorticoids for 14 days, oral doxycycline at a dose of 100 mg daily for 3 weeks (although data are limited with regard to showing that the combination of doxycycline and oral glucocorticoids results in better outcomes than either alone), and topical glucocorticoid drops, applied in a head-down position for 4 weeks.

If the patient had a good response, I would recommend that he use an intranasal glucocorticoid spray daily to maintain benefit, as well as saline irrigation for symptomatic relief. This regimen would also be suitable as first-line treatment in patients with mild symptoms. If the patient continued to have moderate-to-severe symptoms at the 4-week follow-up, he should be referred to an otorhinolaryngologist for consideration of sinus surgery.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl 2012;23:1-298.
2. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg 1995;113:104-9.
3. Abdalla S, Alreefy H, Hopkins C. Prevalence of Sinonasal Outcome Test (SNOT-22) symptoms in patients undergoing surgery for chronic rhinosinusitis in the England and Wales National prospective audit. Clin Otolaryngol 2012;37:276-82.
4. Hox V, Bobic S, Callebaux I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology 2010;48:426-32.
5. Larsen K, Tos M. The estimated incidence of symptomatic nasal polyps. Acta Otolaryngol 2002;122:179-82.
6. Johansson L, Akerlund A, Holmberg K, Melén I, Bende M. Prevalence of nasal polyps in adults: the Skövde population-based study. Ann Otol Rhinol Laryngol 2003;112:625-9.
7. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis: a review of 6,037 patients. J Allergy Clin Immunol 1977;59:17-21.
8. Woodard T, Sindwani R, Halderman AA, Holy CE, Gurrola J II. Variation in delivery of sinus surgery in the Medicaid population across ethnicities. Otolaryngol Head Neck Surg 2016;154:944-50.
9. Kim JE, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. Ear Nose Throat J 2007;86:396-9.
10. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. Laryngoscope 2001;111:1006-19.
11. DelGaudio JM, Loftus PA, Hamizan AW, Harvey RJ, Wise SK. Central compartment atopic disease. Am J Rhinol Allergy 2017;31:228-34.
12. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy 2006;61:1280-9.
13. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol 2016;137(5):1449-1456.e4.
14. Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. Am J Rhinol 2004;18:15-21.
15. Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. Int Forum Allergy Rhinol 2016;6:373-7.
16. Grigoreas C, Vourdas D, Petalas K, Simeonidis G, Demeroutis I, Tsioulos T. Nasal polyps in patients with rhinitis and asthma. Allergy Asthma Proc 2002;23:169-74.
17. Beule A. Epidemiology of chronic rhinosinusitis, selected risk factors, comorbidities, and economic burden. GMS Curr Top Otorhinolaryngol Head Neck Surg 2015;14:Doc11.
18. Cohen NA, Widelitz JS, Chiu AG, Palmer JN, Kennedy DW. Familial aggregation of sinonasal polyps correlates with severity of disease. Otolaryngol Head Neck Surg 2006;134:601-4.
19. Veloso-Teles R, Cerejeira R, Roque-Farinha R, von Buchwald C. Higher preva-

lence of nasal polyposis among textile workers: an endoscopic based and controlled study. Rhinology 2018;56:99-105.
20. De Schryver E, Derycke L, Campo P, et al. Alcohol hyper-responsiveness in chronic rhinosinusitis with nasal polyps. Clin Exp Allergy 2017;47:245-53.
21. Naclerio RM, Bachert C, Baraniuk JN. Pathophysiology of nasal congestion. Int J Gen Med 2010;3:47-57.
22. Kim JK, Cho JH, Jang HJ, Shim DB, Shin HA. The effect of allergen provocation on the nasal cycle estimated by acoustic rhinometry. Acta Otolaryngol 2006;126:390-5.
23. Stanton AE, McGarry GW, Carter R, Bucknall CE. Spectrum of nasal disease in an asthma clinic: when is an ENT opinion indicated? J Laryngol Otol 2009;123:613-8.
24. Lund VJ, Clarke PM, Swift AC, McGarry GW, Kerawala C, Carnell D. Nose and paranasal sinus tumours: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016;130:S2:S111-S118.
25. Tosun F, Arslan HH, Karslioglu Y, Deveci MS, Durmaz A. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. Ann Otol Rhinol Laryngol 2010;119:455-9.
26. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol 2016;6:Suppl 1:S22-S209.
27. Rudmik L, Hopkins C, Peters A, Smith TL, Schlosser RJ, Soler ZM. Patient-reported outcome measures for adult chronic rhinosinusitis: a systematic review and quality assessment. J Allergy Clin Immunol 2015;136(6):1532-1540.e2.
28. Hopkins C, Hettige R, Soni-Jaiswal A, et al. CHronic Rhinosinusitis Outcome MEasures (CHROME), developing a core outcome set for trials of interventions in chronic rhinosinusitis. Rhinology 2018;56:22-32.
29. Doulaptsi M, Prokopakis E, Seys S, Pugin B, Steelant B, Hellings P. Visual analogue scale for sino-nasal symptoms severity correlates with Sino-Nasal Outcome Test 22: paving the way for a simple outcome tool of CRS burden. Clin Transl Allergy 2018;8:32.
30. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev 2016;4:CD011993.
31. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. J Investig Allergol Clin Immunol 2012;22:1-12.
32. Rudmik L, Xu Y, Liu M, Bird C, Kukec E, Quan H. Utilization patterns of topical intranasal steroid therapy for chronic rhinosinusitis: a Canadian population-based analysis. JAMA Otolaryngol Head Neck Surg 2016;142:1056-62.
33. Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ. Topical steroids for nasal polyps. Cochrane Database Syst Rev 2012;12:CD006549.
34. Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. Int Forum Allergy Rhinol 2018;8:461-70.
35. Head K, Chong LY, Hopkins C, Philpott C, Burton MJ, Schilder AG. Short-course oral steroids alone for chronic rhinosinusitis. Cochrane Database Syst Rev 2016;4:CD011991.
36. Ou J, Wang J, Xu Y, et al. Staphylococcus aureus superantigens are associated with chronic rhinosinusitis with nasal polyps: a meta-analysis. Eur Arch Otorhinolaryngol 2014;271:2729-36.
37. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol 2010;125(5):1069-1076.e4.
38. Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. Int Forum Allergy Rhinol 2014;4:533-41.
39. Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane Database Syst Rev 2011;8:CD008263.
40. Rudmik L, Soler ZM, Hopkins C, et al. Defining appropriateness criteria for endoscopic sinus surgery during management of uncomplicated adult chronic rhinosinusitis: a RAND/UCLA appropriateness study. Rhinology 2016;54:117-28.
41. Kilty SJ, Lasso A, Mfuna-Endam L, Desrosiers MY. Case-control study of endoscopic polypectomy in clinic (EPIC) versus endoscopic sinus surgery for chronic rhinosinusitis with polyps. Rhinology 2018;56:155-7.
42. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Laryngoscope 2009;119:2459-65.
43. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. Laryngoscope 2017;127:550-5.
44. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology 2005;43:2-10.
45. Klimek L, Dollner R, Pfaar O, Mullol J. Aspirin desensitization: useful treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) in aspirin-exacerbated respiratory disease (AERD)? Curr Allergy Asthma Rep 2014;14:441.
46. Levy JM, Smith TL. Is aspirin desensitization indicated for the treatment recalcitrant chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease? Laryngoscope 2017;127:776-7.
47. Leopold DA, Elkayam D, Messina JC, Kosik-Gonzalez C, Djupesland PG, Mahmoud RA. NAVIGATE II: randomized, double-blind trial of the exhalation delivery system with fluticasone for nasal polyposis. J Allergy Clin Immunol 2019;143(1):126-134.e5.
48. Kern RC, Stolovitzky JP, Silvers SL, et al. A phase 3 trial of mometasone furoate sinus implants for chronic sinusitis with recurrent nasal polyps. Int Forum Allergy Rhinol 2018;8:471-81.
49. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013;131(1):110-6.e1.
50. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol 2011;128(5):989-95.e1.
51. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016;315:469-79.
52. Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. J Allergy Clin Immunol 2005;116:1275-81.
53. Bachert C, Akdis CA. Phenotypes and emerging endotypes of chronic rhinosinusitis. J Allergy Clin Immunol Pract 2016;4:621-8.