

Comparison of Cefuroxime With or Without Intranasal Fluticasone for the Treatment of Rhinosinusitis

The CAFFS Trial: A Randomized Controlled Trial

Rowena J. Dolor, MD, MHS

David L. Witsell, MD, MHS

Anne S. Hellkamp, MS

John W. Williams, Jr, MD, MHS

Robert M. Califf, MD

David L. Simel, MD, MHS

for the Ceftin and Flonase for Sinusitis (CAFFS) Investigators

ALTHOUGH USE OF INHALED intranasal corticosteroid therapy with antibiotics has not been rigorously studied in the treatment of sinus disease, this combination is often prescribed for patients with chronic, persistent sinusitis. The relative safety of intranasal corticosteroids makes their use appealing for treatment of sinusitis. Intranasal corticosteroids have proven efficacy in controlling the symptoms of allergy and postnasal drip by reducing inflammation and mucosal edema of the nasal turbinates and sinus ostia.¹ In theory, by decreasing the inflammatory response and reducing mucosal swelling, these agents should promote drainage and increase aeration of the sinuses, hasten the elimination of the infectious organisms, and decrease the frequency and severity of recurrences.¹

Investigations of whether intranasal corticosteroids promote resolution of symptoms and prevent recurrences of sinusitis have yielded conflicting results.²⁻⁷ Previous studies, involving small cohorts of patients with chronic

Context It is not known whether intranasal corticosteroids are beneficial to treat acute rhinosinusitis in patients with a history of chronic or recurrent sinus symptoms.

Objective To assess whether the addition of an intranasal corticosteroid to antibiotic therapy affects the speed and rate of recovery of such patients with acute rhinosinusitis.

Design, Setting, and Patients A double-blind, randomized, placebo-controlled multicenter trial of 95 patients (median age, 39 years) with a history of recurrent sinusitis or chronic rhinitis and evidence of acute infection by sinus radiograph or nasal endoscopy, which was conducted from October 1998 through April 2000 at 22 sites (12 primary care and 10 otolaryngology).

Intervention Two puffs (total dose, 200 µg) of fluticasone propionate (n=47) or placebo nasal spray (n=48) in each nostril once daily for 21 days; all received 2 puffs of xylometazoline hydrochloride in each nostril twice daily for 3 days and 250 mg of cefuroxime axetil twice daily for 10 days.

Main Outcome Measure Time to clinical success (patient reported cured or much improved) during telephone follow-up at 10, 21, and 56 days.

Results A total of 88 patients (93%) completed follow-up. Patients recorded their symptoms, work assessment, and compliance during the 3-week treatment phase. Patients receiving fluticasone achieved a significantly higher rate of clinical success than patients receiving placebo (93.5% vs 73.9%; $P=.009$). Patients treated with fluticasone improved significantly more rapidly (median of 6.0 days to clinical success) vs patients in the placebo group (median of 9.5 days; $P=.01$).

Conclusions The addition of fluticasone to xylometazoline and antimicrobial therapy with cefuroxime improves clinical success rates and accelerates recovery of patients with a history of chronic rhinitis or recurrent sinusitis who present for treatment of acute rhinosinusitis.

JAMA. 2001;286:3097-3105

www.jama.com

bacterial sinusitis and/or nasal polypoidosis, showed a trend toward improvement in patients who received nasal corticosteroids, but were underpowered to show an effect on clinical outcome. Overall, none of the previous studies unequivocally proved the efficacy or justified the routine use of nasal corticosteroids in sinusitis. To assess the role of these agents for the effective management of rhinosinusitis, the Ameri-

can Academy of Allergy, Asthma, and Immunology and the American Academy of Otolaryngology–Head and Neck Surgery Foundation have recommended additional studies comparing antibiotic with and without nasal cor-

Author Affiliations, Financial Disclosures, and a list of CAFFS Investigators are at the end of this article. **Corresponding Author and Reprints:** Rowena J. Dolor, MD, MHS, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705 (e-mail: dolor001@mc.duke.edu).

ticosteroid treatment for patients with either chronic or recurrent symptoms.⁸

We assessed the effectiveness of fluticasone propionate nasal spray in combination with cefuroxime axetil in acute rhinosinusitis in a diverse population of patients. Fluticasone nasal spray is a once-a-day intranasal corticosteroid indicated for the management of seasonal and perennial allergic rhinitis and perennial nonallergic rhinitis. It is a potent topical glucocorticoid with 2-fold greater affinity for the glucocorticoid receptor than beclomethasone and a 3-fold greater affinity than budesonide.⁹ A favorable efficacy and safety profile for fluticasone aqueous nasal spray in rhinitis has been demonstrated in prospective, double-blind, placebo-controlled, parallel-group studies.^{10,11} Cefuroxime has been shown to be effective in the treatment of acute bacterial sinusitis.¹² We examined whether the addition of fluticasone to cefuroxime could affect the speed and rate of recovery in patients with rhinosinusitis. To better understand patient perceptions of this combination treatment, we also measured factors affecting quality of life (eg, number of telephone calls to the clinic, days missed from work, and adverse events).

METHODS

The Ceftin and Flonase for Sinusitis (CAFFS) trial was a double-blind, randomized, placebo-controlled study designed to determine the effectiveness of a 10-day course of cefuroxime combined with a 3-day treatment with xylometazoline, with or without a 21-day course of intranasal fluticasone in patients with acute rhinosinusitis. The institutional review board for each participating site approved the study. All patients gave written informed consent.

Patients and Setting

Patients 18 years or older presenting with acute sinonasal symptoms and a history of previously diagnosed recurrent or chronic sinusitis that necessitated antibiotic therapy were eligible for

enrollment. Subjects were enrolled between October 1998 and April 2000 from 22 sites (12 primary care and 10 otolaryngology). Study sites were chosen from 3 research networks: the Surgeons' Outcomes Research Cooperative in Otolaryngology, the Duke Primary Care Research Consortium, and the Primary Care Network. Eighteen of the 22 sites (82%) were community-based primary care or otolaryngology clinics. The other sites consisted of 2 academic and 2 Veterans Affairs clinics. This sample was assembled to be representative of the type of patients seen in general practice. We believed that patients from either recurrent or chronic sinusitis groups were optimal candidates for randomization to a 3-week course of nasal corticosteroids, with subsequent measurement of disease response over the 8-week follow-up period.

All patients were required to have evidence of sinus infection on either plain film sinus radiograph (Waters view) or nasal endoscopy. Criteria for acute sinusitis on the Waters view consisted of an air-fluid level, mucosal thickening, or opacification of a maxillary sinus.¹³⁻¹⁵ All radiographs were interpreted by a local radiologist or otolaryngologist. The endoscopic criterion for sinusitis was purulent drainage from the middle meatus or sinus ostium.

To increase the probability of identifying patients with sinusitis, we screened patients for the major symptom criteria for acute rhinosinusitis developed by the Task Force on Rhinosinusitis of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS).¹⁶ These criteria included headache, facial pain and pressure, nasal congestion, thick, colored nasal discharge, and olfactory disturbance. Patients with 2 or more of these 5 symptoms were eligible for enrollment. Patients were excluded for any of the following conditions: previous sinus surgery, sinus lavage within the past 7 days, nasal polyposis, recurrent moderate epistaxis, chronic bacterial sinusitis with failure of antimicrobial therapy, intranasal corticosteroid use within the

past 14 days, chronic use of corticosteroids or immunosuppressive agents, immunocompromised state, or allergy to cephalosporins or penicillins. Patients with no home telephone were also excluded. Antibiotic use in the past 7 days was not permitted; antimicrobials with a longer half-life (ie, cefpodoxime and all fluoroquinolones) could not have been administered within the past 21 days. Pregnant and nursing women were excluded; women of childbearing potential were required to have a negative serum pregnancy test result prior to enrollment and to use an effective form of birth control during the trial and follow-up period.

Randomization

A permuted block randomization scheme, stratified by site and with a block size of 4, was used to ensure even treatment allocation and was generated using SAS version 6.12 (SAS Institute, Cary, NC). Site personnel were blinded to block size and given study kits to administer sequentially. Subjects, investigators, and research coordinators were unaware of the assigned treatment. To assess the effectiveness of blinding, we asked patients whether they thought they received fluticasone or placebo nasal spray at the 21-day telephone follow-up.

Treatment

Patients were randomly assigned to 2 puffs (total dose, 200 µg) of either fluticasone propionate (Flonase, GlaxoSmithKline) or placebo nasal spray, taken once a day in each nostril for 21 days. All patients received cefuroxime axetil (Ceftin, GlaxoSmithKline) 250 mg twice daily for 10 days, as well as 2 puffs of xylometazoline hydrochloride per nostril twice daily for 3 days, 10 minutes before using the study nasal spray. Patients received booklets containing specific instructions for use of intranasal fluticasone or placebo nasal spray. Patients were also given a standardized form to assess compliance with medications. Oral decongestants, antihistamines, and mucolytics were not permitted; patients taking any of these agents

prior to enrollment were asked to discontinue them during the study. Corticosteroids (oral or parenteral) and immunosuppressive medications were not permitted. However, patients were allowed to continue immunotherapy for allergies, orally inhaled corticosteroids, and analgesics, including nonsteroidal anti-inflammatory agents, during the trial. Sinus lavage or sinus surgery was discouraged during the first 3 weeks of the trial to reduce the number of cointerventions performed during the medication phase of the study.

Assessments

Demographic variables collected at baseline included age, ethnicity, sex, employment status, history of recent upper respiratory tract infection, history of allergy, history of asthma, tobacco use, other significant comorbidities, and prestudy medications (eg, decongestants, intranasal or systemic corticosteroids, mucolytics, analgesics, anti-inflammatory agents, and antihistamines).

Clinical variables included the presence or absence of nasal discharge, cough, colored nasal discharge, facial pain, maxillary toothache, fever, and symptom duration. All patients underwent physical examination, including palpation of the sinuses and assessment for nasal edema, erythema, or discharge.

Measurements

Patients recorded their daily symptom status, work attendance, and work performance in a standardized diary, which was also used to assess compliance during the 3-week treatment phase. Patients were asked to rate their overall sinus symptoms on a numeric scale, with 0 representing no sinus symptoms and 10 representing the worst possible sinus symptoms. Employed patients were asked to record whether they were able to attend work and the number of hours missed, if applicable. Also, they were asked to estimate their level of job performance while working with sinusitis on a scale of 0% to 100%, with 0% representing total in-

ability to perform usual work and 100% representing full ability to perform usual work. To improve compliance, patients were asked to mark a reminder box stating that they took the medications according to schedule.

At baseline, 10, 21, and 56 days, sinusitis quality of life was measured by using the Sinonasal Outcome Test-20 (SNOT-20).¹⁷ This 20-item, patient-based questionnaire that was adapted from the Rhinosinusitis Outcome Measure-31¹⁸ measures health status and health-related quality of life for patients with rhinosinusitis. A measure of each patient's general quality of life was obtained at baseline and at day 21 by using the acute version of the Short Form-12 (SF-12) survey, in which patients rate their quality of life within the past week.¹⁹

Telephone follow-up at 10, 21, and 56 days after enrollment was obtained to ensure collection of primary end point data, work attendance and performance, additional visits, adverse events, and recurrences. Patients rated their sinus symptoms on a 6-point Likert scale: cured, much improved, somewhat improved, no change, somewhat worse, and much worse. If symptoms were cured or much improved, patients were then asked to refer to their diary to find and report the date that they noted the change. Patients were asked to rate their overall sinus symptoms on a numeric scale as described above. They were asked to report the number of telephone calls, if any, to the physician's office for adverse effects or treatment problems. Investigators were not required to determine which of the 3 study medications administered was responsible for the adverse effect. Based on the information in the patient diary, a self-report of the number of hours or days missed from work because of sinusitis was also recorded. Recurrence was defined as a flare of symptoms requiring additional visits and/or therapy. Patients were asked if they had had a recent clinic visit or whether they had required any additional medication, diagnostic tests, or surgical procedures for treatment of sinusitis since the last

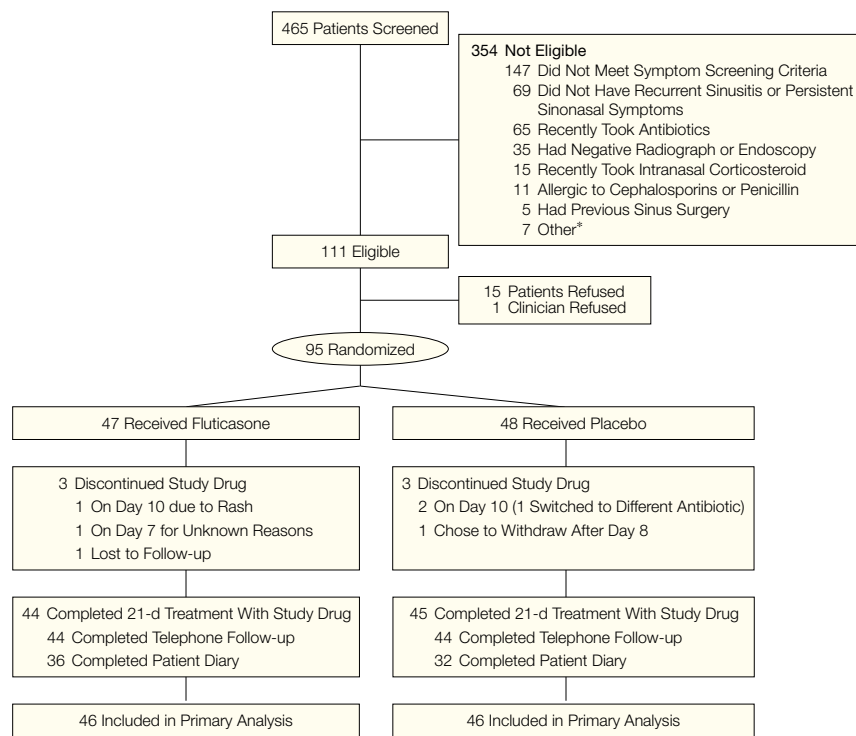
follow-up call. All patient records were reviewed for verification of any events that occurred during follow-up. Patient diaries and records were reviewed without knowledge of treatment assignment.

To ensure consistency of the protocol across all clinical settings, the study sites were given written, standardized instructions for conducting the study and collecting data, as well as a standardized script for conducting telephone interviews. Although we did not formally test the interrater reliability of the telephone interview, an analysis comparing the patient diary sinus symptom responses at days 10 and 21 with the telephone follow-up responses on the same days shows high correlation (Pearson correlation coefficient, 0.88 at day 10 and 0.96 at day 21). Therefore, the agreement between patient-recorded and interviewer-obtained symptoms is very high, suggesting a consistent and reliable approach to interviewer-obtained data across sites. One clinical research associate at the Duke Clinical Research Institute performed in-house monitoring of all the study data (ie, reviewing case report forms and screening logs, generating queries). Enrollment faxes, study reminders, and updates were sent to sites on a regular basis. The research associate also called all sites twice each month to assess site performance and ensure consistency of the study protocol.

Data Analysis

Data were analyzed on the intention-to-treat principle. Patients who discontinued the treatment medication were asked to continue with the follow-up assessments. Continuous variables were analyzed with the Wilcoxon rank sum test. Categorical variables were analyzed by using likelihood ratio χ^2 tests. A Cochran-Mantel-Haenszel test was used for ordinal responses. An α level of .05 determined significance.

The primary outcome was the proportion of patients in each treatment arm who experienced clinical success at 10, 21, or 56 days, based on telephone follow-up. We established a priori that patient reports of cured or

Figure 1. Participant Flow Diagram

*Other reasons for exclusion included 3 with recurrent epistaxis; 2, nasal polyposis; 1, allergy to corticosteroids; and 1, enrolled in another study.

much improved represented clinical successes. The time from enrollment to a status of clinical success was compared between the 2 treatment groups by use of a log-rank test.

A Cox proportional hazards regression model was used to examine the relationship of baseline variables (treatment, practice type, age, number of comorbidities, sex, race, recent upper respiratory tract infection, and history of allergies) to time to clinical success. Tests of the proportional hazards assumption were made using interactions between each variable and time; all tests were nonsignificant, indicating the assumption was met for each variable. These conclusions were further supported by examination of Kaplan-Meier method plots. The linearity of the relationship between numeric variables (age, number of comorbidities) and the log hazard ratio was assessed using restricted cubic splines and goodness-of-fit tests; both relation-

ships were linear. There were no pre-specified interactions of interest and no time-dependent covariates (few patients had a procedure, the only relevant postrandomization variable). Thus, the final model included the 8 variables listed above with no additional terms.

Secondary outcomes included differences over time in the sinusitis and general health quality of life scores from the SNOT-20 and SF-12 surveys. Each element of the SNOT-20 was scored as follows: 0, no problem; 1, mild or slight problem; 2, moderate problem; and 3, severe problem. The mean of scores for the 20 elements is the SNOT-20 score.¹⁷ The mental and physical component scores of the SF-12 were calculated by using the algorithm provided by the Medical Outcomes Trust.¹⁹

All statistical analyses were performed by using SAS version 6.12. No interim analyses were planned or performed during the course of the study.

Patients with missing data were included in the analyses to the extent that they remained evaluable. No missing data were imputed.

Sample size estimates were obtained using nQuery Advisor 3.0 (Statistical Solutions Ltd, Cork, Ireland). Calculations were based on a log-rank test of time to clinical success and assumed 20% difference in clinical success rates, 95% clinical success rate in the active treatment arm, and constant hazard ratio. To achieve 80% power with $\alpha = .05$, we needed to enroll 54 patients in each treatment group. Enrollment was stopped at the end of the respiratory season during the trial's second year of recruitment because there was limited funding to replace the study medication that was due to expire before the third respiratory season. At the time enrollment ended, 95 patients had been randomly assigned to treatment.

RESULTS

Patient Enrollment and Characteristics

Enrollment took place from October 1998 through April 2000. Twenty-two sites actively screened patients (12 primary care, 10 otolaryngology); 19 of these 22 sites (11 primary care, 8 otolaryngology) randomly assigned at least 1 patient to treatment. Of the 465 potential subjects screened for this study, 111 (24%) patients were eligible for the trial and 95 (20% of total screened) were randomly assigned to treatment. The 354 ineligible patients were excluded for the following reasons: 147 did not meet symptom screening criteria, 69 were without previous history of recurrent sinusitis or persistent sinonasal symptoms, 65 were treated recently with antibiotics, 35 had negative radiographs or nasal endoscopy, 15 were treated recently with intranasal corticosteroids, 11 were allergic to cephalosporins or penicillin, 5 had a history of previous sinus surgery, 3 had recurrent moderate epistaxis, 2 had nasal polyposis, 1 was allergic to corticosteroids, and 1 enrolled in another study (FIGURE 1). Of the 95 randomized patients, 47 received fluticasone and 48 received pla-

cebo nasal spray. More than half the subjects (n=51) were enrolled from primary care, with equal proportions of patients from primary care and otolaryngology practices in each treatment arm (TABLE 1). Confirmation of the diagnosis of acute rhinosinusitis was established by nasal endoscopy (n=37 patients), sinus radiograph (n=56), or by sinus radiograph plus nasal endoscopy (n=2). A majority of patients completed the study medications (94% overall, with no difference between treatment groups; Figure 1). Telephone follow-up was complete for 88 patients (93%). Sixty-seven patients (71%) completed diaries. The study drug was discontinued in 6 patients (3 patients per group): 1 developed a rash, 1 was prescribed amoxicillin-clavulanate, 2 chose not to continue, and 2 discontinued for unknown reasons; 4 of the 6 patients continued with telephone follow-up and 2 submitted completed diaries.

Table 1 shows the baseline demographics and medical history for patients enrolled into the study. Overall, there were no statistical differences between groups. Baseline sinus symptom score, sinusitis quality of life (SNOT-20), and general quality of life (SF-12) scores were similar between treatment groups (TABLE 2).

Assessment of Blinding

Among patients randomly assigned to treatment with fluticasone nasal spray, 17 (36%) believed they had received placebo, whereas 22 (47%) believed they had received fluticasone, and 8 (17%) did not answer the question about perceived treatment. Of the 48 patients randomly assigned to treatment with placebo nasal spray, 13 (27%) correctly guessed their treatment, 25 (52%) believed they had received active treatment, and 10 (21%) did not answer the question.

Primary Outcome

Time to clinical success was derived from responses to the telephone survey. FIGURE 2 depicts the Kaplan-Meier method curve reflecting the time to clinical success for each treatment

Table 1. Baseline Characteristics of 2 Treatment Arms*

Characteristics	Fluticasone (n = 47)	Placebo (n = 48)	P Value
Demographics, No. (%)			
Age, y (median, interquartile range)	38 (30-49)	41 (35-55)	.15
Race			
White	43 (91)	41 (85)	.59
African American	3 (6)	6 (13)	
Other	1 (2)	1 (2)	
Female sex	31 (66)	34 (71)	.61
Employment status			
Employed	36 (76)	39 (81)	.17
Unemployed	3 (6)	2 (4)	
Retired	3 (6)	5 (10)	
Full-time student	4 (9)	0	
Disabled	1 (2)	1 (2)	
Other	0	1 (2)	
History			
Recent URI	10 (21)	8 (17)	.57
Allergy to pollen/hay fever	18 (39)	21 (44)	.65
Cigarette smoking			
Current	10 (21)	5 (10)	.30
Former	16 (34)	16 (33)	
Never	21 (45)	27 (56)	
Other comorbidities			
Asthma	6 (13)	5 (10)	.72
Diabetes	3 (7)	0	NA
Depression	5 (11)	6 (13)	.78
Coronary artery disease	0	1 (2)	NA
Current medications			
Decongestants	15 (32)	13 (27)	.61
Mucolytics	3 (6)	2 (4)	.63
Analgesics	11 (23)	7 (15)	.27
Anti-inflammatories	4 (9)	6 (13)	.53
Antihistamines	11 (23)	11 (23)	.96
Site type			
Otolaryngology	21 (45)	23 (48)	.75
Primary care	26 (55)	25 (52)	

*URI indicates upper respiratory tract infection; NA, not applicable due to small numbers. Because of rounding, percentages may not all total 100.

group. A higher proportion of patients achieved clinical success in the fluticasone group compared with the placebo group (93.5% vs 73.9%, $P=.009$). There was a statistically significant difference in time to clinical success favoring the addition of fluticasone ($P=.01$). The treatment effect was consistent across sites with different numbers of patients enrolled ($P=.21$ for global test of site size \times treatment interaction). TABLE 3 demonstrates the relative and absolute effect of therapy over time in terms of the treatment benefit. By the end of follow-up, the relative benefit increase was 26.5% with an absolute benefit increase of 19.6% (95%

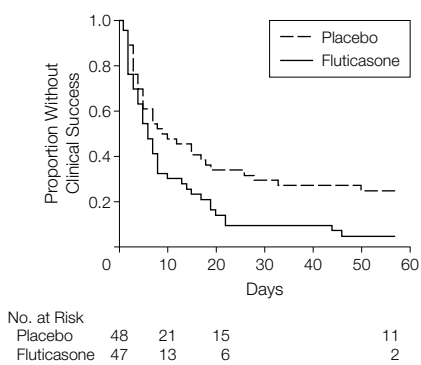
confidence interval [CI], 5.3%-33.9%); hence, the number needed to treat with fluticasone to gain 1 additional cure is 6 patients (95% CI, 3-19).²⁰ For all patients, the median number of days to clinical success was 6.0 in those treated with fluticasone and 9.5 in the patients using placebo nasal spray.

A Cox proportional hazards regression model incorporating treatment group, practice type, age, number of comorbidities, sex, race, recent upper respiratory tract infection, and history of allergies resulted in the treatment group category as the only significant predictor of time to clinical success ($P=.03$,

Table 2. Quality of Life Scores: Baseline and Follow-up*

Quality of Life Measure	Median (Interquartile Range)		P Value
	Fluticasone (n = 47)	Placebo (n = 48)	
Baseline sinus symptom score	7.0 (5.0 to 8.0)	7.0 (6.0 to 8.0)	.44
SNOT-20			
Baseline	1.4 (1.2 to 1.6)	1.4 (1.1 to 1.8)	.90
Change from baseline to			
Day 10	-0.8 (-1.2 to -0.2)	-0.8 (-1.2 to -0.5)	.80
Day 21	-0.8 (-1.3 to -0.2)	-0.8 (-1.3 to -0.2)	.88
Day 56	-1.0 (-1.4 to -0.4)	-1.0 (-1.5 to -0.6)	.54
SF-12			
PCS baseline	41 (37 to 47)	44 (31 to 48)	.85
MCS baseline	45 (35 to 51)	50 (43 to 53)	.21
Change from baseline to 21 days			
PCS-12	7.8 (1.2 to 13.9)	4.6 (0.5 to 9.4)	.39
MCS-12	2.4 (0 to 13.5)	1.4 (-2.8 to 8.2)	.21

*SNOT-20 indicates Sinonasal Outcome Test-20; SF-12, Short Form-12; PCS, physical component score; and MCS, mental component score. Sinus symptoms rated from 0 (none) to 10 (worse). Higher SNOT-20 scores indicate poorer sinusitis quality of life; negative change indicates improvement. Higher SF-12 PCS or MCS scores indicate better quality of life; positive change indicates improvement.

Figure 2. Kaplan-Meier Method Curve of Time to Clinical Success

Clinical success is defined as a patient report of cured or much improved at telephone follow-up. Time from enrollment to clinical success is shown by Kaplan-Meier curve. The log-rank test *P* value is .01 and the median days to clinical success for placebo and fluticasone are 9.5 and 6.0, respectively. Numbers at risk are for days 0, 10, 21, and 56.

Wald χ^2 test) and hazard ratio of 1.7 (95% CI, 1.1-2.7). Patients in the fluticasone group had a 1.7-times greater likelihood of being cured than did those in the placebo group at any given point.

Secondary Outcomes

Sinusitis symptoms scores (0 to 10) primarily improved from baseline to day 10 for both treatment groups. The median score (interquartile range) of patients who received fluticasone decreased from 7 (5-8) to 3 (2-4) at 10 days, 2 (0-4) at 21 days, and 1 (0-4) at

56 days; patients in the placebo group improved from 7 (6-8) to 3 (2-6) at 10 days, 2 (0-5) at 21 days, and 2 (1-4) at 56 days. Differences in improvement between treatment groups were not significant (*P* = .44, Wilcoxon rank sum test area under the curve).

Sinusitis-related quality of life, as determined by SNOT-20 scores, improved equally over time for both treatment groups (Table 2). There was greater improvement on the physical component score of the SF-12 survey (PCS-12) than on the mental component score (MCS-12); however, no significant differences were seen between groups.

Patients treated with fluticasone had a higher subjective level of work performance that was significantly different on day 21 (median, 100% [interquartile range, 90%-100%] vs 90% placebo [interquartile range, 60%-100%]; *P* = .009) (FIGURE 3). No significant differences in work performance were seen at day 10 (fluticasone, 100 [interquartile range, 80-100]; placebo, 90 [interquartile range, 80-100]; *P* = .12). Although more patients treated with fluticasone missed at least 1 hour of work (16 vs 9 patients, respectively; *P* = .10), the difference between groups with respect to the total number of hours missed from work was not significant (11 vs 13 hours, respectively; *P* = .40).

A total of 29 recurrences (11 fluticasone vs 18 placebo) occurred in 20 patients. Fewer recurrences occurred in patients treated with fluticasone (*n* = 7) than in those treated with placebo (*n* = 13) (*P* = .06). The median time to first recurrence was 3 days sooner in the placebo group, 22 days (interquartile range, 21-24) vs 25 days (interquartile range, 13-43) in the fluticasone group. A higher number of the placebo-treated patients were given additional antibiotics (*n* = 10 for placebo vs *n* = 5 for fluticasone) and open-label intranasal corticosteroids (*n* = 7 for placebo vs *n* = 1 for fluticasone).

All adverse events reported are shown in TABLE 4. There were more adverse events occurring in the fluticasone group, but these may also have been attributable to a combination of the medications or 1 of the other medications used. No serious, unexpected adverse events were reported.

COMMENT

We found that patients with acute paranasal sinusitis were more likely to achieve clinical improvement when treated with fluticasone and cefuroxime than with cefuroxime alone. Our findings show that for every 6 patients treated with fluticasone, cefuroxime, and xylometazoline, 1 additional patient is cured, compared with patients treated with cefuroxime and xylometazoline alone.

Our sample primarily consisted of community-dwelling patients presenting with acute rhinosinusitis and a history of recurrent sinusitis previously treated with antibiotics (79%) or sinonasal symptoms for longer than 12 weeks without previous antibiotic therapy (21%). Unlike previous studies that evaluated intranasal corticosteroids,^{2-5,7} we excluded subjects with chronic bacterial sinusitis and nasal polyposis. Our study was able to show clinical benefit with shorter courses of antimicrobial treatment (10 days vs 3 weeks used in previous studies) and intranasal corticosteroid treatment (3 weeks vs 7 weeks) in acute sinus infections in

patients with a history of recurrent sinus infections or chronic rhinitis.

We found that symptom response was greatest during the first 5 days in both groups. This may have been due to the uniform use of nasal decongestants during the first 3 days of treatment with differences in clinical response manifesting thereafter. The most important aspect of early treatment may have been adequate drainage related to reduced nasal congestion. Xylometazoline may have also aided in the distribution of fluticasone in the nasal passages.

All patients showed improvement of their sinusitis symptom scores, sinusitis quality of life (SNOT-20) scores, and general health-related quality of life (SF-12) scores, but there were no significant differences in scores between the treatment groups. Because 70% of patients returned the diary, which contained the quality of life questionnaires, we may not have reached adequate sample size to detect significant differences in these outcome measures between treatment groups. Quality of life assessments may not have achieved significant differences because of comparisons being made at predetermined time points (days 10, 21, and 56) instead of significant clinical, individually determined time points.

Limitations to our study design include the use of patient-derived (ie, subjective) symptom reports to assess clinical improvement instead of objectively assessing treatment response through follow-up radiography or endoscopy. We decided to use diaries and telephone follow-up to assess results for 2 reasons. First, we wanted to measure the actual number of additional visits for sinus symptoms that occurred in the treatment period; hence, mandating follow-up visits for collection of study data would have biased that assessment. Second, there is conflicting evidence regarding the correlation between radiographic and subjective findings. Axelsson and Runze²¹ found acceptable correlation between sinus radiographic healing and symptomatological improvement. Bhattacharya et al²² found poor correlation between sinus computed to-

mography scans and sinusitis quality of life (SNOT-20) scores; therefore, they recommended the use of computed tomography only for delineating the sinus anatomy and pattern of inflammatory paranasal disease prior to surgical intervention. Because we were interested in evaluating alleviation of symptoms and reduction of recurrences and quality of life factors, we focused on patients' clinical responses as our main outcome measure. In addition, this study better simulates clinical practice in providing a more realistic assessment of efficacy and safety.

Our study did not require sinus aspiration for microbial evidence of sinusitis. Because we conducted the study in

primary care sites, we believed that this requirement would have been unrealistic. In addition, recruitment efforts from the otolaryngology practices would have been severely impaired had we required this type of painful, invasive procedure that carries a small risk of potential complications. Evidence reveals an increased accuracy for identifying the predominant bacterial pathogen in sinonasal cultures obtained by endoscopy, as well as high correlation with maxillary sinus cultures obtained either by surgical antrostomy or sinus puncture.²³⁻²⁹

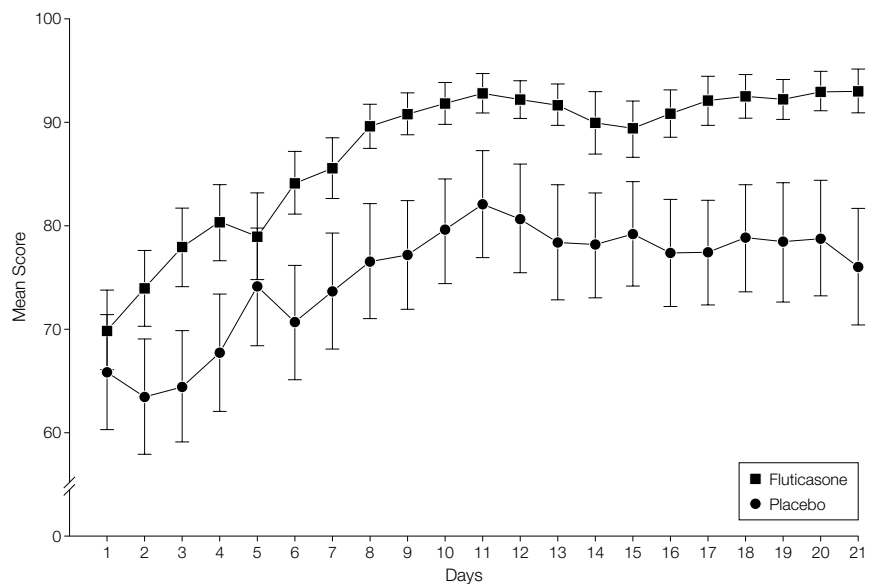
Patients in our study had acute rhinosinusitis consistent with the AAO-HNS symptom criteria with confirma-

Table 3. Clinical Success Rates*

Time Point	Success, No. (%)		Relative Benefit Increase, %	Absolute Benefit Increase, % (95% CI)	No. Needed to Treat (95% CI)
	Fluticasone (n = 46)	Placebo (n = 46)			
Day 10	32 (69.6)	24 (52.2)	33.3	17.4 (-1.9 to 36.7)	6 (3 to 53)
Day 21	39 (84.8)	30 (65.2)	30.1	19.6 (2.7 to 36.5)	6 (3 to 37)
Day 56	43 (93.5)	34 (73.9)	26.5	19.6 (5.3 to 33.9)	6 (3 to 19)

*CI indicates confidence interval; relative benefit increase, absolute difference of control event rate minus experimental event rate divided by control event rate; and absolute benefit increase, absolute difference between control event rate minus experimental event rate. The number needed to treat indicates 1 divided by absolute benefit increase, by convention rounded up to the nearest whole number.²⁰

Figure 3. Level of Work Performance Based on Patient Diaries



Mean (SD) work performance rated from 0 to 100, where 0=unable to perform usual duties and 100=able to perform usual duties. The sample size at each time point ranged from 28 to 35 for the fluticasone group and 24 to 29 for the placebo group.

Table 4. Adverse Effects*

Adverse Effects, No.	Fluticasone (n = 46)	Placebo (n = 46)
Adverse effects, No. (%)	17 (37)	9 (20)
Headache	3	3
Bloody nose/blood mucus	3	1
Vaginal itching/ yeast infection	2	1
Diarrhea	1	2
Nausea or stomach irritation	2	0
Trouble sleeping	1	1
Increased congestion/ hay fever	0	2
Lightheaded	1	0
Thirsty/sore throat	1	0
Itching all over	1	0
Cough	1	0
Rash	1	0
Metallic taste in mouth	1	0
Fatigue	1	0
Felt dried out	1	0
Nasal tissue felt inflamed	0	1
Jitters	0	1

*Some patients reported multiple adverse effects. *P* value for adverse effects is .07.

tion by sinus radiograph or nasal endoscopy. In clinical practice, otolaryngologists are more likely to use nasal endoscopy while generalist physicians are more likely to use radiography for patients similar to those in this sample. To maximize generalizability of the study results, we enrolled a group of patients that physicians would recognize as common in their practice and for whom they could decide whether intranasal corticosteroids would be beneficial. We used sinus radiograph as the diagnostic standard because most primary care physicians do not have the training for or access to endoscopy. There are limitations in using radiographs for diagnosis. Our definition of a positive radiograph as sinus fluid, opacity, or mucus thickening has a sensitivity of 0.9 (95% CI, 0.7-1.0) and a specificity of 0.6 (95% CI, 0.2-0.7).³⁰ The likelihood ratio positive (sensitivity/[1-specificity]) for the abnormal sinus films obtained in our study was 3.0. This means that abnormal films are 3.0 times as likely to be obtained from a patient with acute bacterial sinusitis as opposed to some other disorder. Theoretically, with a sensitivity of 90% for the sinus radiograph and 93.8% for the nasal endoscopy, we may have in-

cluded a small percentage of patients with nonbacterial etiologies for sinusitis.^{29,30} In patients with nonbacterial sinusitis, the antibiotic (cefuroxime) would act as an additional placebo and the differences in treatment response would still be attributed to the use of fluticasone or placebo nasal spray.

Because many physicians treat recurrent sinusitis with antibiotics, we chose to treat all patients in our study with the same antibiotic. Our choice of antibiotic was based on identifying a study sponsor that would supply an antibiotic for this study. Cefuroxime is one of several antibiotics recommended as initial therapy for adults with acute bacterial rhinosinusitis.³¹ In 12 randomized, comparative trials of acute sinusitis and acute exacerbation of chronic sinusitis, the rates of bacteriologic eradication by cefuroxime varied from 85% to 100%.¹² We had no hypothesis that one antibiotic was preferable to another; however, future studies should address the selection of antibiotic use with intranasal corticosteroids, perhaps guided by bacterial sensitivity.

Our study design addresses some of the deficiencies identified in previous sinusitis studies outlined in the Agency for Health Care Policy and Research (AHCPR; now Agency for Healthcare Research and Quality) evidence report on acute sinusitis.³⁰ Most previous studies used differences between 2 time points (typically before and after treatment) to assess effectiveness. Therefore, AHCPR recommended the use of daily symptom measurements to identify any differences that might occur before the end of treatment and further add evidence that could shorten the course of antimicrobial treatment required for sinus infections. We used a daily diary to assess patients' clinical responses and found that a majority of patients improve before day 10 (usually by 5-6 days) and have continued improvement up to 21 days.

We also measured quality of life, work attendance, work performance, and recurrences to help understand the impact of sinusitis on these factors. The decision and cost-effectiveness analy-

ses presented in the AHCPR evidence report on sinusitis were limited by the use of expert consultation and patient interview (2 patients total) to assign the outcome utilities. Our results can be used to estimate patient-derived utilities for future decision models.

In conclusion, our study supports the use of intranasal corticosteroids with antimicrobial therapy for the treatment of acute paranasal sinusitis in patients with a history of recurrent sinusitis or chronic rhinitis. We enrolled these types of patients to maximize our chances of finding patients who were likely to have recurrences. More studies are needed to assess the impact of intranasal corticosteroids on patients with simple, acute sinusitis, as well as those who present with signs and symptoms of sinusitis but have negative radiographs or endoscopic results. Nonetheless, we recommend that sinusitis treatment guidelines be emended to include intranasal corticosteroids as adjunctive therapy. The optimal duration of corticosteroid therapy will need further investigation. Additional studies incorporating microbial sampling before and after treatment and/or follow-up radiography may also be warranted to further support this recommendation.

Author Affiliations: Department of Medicine, Durham Veterans Affairs Medical Center and Division of Internal Medicine (Drs Dolor and Simel), Department of Surgery, Durham Veterans Affairs Medical Center and Division of Otolaryngology (Dr Witsell), and Duke Clinical Research Institute (Dr Califf and Ms Hellkamp), Duke University Medical Center, Durham, NC; South Texas Veterans Affairs Health Care System, Audie L. Murphy Division and Division of Internal Medicine, University of Texas Health Science Center, San Antonio (Dr Williams).

Financial Disclosure: Dr Dolor has received grant support from GlaxoSmithKline and Novartis and honoraria from Bayer. Dr Witsell has received grant support and honoraria from GlaxoSmithKline. Dr Williams received grant support from GlaxoSmithKline and served on an advisory board for Bristol-Myers Squibb. Dr Califf has received grant support for the Duke Clinical Research Institute from AstraZeneca, Aventis, Bayer, Bristol-Myers Squibb, Monarch, Novartis, Procter & Gamble, Schering Plough, and GlaxoSmithKline.

Author Contributions: Study concept and design: Dolor, Witsell, Williams, Califf, Simel.

Acquisition of data: Dolor, Witsell, Williams.

Analysis and interpretation of data: Dolor, Witsell, Hellkamp, Simel.

Drafting of the manuscript: Dolor, Simel.

Critical revision of the manuscript for important intellectual content: Dolor, Witsell, Hellkamp, Williams, Califf, Simel.

Statistical expertise: Hellkamp, Simel.

Obtained funding: Dolor, Witsell.

Administrative, technical, or material support: Dolor, Williams, Calif.

Study supervision: Dolor, Simel.

Funding/Support: GlaxoSmithKline provided funding and supplied study medications. The study protocol originated from the investigators at the Durham Veterans Affairs Medical Center (Drs Dolor, Witsell, and Simel) and Duke Medical Center. Duke Clinical Research Institute staff handled site management, data management, statistical analysis, and assisted with manuscript preparation. This material is the result of the work supported with resources and the use of facilities at the Durham Veterans Affairs Medical Center, Durham, NC, and the Audie L. Murphy Veterans Affairs Medical Center, San Antonio, Tex.

CAFFS Investigators: Michael Armstrong, MD, Virginia Ear, Nose and Throat Associates, Richmond; Anita Blosser, MD, Henderson Family Medicine Center, Henderson, NC; Charles Cassady, MD, ENT Consultants, May Field Heights, Ohio; David Cline, MD, Asheville, NC; Jacquelynn Corey, MD, University of Chicago, Chicago, Ill; Douglas Dawson, MD, Town Square ENT Services, Coralville, Iowa; Rowena Dolor, MD, Durham Veterans Affairs Medical Center, Durham, NC; Matthew Frankel, MD, Philadelphia, Pa; Eric Haas, MD, Atlantic Beach, Fla; Douglas Heinrich, MD, Burlington Ear, Nose & Throat Clinic, West Burlington, Iowa; Lynn Hughes, MD, Northeast Ear, Nose, and Throat, Concord, NC; Jon Langford, MD, Carolina Head and Neck Specialists, Concord, NC; Thomas Long, Jr, MD, Roxboro Medical Associates, Roxboro, NC; James

Miller, MD, Hastings, Neb; Charles Powers, MD, St Cloud, Fla; Hassan Ramadan, MD, West Virginia University, Morgantown; Tamra Stall, MD, Butner-Creedmoor Family Medicine, Creedmoor, NC; James Sumerson, MD, Professional Otolaryngology Associates, Voorhees, NJ; Ted Thompson, MD, Gundersen Lutheran, Lacrosse, Wis; John Williams, MD, South Texas Veterans Affairs Health Care System, Audie L. Murphy Division, San Antonio, Tex; James Winslow, MD, North State Medical, Roxboro, NC; and David Witsell, MD, Duke University Medical Center, Durham, NC.

Acknowledgment: We thank Jay F. Piccirillo, MD, for assistance with the SNOT-20 quality of life questionnaire and Jean Bolte, RN, and Donna Reist, RN, for project and site management.

REFERENCES

1. Spector SL, Bernstein IL, Li JT, et al, and the Joint Task Force of Practice Parameters in Allergy, Asthma and Immunology. Parameters for the diagnosis and management of sinusitis. *J Allergy Clin Immunol*. 1998;102(suppl):S107-S144.
2. Krouse HA, Phung ND, Klausermeyer WB. Intranasal beclomethasone in severe rhinosinusitis and nasal polyps. *Ann Allergy*. 1983;50:385-388.
3. Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis: a controlled study. *Lancet*. 1986;2:359-360.
4. Cuenan G, Stipon JP, Plante-Longchamp G, Baudoin C, Guerrier Y. Efficacy of endonasal neomycin-tixocortol pivalate irrigation in the treatment of chronic allergic and bacterial sinusitis. *ORL J Otorhinolaryngol Relat Spec*. 1986;48:226-232.
5. Qvarnberg Y, Kantola O, Salo J, Toivanen M, Valtonen H, Vuori E. Influence of topical steroid treatment on maxillary sinusitis. *Rhinology*. 1992;30:103-112.
6. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol*. 1997;78:598-601.
7. Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *J Allergy Clin Immunol*. 1993;92:812-823.
8. Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. *Otolaryngol Head Neck Surg*. 1997;116(suppl):S1-S20.
9. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. *J Allergy Clin Immunol*. 1996;97:169-176.
10. Holm AF, Fokkens WJ, Godthelp T, Mulder PGH, Vroom ThM, Rijntjes E. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. *Clin Otolaryngol*. 1998;23:69-73.
11. Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. *Rhinology*. 1993;31:169-174.
12. Pakes GE, Graham JA, Rauch AM, Collins JJ. Cefuroxime axetil in the treatment of sinusitis. *Arch Fam Med*. 1994;3:165-175.
13. Axelsson A, Grebelius N, Chidekel N, Jensen C. The correlation between radiological examination and the irrigation findings in maxillary sinusitis. *Acta Otolaryngol*. 1970;69:302-306.
14. Hayward MW, Lyons K, Ennis WP, Rees J. Radiology of the paranasal sinuses: one or three views? *Clin Radiol*. 1990;41:163-164.
15. Williams JW Jr, Roberts L Jr, Distell B, Simel DL. Diagnosing sinusitis by X-ray: is a single Waters' view adequate? *J Gen Intern Med*. 1992;7:481-485.
16. Hadley JA, Schaefer SD. Clinical evaluation of rhinosinusitis: history and physical examination. *Otolaryngol Head Neck Surg*. 1997;117:S8-S11.
17. Piccirillo JF, Merritt MG Jr, Jones ML. Validity of the 20-Item Sinonasal Outcome Test [abstract]. Paper presented at: 1998 Annual Meeting of the American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc; September 13-16, 1998; San Antonio, Tex.
18. Piccirillo JF, Edwards D, Haiduk A, Yonan C, Thawley SE. Psychometric and clinimetric validity of the 31-Item Rhinosinusitis Outcome Measure (RSOM-31). *Am J Rhinol*. 1995;9:297-306.
19. Ware JE, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220-233.
20. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EB/M*. 2nd ed. New York, NY: Churchill Livingstone; 2000:111-113.
21. Axelsson A, Runze U. Comparison of subjective and radiological findings during the course of acute maxillary sinusitis. *Ann Otol Rhinol Laryngol*. 1983;92:75-77.
22. Bhattacharyya T, Piccirillo J, Wippold FJ 2nd. Relationship between patient-based descriptions of sinusitis and paranasal sinus computed tomographic findings. *Arch Otolaryngol Head Neck Surg*. 1997;123:1189-1192.
23. Chow JM, Hartman J, Stankiewicz JA. Endoscopically directed cultures of the maxillary sinus. *Otolaryngol Head Neck Surg*. 1993;4:86-89.
24. Poole MD. Endoscopically guided vs blind nasal cultures in sinusitis [abstract]. *Otolaryngol Head Neck Surg*. 1992;107:272.
25. Vaidya AM, Chow JM, Stankiewicz JA, et al. Correlation of middle meatal and maxillary sinus cultures in acute maxillary sinusitis. *Am J Rhinol*. 1997;11:139-143.
26. Gold SM, Tami TA. Role of middle meatus aspiration culture in the diagnosis of chronic sinusitis. *Laryngoscope*. 1997;107:1586-1589.
27. Orobello PW Jr, Park RI, Belcher LJ, et al. Microbiology of chronic sinusitis in children. *Arch Otolaryngol Head Neck Surg*. 1991;117:980-983.
28. Nadel DM, Lanza DC, Kennedy DW. Endoscopically guided cultures in chronic sinusitis. *Am J Rhinol*. 1998;12:233-241.
29. Vogan JC, Bolger WE, Keyes AS. Endoscopically guided sinonasal cultures: a direct comparison with maxillary sinus aspirate cultures. *Otolaryngol Head Neck Surg*. 2000;122:370-373.
30. *Evidence Report/Technology Assessment Number 9: Diagnosis and Treatment of Acute Bacterial Rhinosinusitis*. Rockville, Md: Agency for Health Care Policy and Research, US Dept of Health and Human Services; 1999. AHCPR publication 99-E016.
31. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg*. 2000;123(suppl): S1-S32.