Antibiotics and Topical Nasal Steroid for Treatment of Acute Maxillary Sinusitis

A Randomized Controlled Trial

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Context Acute sinusitis is a common clinical problem that usually results in a prescription for antibiotics but the role of antibiotics is debated. Anti-inflammatory drugs such as topical steroids may be beneficial but are underresearched.

Objective To determine the effectiveness of amoxicillin and topical budesonide in acute maxillary sinusitis.

Design, Setting, and Patients A double-blind, randomized, placebo-controlled factorial trial of 240 adults (aged ≥16 years) with acute nonrecurrent sinusitis (had ≥2 diagnostic criteria: purulent rhinorrhea with unilateral predominance, local pain with unilateral predominance, purulent rhinorrhea bilateral, presence of pus in the nasal cavity) at 58 family practices (74 family physicians) between November 2001 and November 2005. Patients were randomized to 1 of 4 treatment groups: antibiotic and nasal steroid; placebo antibiotic and nasal steroid; antibiotic and placebo nasal steroid; placebo antibiotic and placebo nasal steroid.

Intervention A dose of 500 mg of amoxicillin 3 times per day for 7 days and 200 μg of budesonide in each nostril once per day for 10 days.

Main Outcome Measures Proportion clinically cured at day 10 using patient symptom diaries and the duration and severity of symptoms.

Results The proportions of patients with symptoms lasting 10 or more days were 29 of 100 (29%) for amoxicillin vs 36 of 107 (33.6%) for no amoxicillin (adjusted odds ratio, 0.99; 95% confidence interval, 0.57-1.73). The proportions of patients with symptoms lasting 10 or more days were 32 of 102 (31.4%) for topical budesonide vs 33 of 105 (31.4%) for no budesonide (adjusted odds ratio, 0.93; 95% confidence interval, 0.54-1.62). Secondary analysis suggested that nasal steroids were significantly more effective in patients with less severe symptoms at baseline.

Conclusion Neither an antibiotic nor a topical steroid alone or in combination was effective as a treatment for acute sinusitis in the primary care setting.

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SYMPTOMS CONSISTENT WITH acute sinusitis are commonly encountered in primary care practices and are due to a broad group of usually undefined etiologies at the time of the initial treatment decision. Estimates from the United Kingdom suggest that a primary care physician sees 50 or more cases per year.[1] Of the cases in which acute maxillary sinusitis (rhinosinusitis) is suspected on presentation, considerably few are reliably confirmed by the physician.[2,3] Studies conducted in primary care practices suggest that 37% to 63% of patients presenting do not have a confirmed diagnosis.[4-7]

Despite the clinical uncertainty as to a bacterial cause in everyday practice, antibiotic prescribing rates remain as high as 92% in the United Kingdom[8] and 85% to 98% in the United States,[9] and are only slightly lower in Holland (80%)[10] and Norway (67%).[11] Because there are no satisfactory studies of microbiological etiology from typical primary care patient practices, wide-scale overtreatment is likely occurring.[12,13] Additional considerations of widespread antibacterial use include the economic costs associated with antibiotics, which are currently estimated to be approximately £10 million in prescribing costs per year in the United Kingdom, and $2.4 billion per year in the United States[14]

See also p 2543 and Patient Page.

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and increasing antibiotic resistance in the community.[15] In addition, patients given antibiotics attribute symptom resolution to antibiotics (whereas 60%-85% improve over the same time course whether treated or untreated for sinusitis across settings),[16] which reinforces the impression of efficacy. Cases of sinusitis with an underlying acute bacterial etiology require better diagnostic evaluation to appropriately target the use of antibiotics.[2,17]

The role of antibacterials in the management of acute sinusitis in the primary care setting is controversial. The Cochrane review suggests moderate effect sizes of penicillins for acute sinusitis (penicillin: absolute risk reduction, 5.7% and number needed to treat, 18; amoxicillin: absolute risk reduction, 13.7% and number needed to treat, 8).[16] The 95% confidence intervals (CIs) of the relative risks (RRs) for cases cured, however, indicate that the effects are not significant (RR, 1.72 [95% CI, 1.00-2.96] for penicillin; and RR, 2.06 [95% CI, 0.65-6.53] for amoxicillin). The main evidence for use of antibacterials is derived from 5 studies included in the Cochrane review,[16] mainly conducted in the secondary care setting that included patients with x-ray-confirmed sinusitis. Extrapolation of these results to routine clinical practice is impractical because x-rays are not routinely used in the community in which most cases are treated and managed.

Studies of antibacterial use that used patient recruitment by community-based physicians have tended to show either no or smaller effect sizes, and the highest 2 methodologically rated studies (van Buchem et al[18] and Lindbaek et al[19]) came to opposite conclusions about the effectiveness of antibiotics. A recent review[20] has suggested that most cases of acute rhinosinusitis resolve with symptomatic treatment and analgesics, which should remain the mainstay of treatment. Thus, there is no clear evidence base and no consensus to support or refute the benefit of antibiotics. Existing research from primary care populations has lead to no firm conclusions about their effectiveness and use.[18,19,21-27]

The question arises as to whether clinical criteria can help target antibiotic use in the community to patients more likely to have bacterial sinusitis. Comprehensive reviews of diagnosis are found in the Agency for Healthcare Research and Quality guideline,[2] and supported by other studies.[11,28] However, few diagnostic studies exist with patients from any setting that specifically evaluate clinical symptoms and signs compared with the criterion standard of bacterial culture from sinus aspirates. Berg and Carenfelt[29] identified 3 predictive symptoms and 1 sign producing a receiver operating characteristic curve comparable with if not better than standard sinus x-rays. Any 2 symptoms or signs (ie, 2 symptoms and signs out of 4) give a sensitivity of 81%, a specificity of 88% (likelihood ratio for a positive result of 6.75), and a mean positive predictive value of 86%, although for different combinations of the 4 criteria the positive predictive value varies from 63% to 91%.[29]

Intranasal steroids have both an anti-inflammatory and potential decongestant action by inhibiting the transcription of proinflammatory mediators and stabilizing phospholipid membranes; it is reasonable to suppose that they may have a role in the treatment of acute bacterial sinusitis, for example, by improving ostial patency and facilitating drainage from the maxillary sinuses.[30] One early review suggested topical steroids were not helpful in acute sinusitis.[30] A recent Cochrane review,[31] however, found that for every 100 treated patients, 7 additional patients would benefit from topical intranasal corticosteroids and recommended further research as to their effectiveness. The samples in the Cochrane review, however, are not typical primary care–based samples.[32-35] In 1 large study[32] included in the review, the cases were selected for a range of symptom presentations associated with a reduced likelihood of a bacterial cause (ie, exclusion of severe localizing pain or pyrexia) and patients were included on the basis of a list of sinusitis-type symptoms that are not proven to be predictive of bacterial sinusitis.

We report the results of a trial on the effectiveness of an antibiotic (500 mg of amoxicillin 3 times per day for 7 days) and a nasal steroid (200 µg of budesonide in each nostril once per day for 10 days), alone or in combination, among a group of patients presenting in primary care, fulfilling Berg and Carenfelt clinical criteria[29] for acute bacterial sinusitis.

METHODS

Physician Recruitment

The recruitment plan was for 4 recruited cases per family physician (1 block randomized pack of 4 per physician and 2 physicians per practice). In total, 117 practices were visited in 2 phases over a 2.5-year period, with 230 family physicians expressing an interest in participating but only 74 willing to actively take part in the study. Initially, all practices in neighboring localities were invited until the target of 40 participating practices was achieved. To offset a slower than predicted initial recruitment of physicians, 18 further practices were recruited into the study with a second mailing and practice visit to these more distant localities. Family physicians received $50 per patient recruited for their time from government funding but patients received no reimbursement.

Inclusion Criteria

Adult patients older than 15 years with uncomplicated acute illness (<28 days duration) who presented to a primary care practice with symptoms of sinusitis were recruited. The recruiting physician checked for 3 symptoms and 1 clinical sign as defined by the Berg and Carenfelt criteria[29]: purulent nasal discharge with unilateral predominance, local pain with unilateral predominance, purulent nasal discharge bilaterally, and pus on inspection inside the nose. Patients had to be positive for a minimum of 2 of the above criteria to

be entered in the study. X-rays of the sinuses were not used because they are not routinely recommended by UK clinical guidelines, are not routinely used in UK practice, do not perform better than the Berg and Carenfelt criteria, and are not cost-effective.[36]

The practices had informal training by the chief investigator or staff trained by the chief investigator in interpretation of the entry criteria and appropriate examination techniques, and all were visited by at least 1 member of the study team and given the opportunity to ask questions about the trial and methods before commencing.

Exclusion Criteria

Cases with a low probability of acute bacterial sinusitis that had less than 2 of the Berg and Carenfelt criteria were excluded. Because the study was focused on those with a primary bacterial pathogenesis,[17] patients with a history of recurrent sinusitis (defined by ≥2 attacks of acute sinusitis in the previous 12 months) were excluded. This was intended to exclude a significant proportion of cases with an underlying allergic origin, and also those with suspected serious underlying nasal pathologies that require immediate or surgical treatment. Other exclusion criteria included patients with significant comorbidities, such as poorly controlled diabetes or heart failure, pregnant or breastfeeding patients, those with allergies or a history of adverse reactions to either medication, and those receiving antibiotics or steroids in the previous month.

Sample Size and Ethical Considerations

Using the Cochrane meta-analysis for an effect of amoxicillin with 42.5% not cured treated vs 61.4% not cured untreated, we determined a minimum of 208 patients with complete outcomes was required for an α level of .05 and a β level of .20.[16] This sample size ($\approx$200) would allow us to detect an SD difference of 0.4 (a small clinical effect size) on the Total Symptom Severity (TSS) score (a more sensitive continuous outcome). An upper target of 290 patients would be required to achieve a β level of .10.

The study was approved by the Southwest England multicenter research ethics committee and several local research ethics committees across the south: Southampton and Southwest Wiltshire, Isle of Wight, Portsmouth, and Southeast Hampshire, Dorset West and East, and North and Mid-Hampshire. Physicians took full written informed consent after the patient read the patient information leaflet and asked questions.

Factorial Design

The most efficient way of testing more than 1 hypothesis is a factorial trial.[37] Such trials require a prespecified factorial analysis plan with assessments for treatment interactions.[38] The 4 allocated groups in this study were active antibiotic and active topical steroid, active antibiotic and placebo topical steroid, placebo antibiotic and active topical steroid, and placebo antibiotic and placebo topical steroid. Combined analysis was planned as follows: antibiotic (active antibiotic and active topical steroid; active antibiotic and placebo topical steroid) vs no antibiotic (placebo antibiotic and active topical steroid; and placebo antibiotic and placebo topical steroid) (controlling for the effects of a steroid in the model) and topical steroid (active antibiotic and active topical steroid; placebo antibiotic and active topical steroid) vs no topical steroid (active antibiotic and placebo topical steroid; placebo antibiotic and placebo topical steroid) (controlling for the effects of an antibiotic in the model).

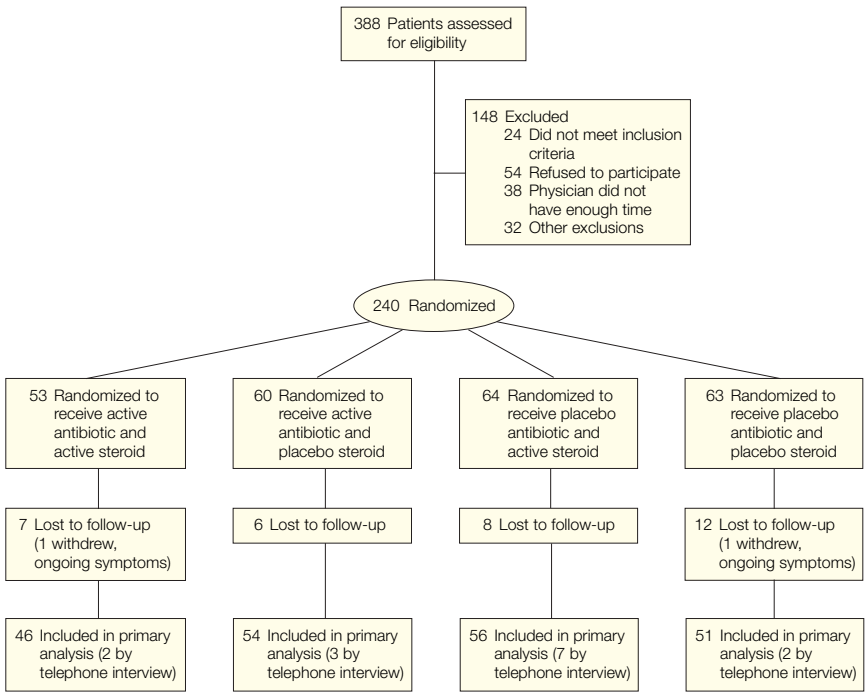
Randomization

Randomization was performed at the level of the patient and occurred during presenting consultations with the physician using blind-sequenced trial packs. This setting ensured that the findings are applicable to routine practice (primary care/family practice). The sealed opaque numbered packages contained physician instructions and either active or placebo drugs that were distributed in batches to participating practices in randomized blocks of 4. Neither the antibiotic nor the nasal steroid spray was recognizable as active or placebo medication from the packs and they were identical in taste and appearance. The packs were made up using random number tables and an independent person to the trial team was employed for distribution using the random sequence and trial code. Each randomized pack therefore consisted of an auditable sequence of the 4 possible combinations of the 2 interventions and physicians were instructed to use the packs in sequence. The code break was kept in a sealed envelope in a locked filing cabinet at the university throughout the study period.

Supplies of trial medications (both active and placebo) were purchased from 2 separate generic suppliers (CTS, Craigavon, Northern Ireland, amoxicillin and placebo; and Generics UK, Hertfordshire, England, budesonide and placebo). All drug containers and all trial materials were identifiable only by the randomization code number. During the 4 years of the study, no serious adverse events or related hospitalizations were reported and the single codebreak envelope was not opened until after all data collection was completed and all variables had been entered into the database.

After obtaining full written informed consent, physicians completed a baseline questionnaire including clinical signs and confirmed the entry criteria. A basic physical examination of temperature recording, sinus tenderness, and anterior nasal cavity inspection (anterior rhinoscopy) were performed and noted. Information on symptom duration and pain severity was recorded and exclusions confirmed. In addition, some baseline demographic details were collected. All participants who agreed to be randomized were instructed in the completion of a 14-day patient symptom diary with entries to be completed on each day and a question-

Figure 1. Flow of Patients Through Trial



naire. Patients also received written and pictorial instructions on the correct method to take the medication.

Outcome and Data Collection

The main study outcome was obtained from a self-reported patient diary. This included 11 symptom variables assessed on 7-point Likert scales and validated in similar pragmatic primary care trials and diagnostic studies from our group.[13,39-41] The diary variables were (1) nasal blockage on the left side, (2) nasal blockage on the right side, (3) discharge from the nose (left nostril), (4) discharge from the nose (right nostril), (5) unpleasant taste or smell, (6) pain in the face on the left side, (7) pain in the face on the right side, (8) pain in the head, jaws, or teeth on bending, (9) level of restriction on daily activity, (10) level of wellness, and (11) headache. Each variable was scored as 0 for normal or not affected, 1 for very little problem, 2 for slight problem, 3 for moderately bad, 4 for bad, 5 for very bad, and 6 for as bad as it could be.

These diaries were combined with a questionnaire on other variables, such as clinical features and satisfaction with the consultation. Patients were contacted by telephone during the first week by a research assistant using a brief structured approach and questions were answered to encourage adherence and improve the quality of the diary returns. When patients were scoring zeros for all their symptoms or at 2 weeks, they were asked to return their completed diaries by mail together with their remaining antibiotic supplies (for counting) and nasal sprays (for weighing). Patients who did not respond were contacted again by telephone or by mail to encourage returns. For some of the nonresponders, it was possible to collect the necessary study data by telephone interview (n=14 or 5.8% of the randomized population). This method previously has been validated by our group.[39-41] Physicians also kept log diaries of cases not entered whenever this was possible and the reasons for refusal. Notes were audited for related reattendance at 6 weeks. All outcome assessments were recorded on a central database and checked and verified when necessary by a research fellow blinded to treatment grouping.

Statistical Analysis

All those with diary information (n=207) were analyzed according to the randomization group to which they were allocated, irrespective of compliance. Our principal analysis did not impute data in which the diary information for symptom resolution (ie, when symptoms became very little or no problem) could not be obtained because there was no basis on which to judge when symptom resolution had occurred in such individuals. However, sensitivity analyses were performed on the blinded data in 2 ways: with imputation of data (assuming those lost to follow-up were still symptomatic at day 14) and with and without the additional telephone information obtained. We found no significant difference in the results. All such and subsequent analyses were performed in accordance with the prespecified analysis plan. We have followed the guidelines for statistical analysis of a factorial trial,[38] no significant interactions between the treatments were noted for all reported outcomes.

Logistic regression was used for the dichotomous primary outcome (proportion cured vs those with symptoms lasting ≥10 days). Cox regression for symptom resolution also was performed. The assumptions of proportional hazards were assessed graphically and also in comparison with Kaplan-Meier curves, which are presented with the log-rank test results. When no symptom information was available, data were censored in the Kaplan-Meier curves. Nonparametric quantile regression was used for the continuous outcome symptom scores. The least absolute value model in Stata (StataCorp, College Station, Texas) was used for quantile regression to esti-

mate the medians. Median regression finds the regression plane that minimizes the sum of the absolute residuals rather than the sum of the squared residuals. The analysis corresponded to the factorial design (ie, the main effects for each factor controlled for the other factor once we had tested for and confirmed that there was no interaction between treatment groups).

The main results are presented as adjusted odd ratios (AORs), favoring treatment or control with their 95% CIs. Factor analysis also was used to help define important symptom groups. After extracting the principal component factors, a varimax rotation was used. This keeps the factors orthogonal but maximizes the sum of the variances of the factor loadings so that each factor has a few large loadings with the remainder being as close to zero as possible. Interactions between baseline severity and outcomes are reported. Stata version 9 (StataCorp) and SPSS version 15 (SPSS Inc, Chicago, Illinois) software was used in the analysis. $P<.05$ was used as the level of significance.

RESULTS

A total of 388 patients were assessed for eligibility and 240 were randomized over a 4-year study period (November 2001 to November 2005). FIGURE 1 shows the flow of patients throughout the trial. A mean of 3 patients were recruited per physician and 4 cases per practice (ie, 1 block randomized pack of 4). One reason for slow recruitment was refusal by some patients (n=54) to be randomized because of reported demand for immediate antibiotics. However most patients were not entered into the study either because the physician did not have sufficient time during office encounters to recruit (n=38; these details were recorded in physician log books and checked in at the end of the study), the patients had other exclusion criteria (n=32), the most common being allergy to penicillin-type antibiotics, or the cases did not meet the inclusion criteria (n=24). Several physicians reported that the entry criteria used excluded a significant number of routine cases of "sinusitis" that they saw in their practices, confirming that our criteria were more stringent than those usually used for clinical diagnosis. The concealment also was assessed and we found that there was no significant difference in patients' belief in the effectiveness of the treatment allocated (0-5

Table 1. Baseline Comparison of Intervention and Control Groups

Characteristic	No./Total (%) of Patients[a]			
	Active Antibiotic and Active Steroid	Active Antibiotic and Placebo Steroid	Placebo Antibiotic and Active Steroid	Placebo Antibiotic and Placebo Steroid
Age, mean (SD), y	42.1 (12.7)	43.8 (15.6)	42.8 (15.0)	41.3 (17.3)
Sex				
Male	12/53 (22.6)	18/60 (30)	18/64 (28.1)	18/63 (28.6)
Female	41/53 (77.4)	42/60 (70)	46/64 (71.9)	45/63 (71.4)
Smoking history				
Never	15/41 (36.6)	21/50 (42)	27/51 (52.9)	23/48 (47.9)
Past	18/41 (43.9)	19/50 (38)	15/51 (29.4)	19/48 (39.6)
Current	8/41 (19.5)	10/50 (20)	9/51 (17.6)	6/48 (12.5)
Asthma				
No	38/41 (92.7)	44/50 (88)	42/51 (82.4)	40/48 (83.3)
Yes	3/41 (7.3)	6/50 (12)	9/51 (17.6)	8/48 (16.7)
Eczema				
No	34/41 (82.9)	39/49 (79.6)	43/51 (84.3)	38/47 (80.9)
Yes	7/41 (17.1)	10/49 (20.4)	8/51 (15.7)	9/47 (19.1)
Hay fever				
No	36/44 (81.8)	44/53 (83)	41/56 (73.2)	37/50 (74)
Yes	8/44 (18.2)	9/53 (17)	15/56 (26.8)	13/50 (26)
Sinusitis before				
No	6/44 (13.6)	11/54 (20.4)	10/56 (17.9)	10/49 (20.4)
Yes	38/44 (86.4)	43/54 (79.6)	46/56 (82.1)	39/49 (79.6)
Pus on inspection				
No	40/53 (75.5)	37/60 (61.7)	39/64 (60.9)	38/63 (60.3)
Yes	13/53 (24.5)	23/60 (38.3)	25/64 (39.1)	25/63 (39.7)
Initial temperature, median (IQR), °C	(n = 50) 36.5 (36.0-36.8)	(n = 57) 36.5 (36.0-36.9)	(n = 61) 36.6 (36.2-37.1)	(n = 58) 36.5 (36.3-36.9)
No. of days had symptoms, median (IQR)	(n = 51) 7 (4-14)	(n = 60) 7 (4-10)	(n = 63) 7 (4-14)	(n = 61) 7 (5-14)
Berg and Carenfelt criteria[29]				
2	35/49 (71.4)	39/59 (66.1)	45/63 (71.4)	40/62 (64.5)
≥3	14/49 (28.6)	20/59 (33.9)	18/63 (28.6)	22/62 (35.5)

Abbreviation: IQR, interquartile range.
[a] Unless otherwise indicated.

scales) for the antibiotic tablet vs placebo tablet ($P=.07$), or for steroid spray vs placebo spray ($P=.25$).

Of the 240 randomized adults aged 16 years or older fulfilling the entry criteria, approximately 70% of the sample had 2 of the Berg and Carenfelt diagnostic criteria[29]; 30% had either 3 or all 4. The median age was 44 years and 4 females were recruited to every male. TABLE 1 shows the baseline characteristics by treatment group. Potential confounders are analyzed by the factorial groupings used for the main analyses (TABLE 2). Age, sex, history of smoking, asthma, eczema, hay fever, previous sinusitis, pus on inspection, initial temperature, number of days with symptoms, and baseline severity as assessed by the Berg and Carenfelt criteria[29] all showed no significant differences between groups at baseline, apart from temperature between those receiving the antibiotic and those not receiving the antibiotic ($P=.05$). Although not significant, those given the antibiotic were slightly less likely to be male (26.5% vs 28.3%) and less likely to have pus on examination (31.9% vs 39.4%). The prevalence of atopy in the sample overall is slightly higher than in the general population. The presence of a past history of atopy did not alter the estimates or inferences. The majority of patients had a previous episode of sinusitis (but not ≥2 episodes in the previous 12 months).[42] The median duration of prior symptoms before seeing a physician was 7 days (interquartile range, 10 days).

In total, 33 patients were lost to follow-up at 2 weeks (13.7% loss to follow-up). Patients who had pus on examination (AOR, 1.50; 95% CI, 0.66-3.40) and were male (AOR, 3.75; 95% CI, 1.66-8.48) were more likely to be lost to follow-up. Clinical records confirmed that 2 of the patients lost to follow-up withdrew from the study: 1 in the antibiotic and steroid group and 1 in the double placebo group. Both withdrew early because of ongoing symptoms.

There were no significant tests for treatment interactions by factor group (antibiotic tablet vs placebo tablet and steroid spray vs placebo spray). The results presented herein are based on patients with diary-returned, completed outcomes (n=193) plus validated interviews (n=14). Colinearity and overfitting of our models were assessed but we found no evidence of either.

Table 2. Antibiotic vs No Antibiotic and Steroid vs No Steroid

Characteristic	No./Total (%) of Patients[a]		*P* Value for Between-Group Difference	No./Total (%) of Patients[a]		*P* Value for Between-Group Difference
	Antibiotic	No Antibiotic		Steroid	No Steroid	
Age, mean (SD), y[b]	43.0 (14.3)	42.1 (16.1)	.64	42.5 (14.0)	42.6 (16.5)	.96
Sex						
Male	30/113 (26.5)	36/127 (28.3)	.76	30/117 (25.6)	36/123 (29.3)	.53
Female	83/113 (73.5)	91/127 (71.7)		87/117 (74.4)	87/123 (70.7)	
Smoking history						
Never	36/91 (39.6)	50/99 (50.5)	.31	42/92 (45.7)	44/98 (45.3)	.89
Past	37/91 (40.7)	34/99 (34.3)		33/92 (35.9)	38/98 (38.8)	
Current	18/91 (19.8)	15/99 (15.2)		17/92 (18.5)	16/98 (16.3)	
Asthma						
No	82/91 (90.1)	82/99 (82.8)	.15	80/92 (87)	84/98 (85.7)	.80
Yes	9/91 (9.9)	17/99 (17.2)		12/92 (13)	14/98 (14.3)	
Eczema						
No	73/90 (81.1)	81/98 (82.7)	.78	77/92 (83.7)	77/96 (80.2)	.54
Yes	17/90 (18.9)	17/98 (17.3)		15/92 (16.3)	19/96 (19.8)	
Hay fever						
No	80/97 (82.5)	78/106 (73.6)	.13	77/100 (77)	81/103 (78.6)	.78
Yes	17/97 (17.5)	28/106 (26.4)		23/100 (23)	22/103 (21.4)	
Sinusitis before						
No	17/98 (17.3)	20/105 (19)	.75	16/100 (16)	21/103 (20.4)	.42
Yes	81/98 (82.7)	85/105 (81)		84/100 (84)	82/103 (79.6)	
Pus on inspection						
No	77/113 (68.1)	77/127 (60.6)	.23	79/117 (67.5)	75/123 (61)	.29
Yes	36/113 (31.9)	50/127 (39.4)		38/117 (32.5)	48/123 (39)	
Initial temperature, median (IQR), °C	(n = 107) 36.5 (36.0-36.8)	(n = 119) 36.5 (36.3-37.0)	.05	(n = 111) 36.5 (36.0-37.0)	(n = 115) 36.5 (36.1-36.9)	.61
No. of days had symptoms, median (IQR)	(n = 111) 7 (4-14)	(n = 124) 7 (4-14)	.56	(n = 114) 7 (4-14)	(n = 121) 7 (4-13.5)	.88
Berg and Carenfelt criteria[29]						
2	74/108 (68.5)	85/125 (68)	.93	80/112 (71.4)	79/121 (65.3)	.32
≥3	34/108 (31.5)	40/125 (32)		32/112 (28.6)	42/121 (34.7)	

Abbreviation: IQR, interquartile range.
[a] Unless otherwise indicated.
[b] The 95% confidence interval for the between-group difference for antibiotic vs no antibiotic is –4.87 to 3.02 and for steroid vs no steroid is –3.84 to 4.05.

The proportions of patients with symptoms lasting 10 or more days were 29 of 100 (29%) for amoxicillin vs 36 of 107 (33.6%) for no amoxicillin (AOR, 0.99; 95% CI, 0.57-1.73). The proportions of patients with symptoms lasting 10 or more days were 32 of 102 (31.4%) for topical budesonide vs 33 of 105 (31.4%) for no budesonide (AOR, 0.93; 95% CI, 0.54-1.62). Cox regression confirmed the lack of a significant effect of amoxicillin (hazard ratio for resolution, 1.08 [95% CI, 0.79-1.48]; $P = .63$) or budesonide (hazard ratio, 1.05 [95% CI, 0.77-1.44]; $P = .75$).

When the sensitivity analysis was calculated using imputation as data for patients that were lost to follow-up, the estimated effect of amoxicillin on symptoms lasting 10 days or more (AOR, 0.90; 95% CI, 0.54-1.50) and budesonide (AOR, 0.90; 95% CI, 0.54-1.50) also were nonsignificant. The small difference in the apparent effect of the antibiotic in the imputed analysis may be in part an artifact of slight differences in randomization groups because the placebo group had more males and more patients with pus on examination and both of these variables predicted loss to follow-up.

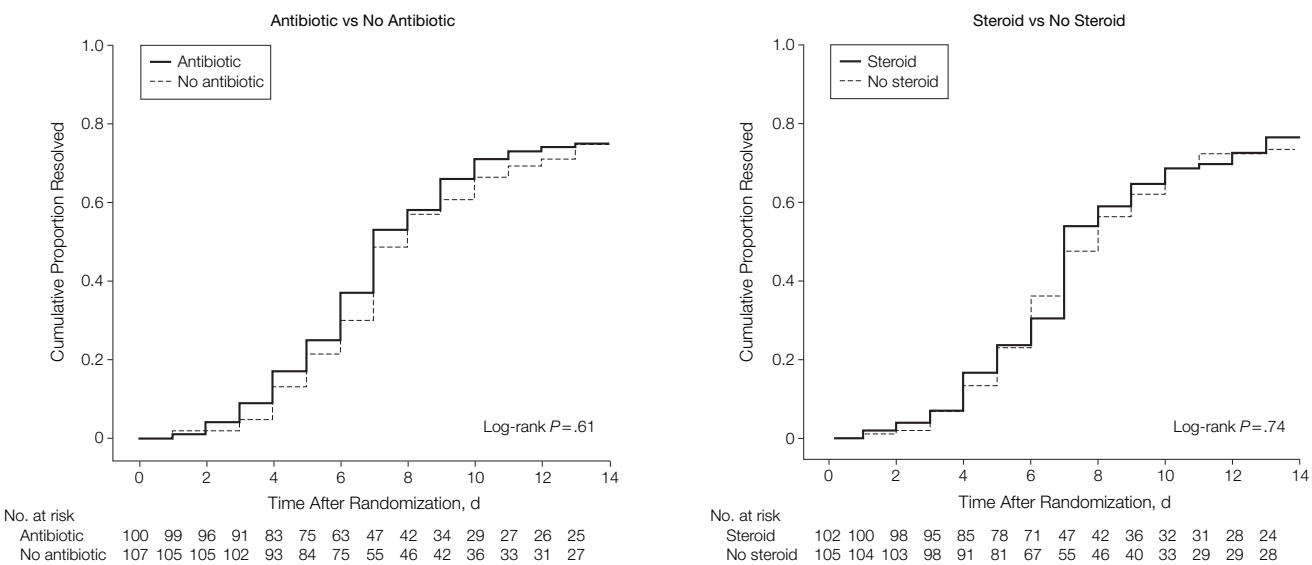
The proportion cured by day until day 14 are shown in FIGURE 2 for amoxicillin vs no amoxicillin and topical budesonide vs no budesonide. Cure for each patient was defined by scoring either no or very little problem (0 or 1) for each and all of the 11 items in the diary. No noticeable differences were observed in time to cure for any of the groups with 40% of patients cured by 1 week. Resolution appears slower during the second week (third week of illness).

A TSS score for each day was based on the summation of all the numeric values from the Likert scales (for days 0-10). To establish any statistically important groupings of related symptoms, a principal factor analysis with varimax rotation was performed. The first 2 component subgroups of symptoms were retained based on eigenvalues greater than 1. These were unwell (determined by symptoms 8-11; Cronbach $\alpha = .92$) and pain (symptoms 6-8; $\alpha = .83$).

The TSS had a maximum score of 66 for the 11 variables. The data were not normally distributed for these scores so the median values were plotted over time for each of the groups and are shown in FIGURE 3 for amoxicillin vs no amoxicillin and topical budesonide vs no topical budesonide. Nonparametric (quantile) regression was performed at day 10. There was no significant difference in the medians for amoxicillin vs no amoxicillin (median difference, 0 [95% CI, –0.70 to 0.70]; $P > .99$) or for budesonide vs no budesonide (median difference 0 [95% CI, –0.70 to 0.70]; $P > .99$). Nor were there any differences between groups when the mean TSS for all 14 days was used.

The pain and unwell group of symptoms identified by the factor analysis were analyzed separately because of their importance to physicians in patient management and to assess any differential treatment effects. For the pain group of symptoms, no significant differences were found between any of the groups for each day; full resolution of pain occurred at day 6 or 7, which was about 1 day ahead of the rest of the diary variables. The unwell group of symptoms were measured using the mean score for severity (score range, 0-6) and was based on the degree to which the patient felt unwell and level of restriction on daily activity. Interactions between baseline severity and treatment groups with severity at 10

Figure 2. Plot of Symptom Resolution[a]



[a] Defined as when a patient reports 0 or 1 for all of the 11 diary items.

days were then tested. A significant interaction between increased severity at baseline and the nasal steroid was found for the unwell group of symptoms. Allowing for this interaction, the effect of the steroid on the unwell group of symptoms at 10 days was –0.75 (95% CI, –1.34 to –0.14) for a baseline severity score of zero. However, the interaction coefficient was 0.28 (95% CI, 0.10 to 0.45; $P=.003$; ie, the effect of the nasal steroid is reduced by 0.28 for each 1 point increase in baseline severity of sinusitis). For example, the effect of the steroid for a patient with a baseline severity score of 1 is $-0.75+0.28=-0.47$, whereas for a patient with a baseline score of 3 it is $-0.75+0.28\times3=0.09$, and for a baseline score of 5 it is $-0.75+0.28\times5=0.65$. Thus, the nasal steroid is beneficial in those cases with less severe symptoms among our probable bacterial sinusitis sample and detrimental among those with more severe symptoms. No serious adverse events occurred according to trial and clinical records and case analysis at 6 weeks.

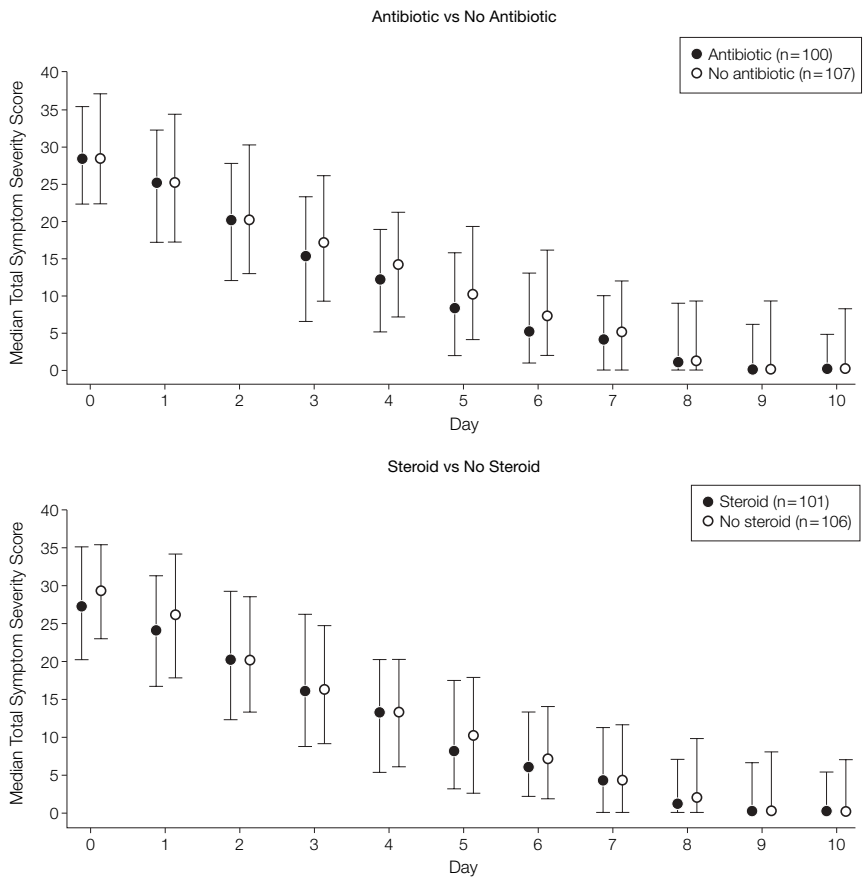
COMMENT

To our knowledge, this is the largest non–pharmaceutically funded double-blind, randomized, placebo-controlled trial assessing the effectiveness of amoxicillin in cases of acute sinusitis (with typical features of bacterial sinusitis) presenting to family physicians, and the only adequately powered trial of budesonide in this patient group. From the main findings, we can be more than 95% confident that the effect size reported in the Cochrane review[16] for amoxicillin (relative risk, 2.06) is not found within the population from which our sample came. Considered with several other primary care studies, it would appear that any effect size present, assuming there is an effect of antibiotics, is significantly smaller than that reported in the Cochrane review,[16] which included data combined from primary and secondary care populations to guide its recommendations. Our more rigorous case definition of sinusitis is likely to mean that less well-defined cases of sinusitis treated routinely by physicians in primary care will show even less effect from taking antibiotics.

A potential study limitation is the power of the study to detect clinically useful effects of an antibiotic, and the possibility of a false-negative finding.[16] Based on the 95% CI for the difference in the proportions, our results suggest that the maximal likely difference between the proportions in those having symptoms for 10 or more days is 13.5% (ie, a number needed to treat of ≥7). Our continuous outcome measures are more sensitive to detect any clinically useful effects (SD of 0.4; ie, a small effect size). Thus, we can be confident we have not missed a 4-point difference on the TSS score, which equates to approximately one-third of patients rating symptoms as a slight vs very little problem or 1 day's less symptoms duration in total. Although we may not have detected small effects, useful clinical effects are not likely to be present, and particularly when weighed against the disadvantages of antibiotics.

A further potential limitation of the study was that the recruitment rate was low (mean value of 3 cases per family physician), although in fact our trial family physicians recruited better than average for community-based studies.[43] The incidence of seasonal flu was low over the study period (thus reduc-

Figure 3. Cure by Antibiotics and Steroids Defined by Total Symptom Severity Score



Data are presented as median scores with interquartile ranges (IQR; N=207). The overall median symptom scores over 10 days were 10 (IQR, 2-22) for patients who received the antibiotic; 12 (IQR, 3-25) for no antibiotic; 11 (IQR, 2-24) for steroid; and 11 (IQR, 2-23) for no steroid. Day 0 indicates day of randomization.

ing the likelihood of secondary bacterial sinusitis). Common recruitment obstacles were work pressures on busy family physicians to recruit (with comparatively low reimbursement rates for the research time), and that our diagnostic criteria were strict and many patients failed to meet them. This suggests that the results should still be generalizable to the population presenting with the Berg and Carenfelt criteria[29] in primary care or family practice populations, and that the effect of antibiotics would be even less in a less selected population.

The Berg and Carenfelt criteria[29] have not been validated in primary care populations and are unlikely to be validated given the invasive nature of the criterion standard used (sinus puncture).[11] Although it is possible that the positive predictive value found by Berg and Carenfelt (86%) in a secondary care population would be lower in a primary care population, the likelihood ratio for a positive test of 6.75 still means that most patients with the Berg and Carenfelt criteria seen in primary care will have bacterial sinusitis. For this likelihood ratio, a pretest probability of 50% gives a posttest probability of approximately 90% but even a 20% pretest probability gives a posttest probability of 65% (using a nomogram for Bayes theorem).[44] We support the use of the Berg and Carenfelt criteria[29] because (1) there is evidence that the 90% posttest probability is a reasonable approximation,[11] (2) they are the best available physician-validated criteria (because they used the best standard of antral aspiration), and (3) the Agency for Healthcare Research and Quality guidelines documented that they are comparable with or better than other methods such as x-rays.

Perhaps most importantly, x-rays, computed tomography scans, and erythrocyte sedimentation rate tests are not performed in UK primary care practice prior to the decision to prescribe (nor in most primary care settings), so their ancillary use in this study would severely limit generalizability to the community population in which the majority of antibiotics are being prescribed. We acknowledge that there are cultural variations in the use of such ancillary tests but the method of recruitment, the use of standardized clinical criteria, and the finding of similar antibiotic prescribing rates between the United States, the United Kingdom, and parts of Europe, all add further weight to the likely generalizability of these findings.

The treatment course of 500 mg of amoxicillin 3 times per day for 7 days is similar to the dosing schedule for the trial by van Buchem et al[18] and several others from primary care.[22-25,27] It is in accordance with UK and US guidelines as a first-choice treatment and particularly when the incidence of *Moraxella* is likely to be low. Three meta-analyses have found no evidence for superior effectiveness of any particular class of antibiotics in acute sinusitis over any other,[16,45,46] so it is unlikely that a different antibiotic would have produced different results. The lack of effectiveness may be because antibiotics do not typically penetrate well into localized cavities.

Similarly, there appears to be no clinically useful effect of topical steroids on average in the studied population. However, a strong interaction between baseline severity and outcome for the nasal steroid ($P = .003$) was noted, indicating that milder cases in the sample did benefit from the topical nasal steroid whereas more severe cases did not. Thus, this work might be interpreted as support of the findings by Meltzer et al[32] in relation to the effectiveness of topical steroids in acute sinusitis, in which that population was defined as less severe and with a lower probability of acute bacterial infection. This suggests that topical steroids (because of their local method of delivery to the mucosa) are more likely to be of benefit at an early stage of the natural history of the condition before more refractory stages develop, characterized by thick secretions, closure of the ostium, and severe inflammation with systemic features.

Our main conclusions are that among patients with the typical features of acute bacterial sinusitis, neither an antibiotic nor a topical steroid alone or in combination are effective in altering the symptom severity, the duration, or the natural history of the condition. Topical steroids are likely to be effective in those with such features but who have less severe symptoms at presentation to the physician.

Author Contributions: Dr Williamson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Williamson, Little.
Acquisition of data: Williamson, Rumsby, Benge, Moore, Cross.
Analysis and interpretation of data: Williamson, Rumsby, Benge, Moore, Smith, Little.
Drafting of the manuscript: Williamson, Benge, Smith, Little.
Critical revision of the manuscript for important intellectual content: Williamson, Rumsby, Benge, Moore, Cross, Little.
Statistical analysis: Williamson, Rumsby, Benge, Smith, Little.
Obtained funding: Williamson, Little.
Administrative, technical, or material support: Rumsby, Benge, Moore, Cross.
Study supervision: Williamson.
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REFERENCES

1. Office of Population Census and Surveys. *Morbidity Statistics From General Practice: Fourth National Study 1991*. London, England: Her Majesty's Stationery Office; 1994.
2. Lau J, Zucker D, Engels EA, et al; Agency for Healthcare Research and Quality. *Diagnosis and Treatment of Acute Bacterial Rhinosinusitis: Evidence Report/Technology Assessment No. 9*. Rockville, MD: Agency for Healthcare Research and Quality; 1999.
3. Lund VJ. Rhinosinusitis. *Br J Hosp Med*. 1997; 57(7):308-312.
4. Lindbaek M, Hjortdal P, Johnsen ULH. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med*. 1996;28(3):183-188.
5. Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. *BMJ*. 1995;311(6999):233-236.
6. Williams JW, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis: making the diagnosis by history and physical examination. *Ann Intern Med*. 1992;117(9):705-710.
7. van Duijn NP, Brouwer HJ, Lamberts H. Use of symptoms and signs to diagnose maxillary sinusitis in general practice: comparison with ultrasonography. *BMJ*. 1992;305(6855):684-687.
8. Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. Variations in antibiotic prescribing and con-

sultation rates for acute respiratory infection in UK general practices 1995-2000. *Br J Gen Pract*. 2005;55 (517):603-608.
9. Hickner JM, Bartlett JG, Besser RE, Gonzales R, Hoffman JR, Sande MA. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann Intern Med*. 2001;134(6):498-505.
10. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, Dieleman JP, Verheij TJM. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. *J Antimicrob Chemother*. 2004;54(6):1116-1121.
11. Lindbaek M, Hjortdahl P. The clinical diagnosis of acute purulent sinusitis in general practice: a review. *Br J Gen Pract*. 2002;52(479):491-495.
12. Williams JW Jr, Simel DL. Does this patient have sinusitis? diagnosing acute sinusitis by history and examination. *JAMA*. 1993;270(10):1242-1246.
13. Williamson I, Benge S, Moore M, Kumar S, Cross M, Little P. Acute sinusitis: which factors do family physicians believe are most diagnostic and best predict antibiotic efficacy? *J Fam Pract*. 2006;55(9):789-796.
14. Osguthorpe JD, Hadley JA. Rhinosinusitis: current concepts in evaluation and management. *Med Clin North Am*. 1999;83(1):27-41.
15. McCormick AW, Whitney CG, Farley MM, et al. Geographic diversity and temporal trends of antimicrobial resistance in *Streptococcus pneumoniae* in the United States. *Nat Med*. 2003;9(4):424-430.
16. Williams JW Jr, Aguilar C, Cornell J, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev*. 2003;(2):CD000243.
17. Gwaltney JM Jr, Jones KG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. *Ann Otol Rhinol Laryngol Suppl*. 1995;167:22-30.
18. van Buchem FL, Knotterus JA, Schrijnemaekers VJ, Peeters MF. Primary care based randomized placebo controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet*. 1997;349(9053):683-687.
19. Lindbaek M, Hjortdahl P, Johnsen UL. Randomised double blind placebo controlled trial of penicillin and amoxicillin in treatment of acute sinus infections in adults. *BMJ*. 1996;313(7053):325-329.
20. Ah-See KW, Evans AS. Sinusitis and its management. *BMJ*. 2007;334(7589):358-361.
21. Stalman W, van Essen GA, van der Graaf Y, de Melker RA. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? *Br J Gen Pract*. 1997;47(425):794-799.
22. Merenstein D, Whittaker C, Chadwell T, Wegner B, D'Amico F. Are antibiotics beneficial for patients with sinusitis complaints? a randomized double-blind clinical trial. *J Fam Pract*. 2005;54(2):144-151.
23. Bucher HC, Tschudi P, Young J, et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: a placebo controlled double blind randomized trial in general practice. *Arch Intern Med*. 2003;163(15):1793-1798.
24. Varonen H, Kunnamo I, Savoleinen S, et al. Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care: a placebo controlled randomised trial. *Scand J Prim Health Care*. 2003;21(2):121-126.
25. De Sutter AI, De Meyere MJ, Christiaens TC, et al. Does amoxicillin improve outcomes in patients with purulent rhinorrhea? *J Fam Pract*. 2002;51(4):317-323.
26. Hansen JG, Schmidt H, Grinstead P. Randomised double blind placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. *Scand J Prim Health Care*. 2000; 18(1):44-47.
27. Nørrelund N. A controlled investigation of pivampicillin. *Ugeskr Laeger*. 1978;140(45):2792-2795.
28. Engels EA, Terrin N, Barza M, Lau J. Meta-analysis of diagnostic tests for acute sinusitis. *J Clin Epidemiol*. 2000;53(8):852-862.
29. Berg O, Carenfelt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. *Acta Otolaryngol*. 1988;105(3-4):343-349.
30. Low DE, Desrosiers M, McSherry J, et al. A practical guide for the diagnosis and treatment of acute sinusitis. *CMAJ*. 1997;156(6)(suppl):S1-S14.
31. Zalmanovici A, Yaphe J. Steroids for acute sinusitis. *Cochrane Database Syst Rev*. 2007;(2):CD005149.
32. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol*. 2005;116(6):1289-1295.
33. Dolor RJ, Witsell DL, Hellkamp AS, et al. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis: the CAFFS trial: a randomized controlled trial. *JAMA*. 2001; 286(24):3097-3105.
34. Nayak AS, Settipane GA, Pedinoff A, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol*. 2002;89:271-278.
35. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran M. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol*. 1997;78(6):598-601.
36. Benninger MS, Sedory Holzer SE, Lau J. Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: summary of the Agency for Health Care Policy and Research evidence-based report. *Otolaryngol Head Neck Surg*. 2000;122(1):1-7.
37. Peto R. Clinical trial methodology. *Biomedicine*. 1978;28:24-36.
38. Day SJ, Graham DF. Sample size and power for comparing two or more treatment groups in clinical trials. *BMJ*. 1989;299(6700):663-665.
39. Little P, Williamson IG, Warner G, et al. Open randomised trial of prescribing strategies in managing sore throat. *BMJ*. 1997;314(7082):722-727.
40. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ*. 2001;322(7282):336-342.
41. Little P, Rumsby K, Kelly J, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *JAMA*. 2005;293(24):3029-3035.
42. Hueston WJ, Eberlein C, Johnson D, Mainous A. Criteria used by clinicians to differentiate sinusitis from viral upper respiratory tract infection. *J Fam Pract*. 1998; 46(6):487-492.
43. Wilson S, Delaney B, Roalfe A, et al. Randomised controlled trials in primary care: case study. *BMJ*. 2000;321(7252):24-27.
44. Fagan TJ. Nomogram for Bayes theorem. *N Engl J Med*. 1975;293(5):257.
45. de Ferranti SD, Ioannidis J, Lauu J, Anninger W, Barza M. Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? a meta-analysis. *BMJ*. 1998;317(7159):632-637.
46. de Bock GH, Dekker FW, Stolk J, Springer MP, Kievit J, Houwelingen JC. Antimicrobial treatment in acute maxillary sinusitis: a meta-analysis. *J Clin Epidemiol*. 1997;50(8):881-890.

Genius, like the inhabitants of the depths of the sea, moves by its own light.
—Santiago Ramón y Cajal (1852-1934)

