Effect of Amoxicillin-Clavulanate in Clinically Diagnosed Acute Rhinosinusitis

A Placebo-Controlled, Double-blind, Randomized Trial in General Practice

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Background: Acute rhinosinusitis is one of the most common reasons for prescribing antibiotics in primary care. However, it is not clear whether antibiotics improve the outcome for patients with clinically diagnosed acute rhinosinusitis. We evaluated the effect of a combination product of amoxicillin–potassium clavulanate on adults with acute rhinosinusitis that was clinically diagnosed in a general practice setting.

Methods: We conducted a randomized, placebo-controlled, double-blind trial with 252 adults recruited at 24 general practices and 2 outpatient clinics. Each patient had a history of purulent nasal discharge and maxillary or frontal pain for at least 48 hours. Patients were given amoxicillin, 875 mg, and clavulanic acid, 125 mg, or placebo twice daily for 6 days. Main outcome measures were time to cure (primary outcome), number of days during which rhinosinusitis restricted activities at home or work, and frequency of adverse effects (secondary outcomes).

Results: The adjusted hazard ratio for the effect of amoxicillin–clavulanate was 0.99 (95% confidence interval [CI], 0.68–1.45) on time to cure and 1.28 (95% CI, 0.80–2.05) in the prespecified subgroup of patients with a positive rhinoscopy result. At 7 days the mean difference between amoxicillin-clavulanate and placebo was −0.29 (95% CI, −0.93 to 0.34) in the number of days with restrictions due to rhinosinusitis and −0.60 (95% CI, −1.41 to 0.21) in patients with a positive rhinoscopy result. At 7 days patients who took amoxicillin-clavulanate were more likely to have diarrhea (odds ratio, 3.89; 95% CI, 2.09-7.25).

Conclusions: Adult patients in general practice with clinically diagnosed acute rhinosinusitis experience no advantage with antibiotic treatment with amoxicillin-clavulanate and are more likely to experience adverse effects.

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cluded in the trial based on clinical diagnostic criteria that are applicable in general practice. We designed a trial that reflects, to the greatest possible extent, a routine approach to patients with uncomplicated acute rhinosinusitis in general practice.

**METHODS**

**PATIENTS AND SETTING**

Patients were recruited during the 4 winter seasons (November 1 to April 30) of 1997 to 2001 from 24 general practices in Basel, Switzerland, and surroundings and in the internal medicine and otolaryngology outpatient clinics of the University Hospital Basel. Outpatient clinics were only allowed to treat walk-in patients or patients who had not been referred. The inclusion criteria were a history of repeated purulent nasal discharge and maxillary or frontal unilateral or bilateral pain for at least 48 hours but less than 1 month and presence of pus under rhinoscopy. Exclusion criteria were younger than 18 years, an upper respiratory tract infection or use of antibiotics for any reason within the previous 4 weeks, an upper respiratory tract infection or intermittent fever that persisted for more than 4 weeks, pathologic features or malformation of nasal cavities or the pharynx, immunosuppressive treatment, human immunodeficiency virus infection, allergy to amoxicillin-clavulanate, pregnancy or breastfeeding, or no fluency in one of the national languages.

After the first winter season, only 43 of 106 patients who fulfilled the first 2 inclusion criteria and consented to participate in the trial had a positive rhinoscopy result. We therefore decided to recruit patients without pus under rhinoscopy but to continue rhinoscopy with all those recruited. In 2000 a patient in the placebo group experienced a brain abscess. After this, all patients with a C-reactive protein (CRP) level greater than 100 mg/L were excluded from the trial (none), and patients with a CRP level between 50 and 99 mg/L were reassessed at day 3 (3 patients) and excluded if clinical worsening was noted or the CRP level had increased to higher than 100 mg/L (none).

**CLINICAL EVALUATION AT BASELINE**

For each patient, physicians recorded a focused medical history for rhinosinusitis-related symptoms, the number of days during which rhinosinusitis restricted activities at home or work, and previous upper respiratory tract infections. They collected clinical data on the presence of pus in the pharynx and in the medial meatus during rhinoscopy, pain on pressure and on percussion of the frontal and maxillary sinuses, and body temperature. Patients completed a questionnaire with questions on rhinosinusitis-related symptoms and adverse effects from antibiotics (eg, purulent rhinorrhea and sputum, frontal or maxillary unilateral or bilateral pain, pain on bending, hyposmia or anosmia, fatigue, sleep and mood disorders, abdominal cramps and diarrhea, and vaginal pruritus or discharge). Patients rated the severity of symptoms on a 10-point, equal-distance scale. The study physicians and the study nurse attended a 3-hour seminar to standardize data collection and the clinical examination of patients. All study physicians were trained in rhinoscopy by an otolaryngologist (A.W.-L.) and were given instructions on how to use a rhinoscope with an integrated light source (the Heine rhinoscope; Heine Optotechnik, Herrsching, Germany). One refresher seminar was held during the study. Patients were informed about the study goals and had to sign an informed consent form. The study protocol and changes to inclusion and exclusion criteria were approved by the ethics committee of the University Hospital Basel.

A radiograph (occipitomental view) of the maxillary and frontal sinus was obtained for each patient. Radiographs were made either in the private practice or by referral to our hospital. General practitioners and their technical staff were instructed by a radiology technician from our hospital to standardize radiographic technique. Two radiologists who were masked to the groups independently assessed each radiograph. We used fluid levels or complete opacity as a positive indicator for acute rhinosinusitis. Agreement between radiologists was only moderate for this criterion (κ = 0.59). A blood specimen for white blood cell count (reference range, 3500-10000/µL) and CRP level (reference range, <10 mg/L) was obtained. All specimens were analyzed at the laboratory of the University Hospital Basel.

**RANDOMIZATION AND INTERVENTION**

We used stratified randomization, with the general practice or outpatient clinic as the stratification unit and patients randomized in blocks of 6. A computer random-number generator was used, and the allocation sequence was performed by a statistician who was not involved in the final analysis. The randomization code was kept at the 24-hour emergency call center in Basel. Operators had to immediately advise the principal investigator of every case for which the code was broken. Patients were consecutively enrolled, and we required study physicians to record the reason why eligible patients were not recruited.

Patients were randomly assigned to receive either amoxicillin, 875 mg, and clavulanic acid, 125 mg, twice daily for 6 days, or placebo. Tablets of equal size, color, and taste were provided in identical, numbered containers by GlaxoSmithKline (Münchenbuchsee, Switzerland). All patients received decongestant therapy with a xylometazoline hydrochloride spray (Otirin; Novartis, Berne, Switzerland) and acetaminophen tablets of 500 mg (Panadol; GlaxoSmithKline Switzerland), with a maximal dose of 3 g/d. Concomitant therapy with steam inhalation was allowed.

**END POINTS AND STATISTICAL ANALYSIS**

The primary outcome was time to cure. We used 0 days (since the previous visit or interview) during which rhinosinusitis restricted activities at home or work as our definition of cure. To confirm the primary outcome, we repeated our analysis using a second definition of cure: a rating of 1 on a 10-point, equal-distance scale for the severity of restricted activity at home or work.

Secondary end points were the number of days during which rhinosinusitis restricted activities at home or work, the frequency of adverse effects, and the recurrence rate of rhinosinusitis at 28 days. Patients were said to have recurrent rhinosinusitis if they were never cured and felt at least as restricted at day 28 as at baseline. At day 7 physicians performed a second clinical examination, and patients completed a second questionnaire. Physicians also noted the number of tablets taken. At days 14 and 28, the study nurse interviewed patients by telephone. Patients were always asked the same questions on rhinosinusitis-related symptoms and adverse effects, plus additional questions on use of other drugs or other visits to physicians. All study physicians and the study nurse were blinded to the treatment given to each patient. Data were entered by the study nurse.

To calculate the sample size, we assumed that 50% of the recruited patients had acute bacterial rhinosinusitis, and the
spontaneous cure rate for acute bacterial rhinosinusitis at 7 days was 80%. We assumed a 50% increase in the cure rate at 7 days for patients with acute bacterial rhinosinusitis treated with amoxicillin-clavulanate (Laurant Kaiser, MD, personal written communication, September 13, 1997) and a spontaneous cure rate of 60% at 7 days for patients without acute bacterial rhinosinusitis. With a type I error of .05 (2-sided), a power of 90%, and an estimated 10% dropout rate, the required sample size was 252.

Our statistical analysis was of the intent-to-treat population and 2 subgroups: those with a positive rhinoscopy result and those who felt restricted at baseline. The first subgroup was prespecified when the inclusion criteria were changed. The second subgroup was not anticipated but became of interest when 10% of those recruited said before treatment that rhinosinusitis did not restrict their activities at home or work. Three regression methods were used: Cox proportional hazards regression for time to cure, linear regression for the number of days with restrictions due to rhinosinusitis, and logistic regression for the proportion of patients with anticipated adverse effects. With all methods, models were fit without stepwise procedures and with a small number of prespecified covariates. Each model included covariates for the severity of the response at baseline, recruitment before or after the change in inclusion criteria, open treatment, and use of concomitant medication.

Statistical analysis was performed using SAS statistical software version 8.02 (SAS Institute Inc, Cary, NC). All significant levels and confidence intervals (CIs) given are 2-sided.

**RESULTS**

**PATIENT ENROLLMENT AND CHARACTERISTICS**

In total, 1565 patients were eligible (Figure 1). The main reason for not participating in the trial was refused consent (441 patients: 220 definitely wanted antibiotics, 74 definitely did not want antibiotics, and 147 refused consent for other reasons). We enrolled 252 patients, and 249 (98.8%) completed the trial. One patient was randomized but never took any medication, 1 medical record was lost, and 1 patient in the placebo group had a severe complication. Eleven patients (8.8%) in the amoxicillin-clavulanate group and 19 patients in the placebo group (14.9%) received open antibiotic therapy. Of these patients, 5 received open amoxicillin-clavulanate (2 patients in the intervention and 3 patients in the placebo group); the remaining patients received antibiotics chosen by their treating physician. Thirty-nine (15.5%) of 251 patients took fewer tablets than instructed, and of these patients 24 (61.5%) were receiving antibiotics. Compliance with the interview schedule was good: at day 7, 93.6% of all visits were within ±1 day of the scheduled date, and at days 14 and 28, 89.2% and 94.8%, respectively, of the interviews were within ±1 day of the scheduled dates.

The 2 groups were similar in terms of sex, age, number of days with rhinosinusitis-related symptoms, and clinical findings for pus under rhinoscopy and in the epipharynx, occipitomalinal x-ray films with fluid levels or complete opacity, laboratory variables (CRP, leukocytes, and neutrophils), and the additional use of concomitant medication (Table 1). More than 50% of participants were women. The median number of days with rhinosinusitis-related symptoms was 5 days in the amoxicillin-clavulanate group and 4 days in the placebo group. In the 2 groups, 65.3% and 66.9% of patients had pus at rhinoscopy, respectively.

**PRIMARY OUTCOME**

We found no difference in the time to cure between the amoxicillin-clavulanate and placebo groups (Figure 2). At 1 week, 29.8% and 30.7% in the amoxicillin-clavulanate and placebo groups were cured and at 2 weeks, the corresponding figures were 76.6% and 74.0%, respectively. In the Cox proportional analysis, with adjustment for severity of restrictions at baseline, modification of the inclusion criteria, open treatment, and concomitant medication with steam inhalation, the hazard ratio for the effect of antibiotic treatment on time to cure was 0.99 (95% CI, 0.68-1.45) (Table 2). In patients with a positive rhinoscopy result, the hazard ratio for time to cure was 1.28 (95% CI, 0.80-2.05), and in patients who reported restrictions at baseline, the hazard ratio was 1.23 (95% CI, 0.81-1.87). We used 0 days (since the previous interview) with restrictions due to rhinosinusitis as a definition of cure. With cure alternatively defined as a rating of 1 on a 10-point, equal-distance scale for degree of restriction at home or work, hazards ratios for the effect of antibiotic treatment on time to cure were 1.03 (95% CI, 0.71-1.50) for all patients, 1.40 (95% CI, 0.88-2.25) for those with a positive rhinoscopy result, and 1.22 (95% CI, 0.81-1.85) for those restricted at baseline. For both
definitions of cure, there was no evidence of correlation between time and the Schoenfeld residuals for treatment, which suggests that a proportional hazards assumption was appropriate.

**SECONDARY OUTCOMES**

At 7 and 14 days, there was no statistically significant difference between amoxicillin-clavulanate and placebo in the mean days of restrictions due to rhinosinusitis in neither the intent-to-treat population nor our subgroups. At 7 days patients with a positive rhinoscopy result had a mean difference of −0.60 days of restrictions due to rhinosinusitis (95% CI, −1.41 to 0.21), and patients restricted at baseline had a mean difference of −0.60 days of restrictions due to rhinosinusitis restricted activities at home or work. Patients treated with antibiotics tended to report more adverse effects, particularly diarrhea, during the first week.

At 7 and 14 days, diarrhea was significantly more likely in the amoxicillin-clavulanate group, but these odds ratios were not statistically significant. There were 4 adverse events of moderate or severe intensity that were thought to be drug related: 2 in the amoxicillin-clavulanate group (diarrhea) and 2 in the placebo group (diarrhea and vomiting). In the placebo group, there was 1 serious disease-related adverse event. After 2 weeks of symptomatic treatment, the patient was then treated for 1 week with amoxicillin-clavulanate (1 g twice daily) but experienced a brain abscess caused by an amoxicillin-clavulanate–sensitive strain of *Streptococcus milleri*. The patient was operated on and recovered but has a frontal syndrome. There were 2 additional serious adverse events in the placebo group, 1 myocardial infarction and 1 severe depressive episode; both were thought to be neither disease nor drug related.

In this randomized controlled trial in general practice, we were unable to show that antibiotic treatment with amoxicillin-clavulanate improves time to cure in adults with clinically diagnosed acute rhinosinusitis. We also found no difference in the number of days during which rhinosinusitis restricted activities at home or work. Patients treated with antibiotics tended to report more adverse effects, particularly diarrhea, during the first week.

Our study has several limitations. First, time to cure could be insensitive to any treatment difference, because there were only 2 measurements during the period when cure typically takes place (within 14 days). We decided not to use patient diaries, because we believed that patients might not complete these at the pre-specified time points. In practice, this limitation is unlikely to affect the findings of our study. Any appreciable difference in the rate of cure between amoxicillin-clavulanate and placebo should have been seen at either 7 or 14 days but was not. Second, the prevalence of acute bacterial rhinosinusitis is likely to have been lower in our trial than anticipated. The inclusion criteria of our trial had to be modified, because we could not recruit enough patients with a positive rhinoscopy result. The study phy-

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**Table 1. Characteristics of Randomized Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amoxicillin-Potassium Clavulanate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>124</td>
<td>127</td>
</tr>
<tr>
<td>No. (%) of women</td>
<td>67 (54.0)</td>
<td>69 (54.3)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>37 (13)</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Symptoms at baseline, median No. of days (quartiles)</td>
<td>5.0 (3.0-7.0)</td>
<td>4.0 (3.0-7.0)</td>
</tr>
<tr>
<td>Rhinosinusitis-related symptoms</td>
<td>4.0 (2.0-7.0)</td>
<td>3.0 (2.0-6.0)</td>
</tr>
<tr>
<td>Putrid discharge</td>
<td>3.0 (2.0-5.0)</td>
<td>3.0 (2.0-5.0)</td>
</tr>
<tr>
<td>Cranial pain</td>
<td>3.0 (2.0-5.0)</td>
<td>3.0 (2.0-5.0)</td>
</tr>
<tr>
<td>Clinical findings at baseline, No. (%) of patients</td>
<td>50 (40.3)</td>
<td>57 (44.9)</td>
</tr>
<tr>
<td>Positive rhinoscopy result</td>
<td>28 (22.5)</td>
<td>25 (19.7)</td>
</tr>
<tr>
<td>X-ray examination at baseline, No. (%) of patients</td>
<td>8 (6.5)</td>
<td>10 (7.9)</td>
</tr>
<tr>
<td>Laboratory parameters at baseline, median (range)</td>
<td>10 (5-214)</td>
<td>13 (5-177)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>3600 (1700-5400)</td>
<td>3100 (1300-17 300)</td>
</tr>
<tr>
<td>Leukocytes, cells/µL</td>
<td>5.3 (1.6-21)</td>
<td>5.3 (0-11.9)</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>10 (8.0)</td>
<td>10 (8.9)</td>
</tr>
<tr>
<td>Concomitant medication during trial, No. (%) of patients</td>
<td>10 (8.0)</td>
<td>12 (8.9)</td>
</tr>
<tr>
<td>Steam inhalation</td>
<td>7 (5.6)</td>
<td>16 (12.6)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>81 (65.3)</td>
<td>85 (66.9)</td>
</tr>
<tr>
<td>Potassium</td>
<td>8600 (3700-14 700)</td>
<td>8100 (3900-17 300)</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>300 (150-450)</td>
<td>300 (150-400)</td>
</tr>
<tr>
<td>Chloride, mEq/L</td>
<td>130 (90-150)</td>
<td>120 (80-170)</td>
</tr>
<tr>
<td>Protein, g/L</td>
<td>10 (5-214)</td>
<td>13 (5-177)</td>
</tr>
</tbody>
</table>

*Independent agreement by 2 radiologists.*

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**Figure 2.** Time to cure for patients treated with amoxicillin-potassium clavulanate combination product or placebo, with cure defined as 0 days (since the previous interview) during which rhinosinusitis restricted activities at home or work.

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**COMMENT**

In this randomized controlled trial in general practice, we were unable to show that antibiotic treatment with amoxicillin-clavulanate improves time to cure in adults with clinically diagnosed acute rhinosinusitis. We also found no difference in the number of days during which rhinosinusitis restricted activities at home or work. Patients treated with antibiotics tended to report more adverse effects, particularly diarrhea, during the first week.
The strengths of our trial are the double-blind design with blinded outcome assessment, a high follow-up rate of more than 98%, and high external validity. We recruited all patients in a general practice setting. Most of those who refused consent did so because they had their own opinion about the benefit or otherwise of antibiotic treatment. Physicians were experienced, highly motivated general practitioners trained for this trial. A lack of technical skill is therefore unlikely to be the reason for this slow recruitment. In addition, US guidelines recommend treatment of acute rhinosinusitis with antibiotics only after 7 days of symptoms or in patients with severe facial pain irrespective of the duration. In our trial, only 32% of patients had a history of 7 days or more of rhinosinusitis-related symptoms. Therefore, both the necessary modification of the inclusion criteria and the short duration of symptoms suggest a lower prevalence of bacterial rhinosinusitis than planned, reducing the power of this trial to detect differences between treatments.

We do not believe that bacterial infection with resistant strains could be an explanation for the negative findings of this study. Amoxicillin-clavulanate shows excellent activities against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, the most common bacteria in upper respiratory tract infection and acute bacterial rhinosinusitis. In Switzerland, prevalence of penicillin resistance against S pneumoniae is approximately 5% and β-lactamase production in H influenzae and M catarrhalis is lower compared with most other European countries.14

The strengths of our trial are the double-blind design with blinded outcome assessment, a high follow-up rate of more than 98%, and high external validity. We recruited all patients in a general practice setting. Most of those who refused consent did so because they had their own opinion about the benefit or otherwise of antibiotics and explicitly required or declined antibiotics. We used inclusion criteria that are applicable in general practice and correspond with generally accepted procedures in general practice. We strictly limited the inclusion criteria to clinical signs and symptoms known to generate the highest likelihood ratio for acute bacterial rhinosinusitis when compared with the gold standard of sinus puncture.15 We also collected additional information about laboratory and x-ray data. Only 1 in 4 patients showed fluid levels or complete opacity on x-ray films, radiologic signs that are most likely associated with bacterial rhinosinusitis. This underlines how difficult it is to accurately diagnose acute rhinosinusitis using clinical signs and symptoms.

Patients treated with amoxicillin-clavulanate were more likely to experience adverse effects such as diarrhea and abdominal pain. Other randomized controlled trials of antibiotic treatment for acute rhinosinusitis or for sinusitis-like symptoms report similar findings using different antibiotics. Three placebo-controlled, randomized trials (all somewhat smaller than the present study) have evaluated different antibiotics in general practice for the treatment of acute rhinosinusitis. Two trials included patients based on clinical symptoms for acute rhinosinusitis in conjunction with either radiologic signs for maxillary sinusitis or raised values of CRP or erythrocyte sedimentation. The third trial included patients solely on the basis of clinical signs and symptoms. Although these studies used different diagnostic criteria to identify patients with suspected acute bacterial rhinosinusitis, they all showed no difference in improvement of symptoms or cure rates under treatment with antibiotics. The present study suggests that adults with a positive rhinosinusitis result who are undergoing antibiotic treatment may have fewer days during which rhinosinusitis restricts their activities at home or work. The
expected benefit from antibiotic therapy, however, might be at best moderate and comparable to the treatment with neuraminidase inhibitors in patients with early symptoms from influenza.18,19 Further studies are needed using better diagnostic tests for acute bacterial rhinosinusitis. These tests might include a refined symptom score that identifies those severely restricted by rhinosinusitis or with a prolonged upper respiratory tract infection.

Most patients with acute rhinosinusitis are seen in general practice. Because of the low specificity of available imaging tests, the costs, and the need to refer patients, most patients with acute rhinosinusitis in general practice do not receive a diagnostic workup that allows the physician to accurately differentiate between acute viral and bacterial rhinosinusitis. The decision to treat with antibiotics is therefore based on clinical diagnostic criteria or other reasons related to physicians’ or patients’ preferences.

Evidence from the present study suggests that antibiotic treatment with amoxicillin-clavulanate offers no benefit for adults with acute rhinosinusitis clinically diagnosed in general practice. We conclude that antibiotics should not be given at first to patients with acute rhinosinusitis, and symptomatic treatment is justified. This policy should help limit the emergence of antibiotic-resistant strains and reduce costs. Some individual patients profit from antibiotic therapy. Whether such individuals can be identified by clinical tests such as rhinoscopy has yet to be shown.

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REFERENCES