

Prognosis and prediction of response to surgery in allergic patients with chronic sinusitis

François Lavigne, MD,^a Cong Thu Nguyen, MD,^a Lisa Cameron, PhD,^b Qutayba Hamid, MD, PhD,^b and Paolo M. Renzi, MD^{a,b}
Montreal, Quebec, Canada

Background: Chronic rhinosinusitis (CRS) occurs frequently in patients with atopy, but little is known of the prognosis after surgery and of factors that may predict a poor outcome.

Objective: Our purpose was to assess the long-term prognosis in atopic patients with CRS who undergo surgery and whether certain immune markers could predict a worse prognosis in this setting.

Methods: Fifteen patients with diffuse involvement of the sinuses on computed tomographic (CT) scan but without nasal polyposis underwent ethmoidectomy with middle meatotomy for CRS when it was clinically indicated. All patients had a biopsy of the inferior turbinate and of the most inflamed areas of the maxillary and ethmoid sinuses at the time of surgery. Follow-up was performed by video endoscopy and by assessment of 2 chronic sinusitis questionnaires at 0, 6, and 24 months postoperatively. The number of lymphocyte subsets (CD3, CD4, CD8), mast cells and eosinophils, and cells expressing IL-4 and IL-5 messenger RNA (mRNA) in all 3 biopsy sites at the time of surgery were compared with the clinical response after surgery.

Results: Seven patients had persistent improvement after surgery, with a decrease in pain, rhinorrhea, or nasal obstruction and a decrease in the need for medication. Eight patients were unchanged or worsened after surgery with disabling rhinorrhea and repeated sinusitis. We found no difference in the number of inflammatory cells, lymphocyte subsets, or IL-4 mRNA-positive cells in the sinus mucosa between responders and nonresponders. However, an increased number of cells expressing IL-5 mRNA was found in the ethmoid sinus at the time of surgery in patients who did not respond to the surgical intervention ($P = .007$).

Conclusion: More than 50% of patients with perennial rhinitis and CRS do not improve after surgery, a response that may be predicted by more cells expressing IL-5 mRNA in the ethmoid sinuses. The increased number of cells expressing IL-5 mRNA may have the potential to be used as a marker for prediction of the response to surgery. The worsening of symptoms in some patients with CRS after sinus surgery could be a result of the disturbance of the anatomy of the sinuses and exposure to the environmental allergens. (*J Allergy Clin Immunol* 2000;105:746-51.)

Key words: Chronic rhinosinusitis, allergy, IL-5, complications of sinus surgery, outcome after sinus surgery

Surgery is necessary in patients with chronic rhinosinusitis (CRS) when recurrent infection or the major symptoms of facial pain, nasal obstruction, and rhinorrhea are not improved by medical therapy.¹ The current surgical intervention that is recommended in these patients is functional endoscopic sinus surgery (FESS).² This intervention is a drainage procedure that seems more compatible with the physiologic features of the sinuses than prior surgical interventions and consists of infundibulotomy, middle meatal antrostomy, and selective exposure of some of the ethmoidal cells. Subjective improvement after FESS has been reported in up to 91% of patients after surgery.³ However, objective assessments of nasal resistance,⁴ olfactory perception,⁵ and endoscopic evaluation⁶ revealed that in almost 50% of the cases there is persistence of some of the preoperative abnormalities or significant residual disease. Outcome studies on FESS have shown that the most reliable determinant of a poor prognosis is the extent of sinus opacification on a computed tomographic (CT) scan of the sinuses. Interestingly, the patients with the most extensive involvement of the sinuses also have concomitant atopy and asthma.⁷ The presence of allergy may be a risk factor for the development of rhinosinusitis.^{8,9} This hypothesis has been predicated on the findings of positive skin tests in 57% of patients operated for CRS.⁶ In our experience allergic subjects with perennial rhinitis have less benefit from surgical procedures for CRS compared with those without allergies (unpublished data). Indeed, they often have persistence of disabling posterior rhinorrhea and recurrent infection.¹⁰

When the pathologic features of CRS are assessed, a different inflammatory response can be found in the sinuses of allergic and nonallergic subjects with this disease. Allergic subjects with CRS have an increase in tissue eosinophils, mast cells, and lymphocytes¹⁰ and also a different expression of cytokines and chemokines.¹¹⁻¹³ We have recently demonstrated that the inflammatory response that is present in allergic subjects with CRS also differs between anatomic locations (ie, the inferior turbinate, the ethmoid complex, and the sinus cavities).¹⁴ The inflammatory response seemed to be influenced by the amount of environmental exposure that occurred among the different sites, increasing in sites where environmental exposure is the most important.

From ^aCentre Hospitalier de l'Universitaire de Montréal, Notre-Dame Hospital, University of Montreal, and the ^bMeakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada.

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Reprint requests: F. Lavigne, MD, CHUM, Notre Dame Hospital, 1560, Sherbrooke St E, Montreal, PQ H2L 4M1, Canada.

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Abbreviations used

CRS:	Chronic rhinosinusitis
CT:	Computerized tomography
FESS:	Functional endoscopic sinus surgery
HPF:	High-power field
MBP:	Major basic protein
mRNA:	Messenger RNA
SSC:	Standard saline citrate
VAS:	Visual analog score

To determine the prognosis after surgery in patients with CRS, efforts have been undertaken to create a better staging system of sinus disease¹⁵ and an appropriate scoring of the surgical results according to subjective symptom surveys and objective assessments.¹⁶ We have applied these tools to the study of allergic patients with perennial rhinitis and diffuse mucosal thickness who met the criteria for surgery because of CRS. Our first objective was to determine the prognosis of a homogeneous group of patients with perennial rhinitis who undergo surgery for CRS. Our second objective was to determine whether an indicator of the immune response in biopsy specimens obtained at the time of surgery could predict a poor response to ethmoidectomy and middle meatotomy in these patients. The results from this study provide evidence that approximately half the allergic subjects with perennial rhinitis and CRS do not improve after surgery and that the presence of more cells expressing IL-5 messenger RNA (mRNA) in the ethmoid sinuses predicts a poor response to surgery.

MATERIAL AND METHODS

Study design

We undertook this study after approval by the Ethics Committee of Notre Dame Hospital. Patients were enrolled between November 1994 and January 1995 and were followed up until December 1997. Written informed consent was obtained in 16 consecutive atopic adults after their physician (F. L.) determined that there was a clinical indication for ethmoidectomy and middle meatotomy because of persistent CRS. Chronic sinusitis was defined as a clinical syndrome of rhinorrhea, congestion, and facial pain lasting for more than 3 months and resistant to medical therapy that included decongestants, antibiotics, and corticosteroids. The duration of persistent symptoms before surgery ranged from 18 to 38 months. Cigarette smoking was reported as more than 1 pack of cigarettes per day for 5 years (5 pack/years) in 2 patients. In all patients but one bilateral CRS was confirmed by CT examination that showed diffuse thickening in both the ethmoid and maxillary sinuses bilaterally with scores higher than 12 by the Lund-Mackay staging system.¹⁷ The one patient with unilateral CRS was withdrawn from the study before surgery. Patients with nasal polyposis or immunodeficiency and individuals who had undergone prior sinus surgery were excluded from the study. The presence of atopy in these subjects was confirmed clinically by positive skin tests (wheal of 3 mm or more) to at least 1 allergen in a panel of 11 common aeroallergens. All patients had a positive skin test to house dust mites, perennial rhinitis, or conjunctivitis with seasonal exacerbation of the symptoms in some. Peripheral eosinophil counts with complete blood cell counts were performed in all patients at the same time as specific IgE determination by radioallergosorbent testing when a doubt

persisted after skin tests. All patients were receiving nasal topical corticosteroids at the time of enrollment. These medications were withheld for 14 days before surgery and systemic corticosteroids had to be withheld for 2 months before surgery. Patients allergic to pollen underwent surgery out of the respective pollen season.

Symptoms and endoscopic assessment

We categorized the subjects into responders and nonresponders to surgery by use of a total score based on 2 questionnaires and endoscopic evaluation. The patients were assessed by questionnaires before surgery and 6 months and 24 months later. Results from the baseline evaluation and follow-up visit from 2 years later are presented in this article. The Chronic Sinusitis Survey-Duration Based questionnaire was used as previously described by Gliklich and Metson.¹⁸ This questionnaire is based on an assessment of the symptoms and the use of different medications in the last 8 weeks before the evaluation. The symptoms that were assessed were pressure pain, rhinorrhea, and nasal congestion. The medications assessed consisted of antibiotics, topical nasal sprays, and systemic sinus medications. If medication was used or symptoms were present for 2 of the last 8 weeks, the score was 2. This questionnaire does not assess the severity of the symptoms or the total amount of medication. A second symptom-based questionnaire was used. This questionnaire focused on 3 major symptoms: nasal obstruction and pressure pain, congestion, and rhinorrhea.¹⁹ These were assessed by the patient on a scaled visual analog score (VAS) of 0 to 10 according to severity, where 0 is no symptom present and 10 the most severe.

Videendoscopy was performed before surgery and at the last visit (2 years) for an objective evaluation of the nose and maxillary sinus cavity. Although the endoscopist was aware of the patients' symptoms, he was not aware of the results obtained from biopsy specimens, and pictures were taken to quantify the endoscopic appearances. The endoscopic appearances were quantified on a 0 to 2 point basis for the presence of discharge (0, none; 1, clear and thin; 2, thick and purulent) and mucosal status (0, normoplasia; 1, light hyperplasia with no erythema; 2, hyperplasia). A total score was calculated for each chronic sinusitis survey and endoscopic assessment.

Criteria for response to surgery

It was determined a priori that responders would have either a VAS score of less than 2.5 for all the symptom scores or a decrease of 5.0 from the initial score at 2 years after the surgery. For the Chronic Sinusitis Survey-Duration Based questionnaire, a reduction by 50% of the total score would be considered as a significant response to surgery. An improvement in the endoscopic score to <2 would also be considered a significant improvement.

Tissue collection

Patients were under general anesthesia when the biopsies were performed. Biopsy specimens were obtained within the sinuses from the regions that appeared the most hypertrophied and hyperemic. A Blekesly forceps was used in the ethmoid sinus, a flexible optical biopsy and grasping forceps was used in the maxillary sinus (Karl Storz Endoscopy, Culver City, Calif), and endoscopic scissors were used to obtain a biopsy specimen from the nasal inferior turbinate. Each tissue sample was divided into two and processed for in situ hybridization (fixed in fresh paraformaldehyde) and immunohistochemistry (quick frozen in ornithine carbamoyltransferase) as previously described.¹⁴

Immunohistochemistry

Immunohistochemistry was performed with mouse antihuman antibodies. The lymphocyte subsets that were assessed consisted of CD3 (total T cells, 1:100 dilution), CD4 (helper lymphocytes, 1:10 dilution), CD8 (suppressor/cytotoxic lymphocytes, 1:10 dilution)

from DAKO Diagnostics Canada, Mississauga, Ontario. Other cells included eosinophils that were major basic protein (MBP)-positive (culture supernatant of the BMK-13 cell line, 1:30 dilution, a kind gift from Dr R. Moqbel, Edmonton) and mast cells that were tryptase positive (1:250 dilution, Chemicon International, Temecula, Calif). The modified alkaline phosphatase-antialkaline phosphatase technique was used as previously described.¹⁴ Sections were incubated with the primary antibody diluted in TRIS-buffered saline solution at 4°C overnight. Rabbit antimouse Ig secondary Ig was then applied for 30 minutes, followed by the alkaline phosphatase-antialkaline phosphatase complex. The reaction was visualized with Fast Red TR (Sigma, St Louis, Mo) and alkaline phosphatase substrate.

In situ hybridization

Sections were permeabilized with 0.3% Triton X-100 in PBS for 10 minutes followed by exposure to proteinase K (1 g/mL in 20 mmol/L TRIS-hydrochloric acid and 1 mmol/L EDTA, pH 7.2) for 30 minutes at 37°C. The reaction was stopped by treating the slides with 4% paraformaldehyde for 5 minutes. Prehybridization was performed in 50% formamide and 2× standard saline citrate (SSC) for 30 minutes at 40°C.

For hybridization riboprobes, both antisense and sense were prepared from complementary DNA encoding IL-4 and IL-5 as previously described.¹⁴ Complementary DNAs were inserted into different pGEM vectors and linearized with appropriate enzymes before transcription. Transcription was performed in the presence of sulfur 35-labeled uridine triphosphate and T7 or SP6 RNA polymerases. Radiolabeled probes (1 million counts/min/section) diluted in hybridization buffer were used. Hybridization was conducted for 12 hours in a humid chamber at 40°C. Posthybridization washing was performed in decreasing concentrations of SSC (4× SSC to 0.05× SSC and ribonuclease) at 43°C. After dehydration, the slides were immersed in emulsion and left to dry overnight. The autoradiographs were developed after 12 days in Kodak D-19 and counterstained with hematoxylin. As a control, sections were hybridized with sense probes or treated with ribonuclease solution at 37°C for 40 minutes before the prehybridization step. No positive signals were observed in any of the control experiments.

Quantitation of the cellular infiltrate, lymphocyte subsets, and mRNA-positive cells

The cellular infiltrate was quantitated by performing immunohistochemistry or in situ hybridization on sections of biopsy specimens obtained from the inferior turbinate, the ethmoid, and the maxillary sinuses as previously described.^{12,14} Slides were counted in a blind manner with use of a light microscope with a 0.202 mm² graticule. At least 2 slides per measure were assessed from which 3 to 4 fields were counted. The graticule was oriented along the epithelial basement membrane and the results were expressed as positive cells per high power field. The within-observer coefficient of variation for repeated counts of immunostaining was 8% and for hybridized sections less than 5%.

Statistical analysis

For questionnaires and endoscopic score, comparisons were performed between responders and nonresponders with the Mann-Whitney *U* test. For demographic comparisons and histologic analysis, comparisons were performed between responders and nonresponders for mast cells (tryptase), eosinophils (MBP), lymphocyte subsets (CD3, CD4, CD8), and cells expressing mRNA for IL-4 and IL-5 in all 3 sites by use of the Student unpaired *t* test. Results of the questionnaires and endoscopic scores are presented as median. *P* values <.0166 were accepted as statistically significant according to the Bonferroni adjustment test because 3 sites were evaluated.

RESULTS

Patient characteristics and response to surgery

Sixteen patients were enrolled into the study after giving written informed consent. One patient was withdrawn before surgery because disease was unilateral, and all the remaining 15 subjects were enrolled and completed the study. Patient demographics are presented in Table I. All patients had perennial rhinitis and CRS without nasal polyposis. Of the subjects, 9 were female and 6 were male with a mean age of 35 ± 13.7 years. Seven of 15 patients improved (responders) after surgery and 8 were unchanged or worsened after surgery (nonresponders). There were only 2 current smokers, one in each group, having smoked the equivalent of 30 and 29 pack/years. The mean duration of symptoms before surgery was $4.4 \text{ years} \pm 2.8 \text{ years}$; responders had symptoms for $4.2 \pm 3.1 \text{ years}$ and nonresponders for $4.5 \pm 2.5 \text{ years}$. Seven patients of the 15 were asthmatics; 5 of 7 asthmatic patients were classified into the nonresponder group after surgery.

As shown in Table II, at the preoperative evaluation there was no difference between the 2 groups in symptoms, medication use, and endoscopic score. However, after surgery the 2 groups that were formed (responders and nonresponders) were significantly different for all the symptoms, medication assessments, and endoscopic score. Each patient was categorized into the same group whether the VAS symptom questionnaire or the Chronic Sinusitis Survey-Duration Based questionnaire were used. The endoscopic score categorized all patients but one into the same group as that of the questionnaires. One patient had a very impressive hypertrophy of the sinus mucosa and erythema with pus in the maxillary sinus cavity when he was evaluated at the 2-year visit, although he had improved by the questionnaires. He was treated with antibiotics and oral steroids, without success because the mucosa remained hypertrophied and associated with thick secretion. This patient was considered a nonresponder.

Pathologic assessment and response to surgery

Immunohistochemistry was performed to compare the amount of inflammatory cells present at the time of surgery in the subepithelium of the ethmoid sinus, maxillary sinus, and nasal turbinate to the clinical evaluations obtained 2 years later. The number of cells that stained positively for MBP, tryptase, CD3, CD4, and CD8 in the 3 sites where biopsies were performed did not differ between responders and nonresponders (Table III). A trend was found for an increased CD4/CD8 ratio in the ethmoid submucosa of responders ($P = .06$). Cells expressing IL-5 mRNA were higher in the maxillary sinus compared with the other sites, but the amount of cells did not correlate with response to surgery ($P = .06$). Cells expressing IL-5 mRNA were increased at the time of surgery in the ethmoid sinus of nonresponders (Table III and Fig 1). Responders after surgery had a median of

TABLE I. Patient characteristics

	Age (y)/ Sex	Smoking (pack/y)	Positive skin tests	Duration of symptoms (y)	CT staging	History
Nonresponder						
1	38/F	29	Dust, ragweed, cat, grass	10	18	Septoplasty, asthma
2	26/M	<5	Dust, pollens	3	22	Asthma
3	29/F	0	Dust, pollens	2	20	Asthma
4	49/M	0	Dust, animals	4	18	None
5	25/F	0	Dust	4	13	Septoplasty, asthma
6	22/F	0	Dust, grass	2	14	None
7	40/M	0	Dust, cat	6	19	Asthma, neutropenia
8	26/F	0	Dust, animals	3	16	None
Responder						
1	42/M	30	Dust, ragweed, grass	2	12	Tonsillectomy, septoplasty
2	75/F	0	Dust, pollens	15	12	Asthma
3	30/M	0	Dust, ragweed, animals	8	14	None
4	34/F	0	Dust, molds, pollens	2	19	None
5	25/M	<5	Dust, pollens, animals	4	20	None
6	44/F	<5	Dust, molds	5	20	Asthma
7	18/F	0	Dust, ragweed	2	14	None

F, Female; M, male.

TABLE II. Clinical symptoms and endoscopic assessment

	Symptom-based questionnaire (0-10)				Duration-based questionnaire (0-8 of last 8 wk)						Endoscopic score (0-4)
	Pressure	Rhinorrhea	Congestion	Total	Pressure	Rhinorrhea	Congestion	Antibiotics	Sprays	Medication	
Preoperative assessment											
Nonresponders	6	8	8	8	6	7	8	4	8	3	4
Responders	7	8	8	8	7	8	8	4	8	2	4
Statistical significance*	<i>P</i> = .71	<i>P</i> = .46	<i>P</i> = .7	<i>P</i> = .9	<i>P</i> = 1.0	<i>P</i> = .3	<i>P</i> = .21	<i>P</i> = .54	<i>P</i> = .7	<i>P</i> = .7	<i>P</i> = .8
Postoperative assessment†											
Nonresponders	4	8	8	8	4	8	6	3	8	4	4
Responders	1	2	1	2	0	0	0	0	0	0	1
Statistical significance*	<i>P</i> < .001	<i>P</i> = .001	<i>P</i> = .001	<i>P</i> = .002	<i>P</i> = .004	<i>P</i> = .002	<i>P</i> < .001	<i>P</i> = .001	<i>P</i> < .001	<i>P</i> < .001	<i>P</i> < .001

Results are presented as median for the 7 responders and 8 nonresponders. *Sprays*, Topical nasal medication; *Medication*, oral nasal medication.

*Mann-Whitney *U* test.

†At 2 years of follow-up.

TABLE III. Statistical comparisons between responders and nonresponders

	IL-4	IL-5	CD3	CD4	CD8	CD4/CD8	MBP	Tryptase
Inferior turbinate								
Responders	13 (5, 18)	4 (0, 7)	55 (35, 81)	40 (25, 60)	11 (9, 17)	4 (4, 7)	4 (1, 12)	19 (14, 29)
Nonresponders	12 (6, 21)	4 (2, 9)	54 (48, 81)	42 (32, 62)	10 (8, 18)	5 (3, 8)	6 (0, 9)	14 (12, 27)
Maxillary sinus								
Responders	5 (2, 10)	9 (7, 13)	81 (39, 92)	65 (30, 80)	13 (8, 19)	6 (3, 9)	10 (7, 17)	8 (2, 18)
Nonresponders	3 (2, 7)	12 (8, 17)	71 (39, 100)	53 (25, 78)	10 (10, 17)	6 (4, 9)	12 (5, 15)	9 (4, 11)
Ethmoid sinus								
Responders	8 (5, 9)	9 (8, 12)*	74 (49, 118)	65 (40, 100)	6 (4, 10)	15 (9, 19)†	14 (8, 26)	14 (7, 33)
Nonresponders	10 (7, 22)	15 (7, 22)	55 (45, 81)	47 (38, 75)	4 (3, 8)	9 (8, 15)	16 (11, 25)	17 (8, 30)

Results are presented as mean (minimum, maximum). Comparisons were performed with the number of cells or the number of cells expressing cytokines per HPF in between responders and nonresponders.

*Significant after Bonferroni correction.

† $P = .06$.

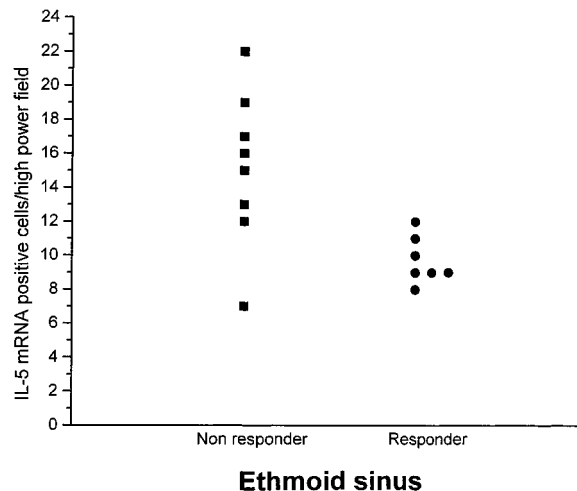


FIG 1. CD4/CD8 ratio and IL-5 mRNA-positive cells in ethmoid sinus of responder and nonresponder patients. CD4/CD8 ratio (left) or IL-5 mRNA– (right) positive cells per HPF were measured in the ethmoid sinus at the time of surgery and patients were classified 2 years later as either nonresponder or responder to surgery (see Methods). There was significant difference in IL-5 mRNA-positive cells between responder and nonresponder groups ($P = .007$, Mann-Whitney U test).

9 positive cells per high-power field (HPF) (minimum 8, maximum 12) and nonresponders had a median of 15.5 cells per HPF (minimum 7, maximum 22), $P = .007$. If a test using IL-5 mRNA-positive cells in the ethmoid sinuses was used, to differentiate responders from nonresponders with an arbitrary cutoff value of >11 positive cells per HPF, the sensitivity of this test would be 86% and the specificity 88%.

DISCUSSION

This study was undertaken to establish the long-term prognosis after ethmoidectomy and middle meatotomy in atopic patients with CRS and to determine whether there were some characteristics of the inflammation that is found in the sinuses at the time of surgery that predict a worse prognosis. The group as a whole was homogeneous because all patients were atopic with perennial rhinitis and extensive bilateral mucosal disease on the CT scan of the sinuses. Two years after surgery, we have found by 3 different methods of assessment that more than half the patients did not improve after surgery. In addition, an increased number of cells expressing IL-5 mRNA was found in the ethmoid sinus at the time of surgery in nonresponders.

Patients with CRS consult their physicians mainly because of persistent nasal obstruction or discharge and less often because of sinus pain and headache.²⁰ A surgical intervention is indicated when symptoms are not improved by conventional medical therapy. Endoscopic sinus surgery with ethmoidectomy and drainage of the natural ostia gives the best relief of pressure pain and

nasal obstruction,⁴ but, as our experience shows, nasal discharge will often persist, infections recur, and occasionally pain recurs, even when the meatotomy remains patent.²¹ The reported percentage of overall subjective improvement after surgical intervention for nonpolypoid patients with CRS is between 80% and 90%.^{3,6,19} However, the percentage of patients that improve after surgery drops to 50% when objective assessment by sinus endoscopy is performed.⁶ In this study we found less than a 50% response to surgery when the patients were followed up for 2 years. Pain, nasal obstruction, and nasal discharge were equally distributed in both groups before surgery, but nasal discharge and congestion persisted as main complaints in nonresponders after surgery and explained their persistent use of medication after surgery. The response to surgery reported in this study is similar to that reported by Senior et al.⁷ It thus seems that surgery is of limited value in the control of the most frequent symptoms that are present in patients with perennial allergic rhinitis, extensive sinusitis, and diffuse mucosal disease.

We assessed the response to surgery with 2 questionnaires: the Chronic Sinusitis Survey-Duration Based questionnaire and the symptom-based VAS. Although both questionnaires do not assess compliance, a weakness of the current study, both questionnaires classified each patient into the same group, suggesting that each method of assessment could be used interchangeably in homogeneous groups such as the one that we have studied here.

To assess whether a biologic marker could predict the absence of response to surgery, we obtained biopsy specimens from the inferior nasal turbinate and the most affected regions of the maxillary and ethmoid sinuses at the time of surgery. We measured the amount of inflammatory cells present, lymphocyte subsets, and the number of cells expressing IL-4 and IL-5 mRNA and compared these parameters between responders and nonresponders. We found no differences in the number of mast cells or eosinophils between responders and nonresponders. In a previous study we reported a significant increase in the CD4/CD8 ratio in the ethmoid sinus mucosa compared with that in the maxillary sinus and the inferior turbinate in allergic patients with CRS.¹⁴ The assessment of T-lymphocyte subsets in this study showed a trend for more T cells in the ethmoid sinuses of responders, with a clear predominance of CD4⁺ helper cells. The ethmoid sinuses are the sinuses that are the most exposed to the environment. Exposure of sinus mucosa to environmental allergens and irritants could lead to the presence of more CD4⁺ cells in the ethmoid sinuses because these cells are important in the initiation and regulation of allergic inflammation.²²

Lymphocytes affect the immune response through cell contact and the release of cytokines. The increased production of the T_H2 cytokines IL-4 and IL-5 in the airways of patients with asthma, in the nasal mucosa of patients with allergic rhinitis, and in the sinus mucosa of patients with allergy and CRS has been previously documented.^{12,22,23} However, we did not find a relationship

between the number of cells expressing IL-4 mRNA and the absence of response to surgery. The absence of relationship may be a result of the small number of patients followed up in this study (lack of power) or because IL-4 production is not important in the response to surgery.

IL-5 is another T_H2 cytokine that is involved in allergic inflammation. IL-5 stimulates the differentiation, survival, and activation of eosinophils; acts on mature B cells to cause increased synthesis of IgA²⁴; and potentiates the IL-4 and IL-2 effects on IgM and IgG production.²⁵ CD4-positive T lymphocytes are the major source of IL-5 in allergic tissue,²³ but mast cells and eosinophils also release IL-5. We have previously reported that IL-5 mRNA expression was significantly increased in cells of the ethmoid and maxillary sinuses compared with those of the inferior turbinate.¹⁴ In the current study the number of cells expressing IL-5 mRNA in the ethmoid sinus at the time of surgery was significantly increased in nonresponders. CD4-positive cells with a T_H2 phenotype are increased in CRS.²⁶ It could be that a specific subset of T cells or that other inflammatory cells that produce IL-5 mRNA are important in the response to surgery. It is not surprising to find that the ethmoid sinus is the site where we have found a marker of prognosis in patients with chronic sinusitis that do not respond to surgery because we had previously reported that the ethmoid sinus was the site with the most inflammation.¹⁴

Our results also suggest that in patients with an increased inflammatory response related to IL-5 production opening the sinus cavities would have a negative effect on the response to surgery. This effect might occur by exposing the sinuses to environmental allergens, infectious agents, and irritants and possibly by perpetuating the chronic inflammation that was present in the nasal cavity before surgery. The measurement of IL-5 mRNA-positive cells in the ethmoid sinus may help physicians in determining whether surgery is indicated in atopic patients with diffuse CRS. Because there is no surgical alternative for the time being, environmental control and immunotherapy is suggested in patients with the most cells expressing IL-5 mRNA in the ethmoid sinus to control their symptoms.

In conclusion, approximately half of allergic patients with CRS and diffuse mucosal disease do not respond to surgery. We have found that an increased number of cells expressing IL-5 mRNA in the ethmoid sinuses at the time of surgery could predict a bad prognosis. Randomized controlled studies are needed to determine whether measuring IL-5 mRNA⁺ cells in ethmoidal mucosa can help select atopic patients who will respond to sinus surgery and improve outcomes. It may eventually be possible to classify subjects with CRS into different groups with a different prognosis, which in turn may necessitate different therapeutic interventions.

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