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Amoxicillin for Acute Rhinosinusitis
A Randomized Controlled Trial

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Context Evidence to support antibiotic treatment for acute rhinosinusitis is limited, yet antibiotics are commonly used.

Objective To determine the incremental effect of amoxicillin treatment over symptomatic treatments for adults with clinically diagnosed acute rhinosinusitis.

Design, Setting, and Participants A randomized, placebo-controlled trial of adults with uncomplicated, acute rhinosinusitis were recruited from 10 community practices in Missouri between November 1, 2006, and May 1, 2009.

Interventions Ten-day course of either amoxicillin (1500 mg/d) or placebo administered in 3 doses per day. All patients received a 5- to 7-day supply of symptomatic treatments for pain, fever, cough, and nasal congestion to use as needed.

Main Outcome Measures The primary outcome was improvement in disease-specific quality of life after 3 to 4 days of treatment assessed with the Sinonasal Outcome Test-16 (minimally important difference of 0.5 units on a 0-3 scale). Secondary outcomes included the patient's retrospective assessment of change in sinus symptoms and functional status, recurrence or relapse, and satisfaction with and adverse effects of treatment. Outcomes were assessed by telephone interview at days 3, 7, 10, and 28.

Results A total of 166 adults (36% male; 78% with white race) were randomized to amoxicillin (n=85) or placebo (n=81); 92% concurrently used 1 or more symptomatic treatments (94% for amoxicillin group vs 90% for control group; $P=.34$). The mean change in Sinonasal Outcome Test-16 scores was not significantly different between groups on day 3 (decrease of 0.59 in the amoxicillin group and 0.54 in the control group; mean difference between groups of 0.03 [95% CI, –0.12 to 0.19]) and on day 10 (mean difference between groups of 0.01 [95% CI, –0.13 to 0.15]), but differed at day 7 favoring amoxicillin (mean difference between groups of 0.19 [95% CI, 0.024 to 0.35]). There was no statistically significant difference in reported symptom improvement at day 3 (37% for amoxicillin group vs 34% for control group; $P=.67$) or at day 10 (78% vs 80%, respectively; $P=.71$), whereas at day 7 more participants treated with amoxicillin reported symptom improvement (74% vs 56%, respectively; $P=.02$). No between-group differences were found for any other secondary outcomes. No serious adverse events occurred.

Conclusion Among patients with acute rhinosinusitis, a 10-day course of amoxicillin compared with placebo did not reduce symptoms at day 3 of treatment.

Trial Registration clinicaltrials.gov Identifier: NCT00377403

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ACUTE RHINOSINUSITIS IS A common disease associated with significant morbidity, lost time from work, and treatment costs.[1,2] Considering the public health threat posed by increasing antibiotic resistance,[3] strong evidence of symptom relief is needed to justify prescribing of antibiotics for this usually self-limiting disease. Placebo-controlled clinical trials to evaluate antibiotic treatment have had conflicting results, likely due to differences in diagnostic criteria and outcome assessment. Studies requiring confirmatory tests such as sinus radiography have tended to show treatment benefit,[4-7] but meta-analyses of these studies have generally concluded that clinical benefit with antibiotic treatment was small due to the high rate of spontaneous improvement (approximately 69%).[8,9] Studies using clinical diagnostic criteria tend to show no or minimal treatment benefit and higher spontaneous resolution (approximately 80%).[10-13] Despite the controversy regarding their clinical benefit and concerns about resistance, antibiotics for sinusitis account for 1 in 5 antibiotic prescriptions for adults in the United States.[14,15]

In 2001, an expert panel sponsored by the US Centers for Disease Control and Prevention developed evidence-based guidelines for the evaluation and treatment of adults with acute rhinosinusitis that recommended using clinical criteria for diagnosis, reserving antibiotic treatment for patients with moderately severe or severe symptoms, and treating patients with the most narrow-spectrum antibiotic ac-

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tive against *Streptococcus pneumoniae* and *Haemophilus influenzae*.[1]

The goal of this study was to evaluate these clinical guidelines in the community setting. Our objective was to determine the incremental effect of amoxicillin treatment over symptomatic treatments on disease-specific quality of life in adults with clinically diagnosed acute bacterial rhinosinusitis.

METHODS

We conducted this randomized, placebo-controlled trial in 10 offices of primary care physicians in St Louis, Missouri. The study protocol was approved by the institutional review board at Washington University and written informed consent was obtained from each participant.

Patient Eligibility and Enrollment

Adult patients aged 18 to 70 years who met the Centers for Disease Control and Prevention's expert panel's diagnostic criteria for acute bacterial rhinosinusitis[1] were assessed, and if their symptoms were moderate, severe, or very severe, they were deemed eligible to participate. Diagnosis required history of maxillary pain or tenderness in the face or teeth, purulent nasal secretions, and rhinosinusitis symptoms for 7 days or more and 28 days or less that were not improving or worsening, or rhinosinusitis symptoms lasting for less than 7 days that had significantly worsened after initial improvement.

Patients were excluded if they had an allergy to penicillin or amoxicillin, prior antibiotic treatment within 4 weeks, complications of sinusitis, a comorbidity that may impair their immune response, cystic fibrosis, required an antibiotic for a concurrent condition, were pregnant, or rated their symptoms as very mild or mild.

Eligible patients attending study sites when a research assistant was present (during office hours Monday-Friday) were invited to participate by their primary care physician. The research assistant discussed participation requirements and completed the eligibility assessment and the consent process.

Randomization

Randomization was performed in advance by the investigational pharmacist who did not participate in patient enrollment or outcome assessment. Using a blocked randomization scheme, computer-generated random numbers were used to determine how the 2 study drugs were allocated to the consecutively numbered study treatment packages. Randomization occurred when the research assistant assigned the treatment package.

Study participants received a 10-day course of either amoxicillin at a daily dose of 1500 mg administered in 3 doses per day (500 mg/dose) or placebo similar in appearance and taste and dispensed in the same fashion. Unless their primary care physician felt it was contraindicated, all patients received a 5- to 7-day supply of the following symptomatic treatments to be used as needed: acetaminophen for pain or fever at a dose of 500 mg every 6 hours, guaifenesin to thin secretions at a dose of 600 mg every 12 hours, 10 mg/5 mL of dextromethorphan hydrobromide and 100 mg/5 mL of guaifenesin for cough at a dose of 10 mL every 4 to 6 hours, pseudoephedrine-sustained action for nasal congestion at a dose of 120 mg every 12 hours, and 0.65% saline spray using 2 puffs per nostril as needed.

Measurement

The primary outcome was the effect of treatment on disease-specific quality of life at day 3. We expected any benefit of antibiotic treatment to be evident 48 to 72 hours after the treatment was begun, which was day 3; day 10 was not chosen as the primary outcome due to the high rate of spontaneous resolution of this disease. The primary outcome was measured using the modified Sinonasal Outcome Test-16 (SNOT-16), a validated and responsive measure.[16-18] Considering both severity and frequency, the participant scored how much each of 16 sinus-related symptoms bothered them in the past few days (0=no problem to 3=severe problem). For the SNOT-16 score, the mean score of all completed items ranged from 0 to 3, with a minimally important difference[19] of 0.5 units on this scale.[18] The cohort of patients in this trial were used to evaluate the validity and responsiveness of this measure.[18]

Participants used a 6-point scale (a lot or a little worse or better, the same, or no symptoms) to retrospectively assess symptom change since enrollment. Those reporting their symptoms as a lot better or absent (no symptoms) were categorized as significantly improved. Change in functional status was assessed as days unable to perform usual activities and days missed from work. Recurrent sinus infection was defined as any patient who at days 7 and 10 reported no symptoms, and at day 28 reported their symptoms were unchanged or worse. Relapse was defined as any patient who at day 10 was significantly improved, but on day 28 reported their symptoms were unchanged or worse.

Satisfaction with treatment, adverse effects of treatment, treatment compliance, and adequacy of blinding were assessed at day 10. Participants rated their level of agreement with the statement: "The study medication that I received for my sinus problem helped a lot" (strongly agree, agree, neutral, disagree, or strongly disagree). Responses of strongly agree and agree were classified as satisfied with treatment.

Adverse effects of antibiotic treatment were assessed using this open-ended question: "Have you had any side effects from the study medication?" followed by specific questions about potential adverse effects associated with amoxicillin treatment. Treatment adherence was assessed by self-report (missed <3 doses of study drug), and participants were asked to guess their study group to assess blinding.

Data Collection

At study enrollment (day 0), each participant completed a brief interview with the research assistant to complete the SNOT-16, and provided demographic and disease-related informa-

tion. Demographic information including race and ethnicity were provided by selecting from options included in the baseline questionnaire. The primary care physician completed a 1-page form documenting symptoms and signs. The SNOT-16 was repeated by telephone interview later that day to standardize the mode of data collection. The SNOT-16 score at the office visit on day 0 was used for 4 participants who missed the telephone interview. Outcomes were assessed by telephone interview at 3, 7, 10, and 28 days following treatment initiation. Interviews comprised a structured questionnaire and were conducted by trained research assistants blinded to group assignment.

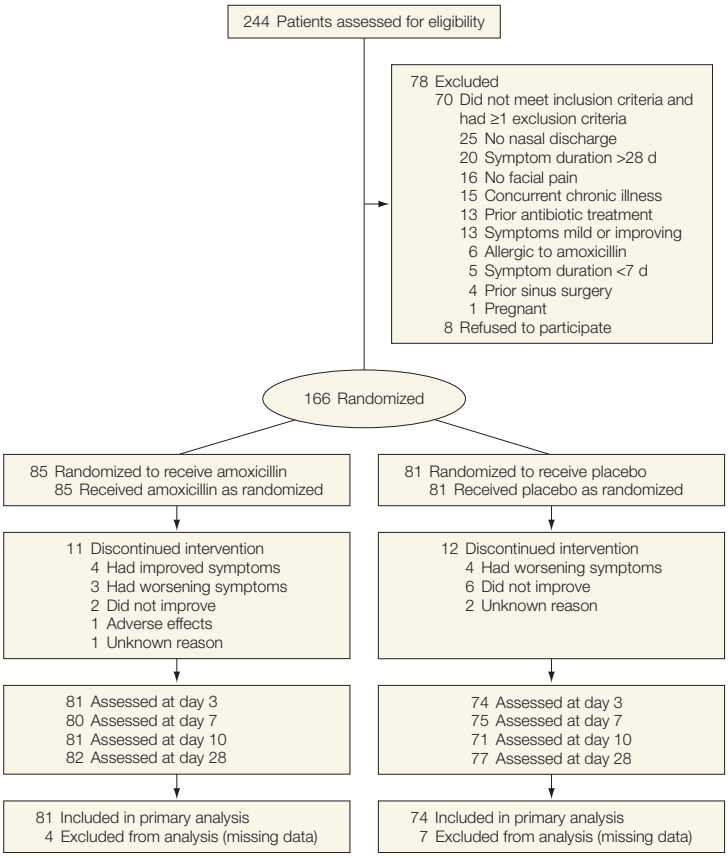
Statistical Analysis

Using pilot data, we estimated that a sample of 100 participants per treatment group would provide 83% power to detect a true difference of 0.25 in SNOT-16 scores at day 3.

The analyses adhered to the intention-to-treat principle (all of the eligible patients as randomized) and a 2-tailed *P* value of less than .05 indicates statistical significance. Improvement in the disease-specific quality of life was assessed as the reduction in SNOT-16 scores from day 0 to days 3, 7, and 10. We compared differences across study groups using analysis of variance, controlling for disease severity at baseline (with the day 0 SNOT-16 score). Reported *P* values were adjusted for this covariate. There were few missing data, but we repeated the primary analyses, imputing the missing SNOT-16 data 20 times. Because the statistical significance pattern for these additional analyses remained the same as with the unimputed data, we report the results of the unimputed data.

For the secondary analyses and to compare treatment groups at baseline, the means of continuous variables were compared by analysis of variance. For categorical data, either a χ^2 test or Fisher exact test was used for comparison of proportions. We used logistic regression to identify predictors of benefit with antibiotic treatment, controlling for study group. All statistical analyses were performed using SAS version 9.12 (SAS Institute Inc).

Figure. Recruitment and Flow of Study Participants in Trial



RESULTS

Patients

Between November 1, 2006, and May 1, 2009, 244 adults were screened, 174 were eligible, and 166 were randomized to amoxicillin (n=85) and placebo (n=81) (FIGURE). Sociodemographic and disease characteristics were similar in both groups (TABLE 1 and TABLE 2). All reported purulent nasal discharge and maxillary pain or tenderness in the face or teeth (94 bilateral, 56 unilateral, and 16 laterality unknown); 143 reported rhinosinusitis symptoms (88%) for 7 days or more and 28 days or less that were worsening (n=105) or not improving (n=38); and 23 reported rhinosinusitis symptoms (14%) for less than 7 days that significantly worsened after initial improvement.

Symptoms most frequently recorded by the clinician were facial congestion or fullness (79%), facial pain or pressure (70%), cough (60%), ear pain (58%), postnasal discharge (55%), nasal obstruction (54%), and headache (54%). Dental pain (10%), hyposmia or anosmia (7%), and halitosis (3%) were rare. The frequency and scores for items on the SNOT-16 are provided in TABLE 3.

Follow-up interviews were completed by 155 participants (93%) at day 3, 155 (93%) at day 7, 152 (92%) at day 10, and 159 (96%) at day 28, with no difference by study group.

Treatment Use

Duration of use or self-reported adherence did not differ between groups (TABLE 4). In total, 23 participants

(14%) (11 in the amoxicillin group and 12 in the control group; *P*=.73) did not complete the 10-day course of treatment. Eight participants had stopped by day 3, 13 by day 7, and 2 more by day 10. Reasons for stopping treatment were failure to improve (2 in the amoxicillin group and 6 in the control group), worsening symptoms (3 in the amoxicillin group and 4 in the control group), improved symptoms (4 in the amoxicillin group), and adverse effects of treatment (1 in the amoxicillin group). No reason was recorded for 3 participants (1 in the amoxicillin group and 2 in the control group). Sixteen were treated with another antimicrobial (5 in the amoxicillin group and 11 in the control group; *P*=.09) including amoxicillin-clavulanate (n=11), amoxicillin (n=4), and azithromycin (n=1). The percentage of participants who guessed their treatment assignment correctly did not differ by study group (36% in amoxicillin group and 37% in the control group; *P*=.20).

Concurrent use of symptomatic treatments was common (92%; 95% CI, 88%-96%) and did not vary by study group (TABLE 5). No new nasal steroid use was reported.

Table 1. Baseline Characteristics of 166 Study Participants With Clinically Diagnosed Acute Sinusitis

	No. (%) of Participants[a]		
	Amoxicillin Group (n = 85)	Control Group (n = 81)	*P* Value
Age, median (range), y	32 (18-69)	31 (18-66)	.22
Male sex	31 (36)	29 (36)	.93
Race			
White	61 (72)	69 (85)	.11
Black	17 (20)	9 (11)	
Other	7 (8)	3 (4)	
Ethnicity			
Hispanic	4 (5)	1 (1)	.37
Educational level			
≤ High school	50 (59)	63 (78)	.02
Bachelor's degree	19 (22)	13 (16)	
Postgraduate or professional degree	16 (19)	5 (6)	
Health insurance			
Employment-based	56 (66)	56 (69)	.59
Government	9 (11)	6 (7)	
No insurance	5 (6)	2 (2)	
Private	15 (18)	17 (21)	
Lives alone	15 (18)	14 (17)	.95
Family income/y, $			
<10 000	5 (6)	4 (5)	.65
10 000-24 999	11 (13)	5 (6)	
25 000-49 999	13 (15)	15 (19)	
50 000-99 999	23 (27)	28 (35)	
≥100 000	20 (24)	16 (20)	
Declined to answer	13 (15)	13 (16)	
Age of child or children living at home, y			
<18	33 (39)	24 (30)	.21
<2	3 (4)	5 (6)	.49
Child in day care	4 (5)	6 (7)	.34
Medical history			
Usual health excellent or very good	41 (48)	50 (62)	.08
History of sinus disease	62 (73)	60 (74)	.39
Allergic rhinitis	27 (32)	27 (33)	.83
Nasal polyps	3 (4)	0	.25
History of allergy	14 (16)	14 (17)	.89
Positive test to mold, dust, pollen, or animal dander	34 (40)	35 (43)	.67
Asthma	9 (11)	9 (11)	.91
COPD	0	0	NA
Takes nasal steroids daily	7 (8)	4 (5)	.39
Smoker	11 (13)	21 (26)	.03

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, data not calculable.
[a] Unless otherwise indicated.

Effectiveness of Treatment

Disease-Specific Quality of Life. The mean change in SNOT-16 scores was similar in both groups at day 3 (amoxicillin group: 0.59 [95% CI, 0.47 to 0.71]; control group: 0.54 [95% CI, 0.41 to 0.67], *P*=.69; mean difference between groups, 0.03 [95% CI, –0.12 to 0.19]) and at day 10 (mean difference between groups, 0.01 [95% CI, –0.13 to 0.15], but differed at day 7, favoring amoxicillin (mean difference between groups of 0.19 [95% CI, 0.024 to 0.35]). Treatment outcomes are presented in Table 4.

Symptom Change. There were no statistically significant differences in reported symptom improvement at day 3 (37% for amoxicillin group vs 34% for control group; *P*=.67) or at day 10 (78% for amoxicillin group vs 80% for control group; *P*=.71). At day 7, more participants treated with amoxicillin reported symptom improvement (74% for amoxicillin group vs 56% for control group, *P*=.02; number needed to treat=6 [95% CI, 3-34]).

We repeated the analyses comparing change in SNOT-16 score and symptom improvement across study groups for those who completed 10 days of treatment with the study drug (per-protocol analysis: n=143; 74 participants in the amoxicillin group and 69 in the control group), and those with symptoms for 7 days or more and 28 days or less (n=143; 73 participants in the amoxicillin group and 70 in the control group). Findings were consistent with the primary analysis.

Other Secondary Outcomes. Days missed from work or unable to perform usual activities, rates of relapse and recurrence by 28 days, additional health care use, and satisfaction with treatment did not differ by study group. The most common additional services were telephone calls to the physician (5% for amoxicillin group and 10% for control group; $P=.35$) and additional office visits (2% for amoxicillin group and 4% for control group; $P=.66$). Only 1 patient had sinus radiography and another saw a specialist (both in the amoxicillin group).

Adverse Events. No serious adverse events occurred. Study groups did not differ in reporting adverse effects from the study medication. The most common adverse effects identified with specific questioning were headache (22% for amoxicillin group and 23% for control group; $P=.96$) and excessive tiredness (11% for amoxicillin group and 21% for control group; $P=.12$). Few patients indicated they had nausea (7%), diarrhea (9%), abdominal pain (5%), or vaginitis (6% of women), with no differences by study group.

Prognostic Factors. The only symptom that predicted benefit with antibiotic treatment at day 7 (self-reported improvement) was nasal obstruction recorded by the physician. Among patients with nasal obstruction (n=83),

Table 2. Baseline Sinus Symptoms

	No. (%) of Participants[a]		
	Amoxicillin Group (n = 85)	Control Group (n = 81)	*P* Value
Sinus symptoms			
SNOT-16 score[b]			
Mean (SD)	1.71 (0.53)	1.70 (0.51)	.88
Median (IQR)	1.75 (1.31-2.12)	1.62 (1.38-2.06)	
Symptom severity			
Moderate	41 (48)	39 (48)	.93
Severe	37 (44)	34 (42)	
Very severe	7 (8)	8 (10)	
Duration of symptoms, d			
Mean (SD)	11.2 (5.7)	11.1 (5.8)	.87
Median (IQR)	10.0 (7.0-14.0)	10.0 (7.0-14.0)	
Period missed from work before visit, d			
Mean (SD)	1.1 (2.0)	1.7 (4.1)	.23
Median (IQR)	0 (0 to 2.0)	0 (0 to 2.0)	
Period unable to do usual nonwork activities before visit, d			
Mean (SD)	3.2 (3.6)	3.3 (3.8)	.88
Median (IQR)	2.0 (0-5.0)	2.0 (0-5.0)	
Used symptomatic treatment before visit	82 (96)	74 (91)	.17
Received flu shot this winter	23 (27)	26 (32)	.48

Abbreviations: IQR, interquartile range (25th-75th percentile); SNOT-16, Sinonasal Outcome Test-16.
[a] Unless otherwise indicated.
[b] Mean of the 16 sinusitis symptoms (0=no symptoms, 3=symptoms are a large problem).

Table 3. Item Scores for the Sinonasal Outcome Test-16 Over Time

	Symptom Present, No. (%)		Mean Sinonasal Outcome Test-16 (SNOT-16) Score							
			Day 0		Day 3		Day 7		Day 10	
	Day 0 (n = 166)	Day 10 (n = 152)	Amoxicillin Group	Control Group	Amoxicillin Group	Control Group	Amoxicillin Group	Control Group	Amoxicillin Group	Control Group
Need to blow nose	154 (93)	96 (63)	1.89	2.12	1.52	1.62	1.03	1.39	0.74	0.86
Sneezing	128 (77)	62 (41)	1.20	1.10	0.79	0.74	0.51	0.47	0.46	0.48
Runny nose	144 (87)	74 (49)	1.64	1.86	1.15	1.22	0.80	1.17	0.60	0.65
Cough	148 (89)	84 (55)	1.87	1.73	1.52	1.45	0.90	1.21	0.70	0.70
Postnasal discharge	153 (92)	84 (55)	2.05	1.85	1.49	1.49	1.15	1.16	0.70	0.75
Thick nasal discharge	154 (93)	71 (47)	1.91	1.95	1.31	1.32	0.88	1.05	0.57	0.66
Ear fullness	123 (74)	47 (31)	1.55	1.51	0.84	1.03	0.58	0.77	0.46	0.48
Headache	138 (83)	59 (39)	1.75	1.74	1.05	1.09	0.66	0.73	0.51	0.55
Facial pain or pressure	149 (90)	47 (31)	1.79	1.85	1.10	1.08	0.54	0.71	0.41	0.37
Wake up at night	136 (82)	40 (26)	1.73	1.63	0.94	0.92	0.54	0.63	0.41	0.24
Lack of a good night's sleep	139 (84)	44 (29)	1.89	1.69	1.00	1.01	0.56	0.73	0.42	0.30
Wake up tired	144 (87)	59 (39)	1.93	1.84	1.12	1.27	0.63	0.83	0.49	0.52
Fatigue	154 (93)	56 (37)	1.93	1.90	1.25	1.24	0.59	0.89	0.49	0.51
Reduced productivity	143 (86)	35 (23)	1.59	1.68	1.02	1.03	0.35	0.60	0.27	0.28
Reduced concentration	133 (80)	36 (24)	1.45	1.47	0.93	0.78	0.34	0.51	0.30	0.28
Frustrated, restless, or irritable	120 (72)	35 (23)	1.27	1.31	0.86	0.89	0.40	0.55	0.22	0.30
SNOT-16 score			1.71	1.70	1.12	1.14	0.65	0.84	0.48	0.49

Table 4. Treatment Use, Outcomes, and Adverse Effects

	Amoxicillin Group (n = 85)	Control Group (n = 81)	*P* Value[a]
Treatment Use			
Treatment duration, d			
Mean (SD)	6.89 (4.55)	6.47 (4.75)	.56
Median (IQR)	10 (0-10)	10 (0-10)	
Adherent with 10-d treatment dosing regimen (self-report), No./total (%)	55/81 (68)	51/71 (72)	.58
Treatment Outcomes			
Change in SNOT-16 scores from day 0, mean (95% CI)[b]			
Day 3	0.59 (0.47-0.71)	0.54 (0.41-0.67)	.69
Day 7	1.06 (0.93-1.20)	0.86 (0.71-1.02)	.02
Day 10	1.23 (1.08-1.37)	1.20 (1.07-1.32)	.85
Self-reported significant improvement in symptoms since day 0, % (95% CI)			
Day 3	37 (27-48)	34 (23-45)	.67
Day 7	74 (64-83)	56 (45-67)	.02
Day 10	78 (69-87)	80 (71-90)	.71
Period missed from work, mean (95% CI), d	0.55 (0.28-0.82)	0.55 (0.22-0.87)	.99
Period unable to do usual nonwork activities, mean (95% CI), d	1.15 (0.76-1.54)	1.67 (1.08-2.26)	.14
Relapse rate, % (95% CI)	9 (3-16)	6 (1-11)	.57
Recurrence rate, % (95% CI)	6 (1-11)	2 (0-6)	.44
Satisfaction with treatment, % (95% CI)	53 (42-64)	41 (29-52)	.13
Treatment Adverse Effects			
Reported any adverse effects, % (95% CI)	16 (8-24)	14 (6-22)	.74
Responded "yes" to ≥1 specific symptom question, % (95% CI)	48 (37-59)	52 (39-62)	.75

Abbreviations: IQR, interquartile range (25th-75th percentiles); SNOT-16, Sinonasal Outcome Test-16.
[a] Refers to the comparison between the 2 treatment groups.
[b] Mean of the 16 sinusitis symptoms (0=no symptoms, 3=symptoms are a large problem).

Table 5. Reported Concurrent Use of Symptomatic Treatment Medications

	Participants, % (95% CI)			
	Amoxicillin Group (n = 85)	Control Group (n = 81)	*P* Value[a]	Medication Use, Median (IQR), d[b]
Any concurrent ancillary medication use	94 (89-99)	90 (84-97)	.34	NA
Types of medication taken				
Pseudoephedrine-sustained action[c]	72 (62-81)	73 (63-83)	.88	4 (2-6)
Guaifenesin[d]	69 (60-81)	68 (58-78)	.83	4 (2-7)
Acetominophen[e]	60 (50-70)	60 (50-71)	.95	4 (2-6)
0.65% Saline spray[f]	49 (39-60)	53 (42-64)	.64	3 (2-6)
Dextromethorphan hydrobromide with guaifenesin[g]	51 (40-61)	49 (38-60)	.88	3 (2-5)

Abbreviations: IQR, interquartile range (25th-75th percentile); NA, data not applicable.
[a] Refers to the comparison between the 2 treatment groups.
[b] No differences were found for duration of use for each symptomatic treatment by study group.
[c] Dose: 120 mg every 12 hours.
[d] Dose: 600 mg taken orally every 12 hours to thin secretions (over-the-counter medication).
[e] Dose: 500 mg every 6 hours for pain and/or fever.
[f] Dose: 2 puffs per nostril as needed.
[g] Dose: 10 mL every 4 to 6 hours for cough (10 mg/5 mL of dextromethorphan hydrobromide and 100 mg/5 mL of guaifenesin).

the odds of improvement by day 7 with antibiotic treatment vs no treatment was 4.59 (95% CI, 1.16-18.12), with no benefit in the group without obstruction. Smoking, duration of symptoms, prior sinus infection, asthma, allergic rhinitis, severity of symptoms (by report and baseline SNOT-16 score), and laterality of disease were not associated with having benefit with antibiotic treatment.

COMMENT

Our findings support recommendations to avoid routine antibiotic treatment for patients with uncomplicated acute rhinosinusitis.[15,20] All study participants met the recommended clinical criteria for acute rhinosinusitis[1] and are representative of patients for whom antibiotics might be prescribed. To our knowledge, this is the first trial of antibiotic treatment for acute rhinosinusitis to assess improvement in disease-specific quality of life as the primary outcome, an outcome that is important to patients. The SNOT-16 instrument was developed using established psychometric methods, including patient input, and assesses functional limitations, physical problems, and emotional consequences of rhinosinusitis; it is valid and responsive to change in patients with acute and chronic sinusitis.[16,18] In both study groups, disease-specific quality of life and sinus symptoms improved over time, with no significant difference at 10 days for these outcomes or functional status, disease relapse or recurrence, satisfaction with care, or treatment adverse effects. Symptoms more frequently identified as bothersome by study participants (including nasal symptoms and cough) were likely to persist for at least 10 days.

Some studies have reported more rapid resolution of rhinosinusitis symptoms for adults treated with antibiotics,[5,11,21] whereas others found no difference.[6,12] In this study, retrospective assessment of change in sinus symptoms suggested that antibiotic treatment may provide more rapid resolution of symptoms for some patients by

day 7. However, when improvement was assessed as the difference in SNOT-16 scores, the statistically significant benefit at day 7 was too small to represent any clinically important change. Inaccurate recollection of the baseline condition may explain the larger effect size observed with retrospective rather than serial measures.[11,22,23]

Clinical criteria used to diagnose acute rhinosinusitis in this community-based clinical trial are likely more rigorous than those routinely used in practice,[1] yet they failed to identify those for whom 10 days of treatment with amoxicillin provided any significant clinical benefit. It is unlikely that this finding was due to an inadequate dose of amoxicillin because the prevalence of amoxicillin-resistant *S pneumoniae* in our community at the time of the study was low,[24] and there is no evidence that any other antibiotic is superior to amoxicillin.[9,13] It is also unlikely that our findings are due to inadequate power. Our post hoc power calculation showed 89% power to detect a between-group difference of at least 0.3 in the 3-, 7-, and 10-day change in SNOT-16 scores, much smaller than the 0.5 minimally important difference representing a clinically significant effect.[18,19,25,26] The triple-blind design, high treatment adherence, and the high level of patient retention across both study groups strengthen the validity of our findings.

Limitations of this study should be noted. It is possible that not all patients included in the study sample had acute rhinosinusitis because absent any accurate, acceptable objective tests to guide management, current guidelines recommend clinical criteria for diagnosis of bacterial infection.[1,2,15] Nevertheless, the study population is representative of patients for whom antibiotics are prescribed. The wording of the SNOT-16 instrument may make it difficult to ascertain the exact timing of significant differences between the study groups because participants were asked to evaluate their symptoms over the past few days. However, because the period of reference is the same for every interview, between-group comparisons at the time point when the instrument was administered is valid. Concurrent use of symptomatic treatments (although common) was similar in both groups and unlikely to bias study findings.

There is now a considerable body of evidence from clinical trials conducted in the primary care setting that antibiotics provide little if any benefit for patients with clinically diagnosed acute rhinosinusitis.[11,12,21] Yet, antibiotic treatment for upper respiratory tract infections is often both expected by patients and prescribed by physicians.[14,27] Indeed, patients' expectation that antibiotic treatment is needed to resolve sinus symptoms may explain their reluctance to participate in this randomized trial in which antibiotic treatment was not assured, but data are not available to confirm this. The National Institute for Health and Clinical Excellence guidelines in the United Kingdom, and more recent guidelines in the United States, suggest watchful waiting as an alternative approach to the management of patients for whom reassessment is possible; this approach delays and may preclude antibiotic treatment while providing symptomatic treatments and an explanation of the natural history of the disease.[15,20] Delayed antibiotic prescriptions, a strategy more commonly used in Europe than in the United States,[27] was effective in a study from the Netherlands.[28] Analgesics are recommended, but additional therapies to provide symptom relief and a feasible alternative to antibiotic treatment are needed. Intranasal steroids have not proved to be as widely effective as first hoped but may reduce symptoms for some patients with mild disease.[12,29,30] Promising alternative treatments such as nasal irrigation[31] need further investigation.

In conclusion, evidence from this study suggests that treatment with amoxicillin for 10 days offers little clinical benefit for most patients with clinically diagnosed uncomplicated acute rhinosinusitis. It is important to note that patients with symptoms indicative of serious complications were excluded from this trial and likely need a different management strategy.

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Study concept and design: Garbutt, Spitznagel, Piccirillo.
Acquisition of data: Garbutt, Banister.
Analysis and interpretation of data: Garbutt, Spitznagel, Piccirillo.
Drafting of the manuscript: Garbutt, Spitznagel.
Critical revision of manuscript for important intellectual content: Garbutt, Banister, Spitznagel, Piccirillo.
Statistical analysis: Spitznagel.
Obtaining funding: Garbutt, Spitznagel.
Administrative, technical, or material support: Banister.
Study supervision: Garbutt, Banister.
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