Does Amoxicillin Improve Outcomes in Patients with Purulent Rhinorrhea?

A Pragmatic Randomized Double-Blind Controlled Trial in Family Practice

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Key Points for Clinicians

- In patients with an acute upper respiratory tract infection that includes purulent rhinorrhea, treatment with amoxicillin has no effect on general recovery and increases the frequency of diarrhea.
- In most patients, symptoms of acute respiratory tract infection last for more than 10 days.
- Treatment without antibiotics and with appropriate follow-up is safe.
- Patients with purulent rhinorrhea caused by an acute infection of the nose or sinuses can initially be treated with symptomatic therapy, whatever the suspected diagnosis, and instructed to return if symptoms worsen.

Diagnoses that include upper respiratory tract infection (UTI), rhinitis, rhinopharyngitis, and rhinosinusitis, which are very difficult to distinguish because of the lack of specific clinical features or simple office-based diagnostic tests. These diagnostic difficulties probably explain why it remains unclear whether and when antibiotics should be used for such patients in clinical practice.

Although evidence shows that a small minority of patients benefit from antibiotic therapy, these patients are extremely difficult to recognize or identify. Three meta-analyses on the effect of antibiotics in rhinosinusitis and 5 of 6 recent trials investigating the effect of antibiotics in rhinosinusitis.

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Infections of the nasal passages are very common and among the most frequent reasons for the prescription of antibiotics. Such infections comprise...
rhinitis, and bacterial rhinopharyngitis almost exclusively studied patients with a diagnosis established by laboratory or imaging investigation. As a result, implementing the findings is difficult in daily practice, where radiologic or laboratory tests are not obtained for most patients with respiratory infections. Only 1 of the 6 trials included patients with a set of clinical symptoms indicating rhinosinusitis. Because inclusion criteria were rather stringent, however, findings are applicable only to a small group of patients.

The purpose of this trial was to investigate the benefits of antibiotic therapy in a larger group of patients with nose or sinus infections, thereby making the results more widely applicable. Accordingly, we conducted a randomized, double-blind, placebo-controlled trial comparing the effect of amoxicillin with that of placebo in family practice patients with an acute upper respiratory tract infection and presenting with purulent rhinorrhea. Purulent rhinorrhea was chosen as the minimal criterion because it is the symptom most consistently associated with rhinosinusitis in diagnostic studies and because its presence often leads family physicians (FPs) to prescribe antibiotics. The trial was designed as a pragmatic effectiveness trial. Patient inclusion and evaluation were defined on a purely clinical basis to maximize relevance for routine daily practice.

**Methods**

**Study Population**

Between October 1998 and December 1999, 69 FPs in Flanders, Belgium, agreed to enroll patients meeting the following inclusion criteria: age 12 years or older, presenting with a respiratory tract infection, and having purulent rhinorrhea. Exclusion criteria were allergy to penicillin or ampicillin; having received antibiotic therapy within the previous week; complaints lasting for more than 30 days; abnormality on clinical chest examination; complications of sinusitis (facial edema or cellulitis; orbital, visual, meningeal, or cerebral signs); pregnancy or lactation; comorbidity that might impair immune competence; and inability to follow the protocol because of language or mental problems. The Ethics Committee of the Ghent University Hospital (GUH) approved the study. All patients (or their guardians, for those younger than 16 years of age) gave written informed consent.

**Treatment Assignment and Masking**

In this double-blind trial, patients were assigned via a computer-generated random number list to receive 500 mg amoxicillin 3 times a day or placebo for 10 days. The trial medication was supplied in numbered uniform cardboard boxes, each containing 30 capsules of the same size, color, and shape for active and placebo treatment. The randomization list, kept at the pharmacy of GUH, was accessible to the participating FPs only in case of a serious adverse event.

To assess the effectiveness of masking, patients and their FPs guessed the treatment group at 10-day follow-up. Data were encoded and entered without knowledge of treatment allocation. Compliance was assessed by counting leftover medication. All patients were allowed to use xylometazoline 1% nose drops and paracetamol or ibuprofen to alleviate symptoms; these data were registered.

**Assessment of Potential Recruitment Bias Caused by Exclusion**

First, we compared the characteristics of patients enrolled by high-recruiting FPs (at least 14 patients recruited) with those of patients from low recruiters (at most 5 patients recruited). Second, we asked all participating FPs to complete a short questionnaire over a 6-week period on all patients eligible for the trial but not included in it (sex, age, body temperature, severity of nasal discharge and pain, reason for non-recruitment). Third, to estimate the proportion of sinusitis cases among included patients, all patients were invited for an optional radiologic examination of the maxillary sinuses (single Waters view). Radiographs were taken in the nearest radiology unit, collected centrally, and evaluated by a radiologist of the GUH who specialized in the ear, nose, and throat.

**Baseline Measurements**

Randomized patients completed an extensive questionnaire and were physically examined by their FP. To evaluate the symptoms, we used the 20 items of the sinonasal outcome test (SNOT-20) supplemented by 3 questions about pain. Symptoms were scored on a 6-category (0-5) Likert scale. Patients were also asked to indicate which of their symptoms (no more than 5) were most troublesome.

**Follow-Up**

During 10 days of treatment, all patients recorded their daily drug intake (trial medication and symptomatic medication); their general feeling of illness; the presence of nasal discharge, pain, and cough; body temperature; the occurrence of presumed adverse drug effects; and absence from work or school. On day 10 they underwent a second physical examination and completed the symptom questionnaire again. In case of insufficient recovery, the FP was then at liberty to prescribe an open antibiotic course (we recommended amoxicillin clavulanate) without revealing the previous treatment phase. Patients who
had recovered on day 10 did not have to return on day 15. Any patient with poor recovery on day 10 was asked, regardless of open antibiotic treatment, to continue writing in the diary and to come back on day 15 if complaints were still present.

The 2 primary endpoints were the therapy success rate on day 10 and the duration of general illness, pain, and purulent rhinorrhea as recorded in the diary. Treatment was considered successful when all symptoms that the patient had included in the list of “most important item affecting my health” scored 0 (absent) or 1 (very mildly present) after 10 days of treatment.

Secondary endpoints were the mean change in severity score between day 1 and 10 on the various symptoms, incidence of unfavorable evolution, incidence of side effects, intake of analgesics, and duration of sick leave. The number of patients needed to demonstrate a difference in the therapy success rate of 15% at day 10 (α = 0.05, β = 0.20) was 168 per treatment group. This determination assumed a success rate of 50% in the placebo group.

### Statistics

Data were analyzed with SPSS-7. Differences in proportions are presented as relative risks with 95% confidence intervals and tested by chi-square test. The duration of symptoms is presented by Kaplan–Meier survival plots. Differences in duration are tested by the log rank test. Other continuous variables are tested by Student’s t test or the nonparametric Mann–Whitney U test.

## RESULTS

### Participant Flow and Follow-Up

Of 416 patients enrolled in the study, 8 were excluded after randomization. Of the 408 patients remaining, 202 received amoxicillin and 206 placebo; 34 patients (8%) withdrew from the trial. Their personal characteristics and clinical conditions at inclusion were not different from those of patients with follow-up. Figure 1 lists reasons for exclusion or withdrawal. The treatment code was broken once for a suspected allergic reaction and once because of an exacerbation of symptoms. In accordance with the intention-to-treat principle, all enrolled patients were included in the analyses in the groups to which they were originally randomized. Patients who had withdrawn because of side effects were also included in the analysis of side effects.

Complete or partial follow-up data were obtained for 374 patients (90%) after 10 days (mean 10.3 days, standard deviation 1.44): 334 patients completed the symptom questionnaire, 348 returned the diary, and 338 underwent a physical examination. In 265 (71%) patients, data (questionnaire, diary, and physical examination) were complete; in 109 (29%), data at day 10 were partly missing. The two treatment groups were very similar in terms of sex, age, duration of preinclusion complaints, and frequency of various physical signs and symptoms (Table 1).*

### Primary Outcomes

Of the 374 patients with follow-up data on day 10, 334 completed the symptom questionnaire twice. Treatment was successful—defined as a score of 0 (absent) or 1 (very mildly present) for all symptoms that had been included as “the most important item affecting my health”—in 35% of patients in the amoxicillin group (59/170) and 29% in the placebo group (47/164) (Table 2). Relative risk of success was 1.14 (95% CI, 0.92-1.42, P = .24); more patients were cured in the amoxicillin group, but this difference was not statistically significant.

In 82 (19.7%) of the 416 randomized patients (37 amoxicillin, 45 placebo), data on this main outcome are missing. In 40 of these 82 patients, follow-up data are available from the diary (n = 38) or physical examination (n = 2). According to these data, in 15/17 of the amoxicillin group and 11/23 of the...
placebo group the outcome was favorable: in the diary, the patient reports feeling “well” again at day 10 or sooner, or on physical examination, all signs of respiratory infection have cleared). Eight patients withdrew for clinical exacerbation and 2 patients after full recovery. Adding the 50 patients with a known course of illness to those in the treatment and result groups does not alter the overall result (RR 1.20, 95% CI, 0.98-1.47, \( P = .08 \)). Furthermore, when considering the 24 nonexcluded patients (13 amoxicillin, 11 placebo) with total lack of follow-up in their allocated treatment group, first as treatment failures (RR 1.18, 95% CI, 0.97-1.44, \( P = .11 \)) and then as successes (1.20, 95% CI, 0.99-1.46, \( P = .07 \)), the result also remains the same. Regarding the success rate from the complete diary data (\( n = 348 \)) and the results of physical examinations (\( n = 338 \)) (Table 3), we find no significant difference between treatment groups.

Duration of purulent rhinorrhea was significantly shorter in the amoxicillin group than in the placebo group (75% of patients were free of purulent rhinorrhea after 9 days versus after 14 days in the placebo group, log rank \( P = .007 \)). There is no difference between treatment groups in the duration of general illness or pain (Figure 2).

### Secondary Outcomes

The mean score reduction on the symptom “thick nasal discharge” between day 1 and day 10 is significantly larger in the amoxicillin group than in the placebo group (2.2 vs 1.5, Student’s t test: \( P < .0001 \)) (Table 3). There is no significant difference in change for any other symptom. Seven patients in the placebo group (3.4%) withdrew before day 10 because of exacerbation of symptoms versus 1 patient (0.5%) in the amoxicillin group (RR 0.25, 95% CI, 0.04-1.56, \( P = .07 \)). All 8 patients recovered after starting open antibiotic therapy and had no complications or referrals.

The chance of receiving open antibiotic treatment at day 10 follow-up (\( n = 34 \): 19 placebo, 15 amoxicillin) or of having to return because of persistent complaints at day 15 (\( n = 73 \): 41 placebo, 32 amoxicillin) was not significantly different between the treatment groups (chi-squared test: \( P = .46 \) and \( P = .26 \), respectively). Diarrhea was more frequent in the amoxicillin group (29% vs. 19%, RR 1.28, CI 1.05-1.57, \( P = .02 \)). There was no difference in incidence of skin rash, abdominal pain, or vomiting. Absence from work or school was comparable in both treatment groups (RR 0.95, 95% CI, 0.86-1.05, \( P = .34 \)). Patients in the amoxicillin group took an analgesic an average of 5 times, mainly in the first days of treatment.

### Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number with Successful Therapy (%)</th>
<th>Relative Risk of Success (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey*</td>
<td>Amoxicillin = 334/170 (192)</td>
<td>Placebo = 47/164 (28)</td>
<td>1.14 (0.92-1.42)</td>
</tr>
<tr>
<td>Diary **</td>
<td>Amoxicillin = 348/174 (189)</td>
<td>Placebo = 91/174 (56)</td>
<td>0.94 (0.77-1.16)</td>
</tr>
<tr>
<td>Physical signs §</td>
<td>Amoxicillin = 338/170 (189)</td>
<td>Placebo = 86/169 (51)</td>
<td>1.13 (0.91-1.40)</td>
</tr>
<tr>
<td>All II</td>
<td>Amoxicillin = 384/189 (215)</td>
<td>Placebo = 59/195 (30)</td>
<td>1.2 (0.98-1.47)</td>
</tr>
<tr>
<td>Sensitivity analysis†</td>
<td>Amoxicillin = 408/202</td>
<td>Placebo = 70/206</td>
<td>1.2 (0.99-1.46)</td>
</tr>
<tr>
<td>Best case</td>
<td>Amoxicillin = 408/202</td>
<td>Placebo = 70/206</td>
<td>1.2 (0.99-1.46)</td>
</tr>
<tr>
<td>Worst case</td>
<td>Amoxicillin = 73/202</td>
<td>Placebo = 59/206</td>
<td>1.18 (0.97-1.44)</td>
</tr>
</tbody>
</table>

* Data on at least one of these outcome measures were obtained in 374 patients (96% of the total population).
** All symptoms indicated by the patients at inclusion as “most important item affecting my health”.
† Patient states in diary that he or she feels generally “well” again on day 10 or sooner.
§ All physical signs have disappeared at day 10 (pain on bending, sinus tenderness, postnasal drip, purulent rhinorrhea on rhinoscopy, elevated body temperature).
¶ Incorporating all available information from the questionnaire, diary, physical examination, and dropouts.

**Table 2: Main Outcome: Rate of Treatment Success at 10-Day Follow-up**

- **Survey**: The chance of receiving open antibiotic treatment was significantly higher in the amoxicillin group (29% vs. 19%, RR 1.28, CI 1.05-1.57, \( P = .02 \)).
- **Diary**: No significant difference in change for any other symptom.
- **Physical Signs**: All patients in the placebo group were free of purulent rhinorrhea at day 10, compared to 75% in the amoxicillin group (RR 0.25, 95% CI, 0.04-1.56, \( P = .07 \)).
- **All II**: There was no difference between treatment groups in the duration of general illness or pain (Figure 2).
- **Sensitivity Analysis**: The results were consistent with the main analysis.
quickly, but this seems to be of little importance in treatment, the purulent rhinorrhea disappears more any important benefit from amoxicillin therapy. With URTI with purulent rhinorrhea do not experience found that patients consulting their FP for acute This study produced 3 important findings. First, we DESCUSSION

The lack of correlation between the estimated and actual treatment demonstrates that masking was maintained. Compliance was good in both groups: 89% of patients in the amoxicillin group and 91% of those in the placebo group took at least 25 of 30 capsules.

Patients from low recruiters were not significantly different from patients enrolled by high recruiters. Included patients had slightly more complaints of pain (58% vs 50%, RR 1.20, CI 1.02-1.42, \( P = .03 \)) than the 332 eligible but excluded patients registered during the 6-week period. The most frequent reasons for exclusion were the presence of an exclusion criterion (22%), the patient’s refusal to participate (16%), the patient’s request for antibiotic therapy (14%), and lack of time by the FP (10%). Of the 292 patients who agreed to undergo a radiologic examination, about two thirds had abnormalities of the maxillary sinuses.

Other Results

The trial was (more or less) effective. Included were patients from low recruiters were not significantly different from patients enrolled by high recruiters. Included patients had slightly more complaints of pain (58% vs 50%, RR 1.20, CI 1.02-1.42, \( P = .03 \)) than the 332 eligible but excluded patients registered during the 6-week period. The most frequent reasons for exclusion were the presence of an exclusion criterion (22%), the patient’s refusal to participate (16%), the patient’s request for antibiotic therapy (14%), and lack of time by the FP (10%). Of the 292 patients who agreed to undergo a radiologic examination, about two thirds had abnormalities of the maxillary sinuses.

**DISCUSSION**

This study produced 3 important findings. First, we found that patients consulting their FP for acute URTI with purulent rhinorrhea do not experience any important benefit from amoxicillin therapy. With treatment, the purulent rhinorrhea disappears more quickly, but this seems to be of little importance in relation to a general recovery. Moreover, amoxicillin therapy increases the risk of diarrhea. We further found that with or without amoxicillin, complaints last long: after 10 days, two thirds of patients still had complaints and about half of the patients still felt ill. The natural course to recovery takes a long time and is not influenced by taking amoxicillin. Finally, we observed that failure to prescribe antibiotics is safe. The placebo group had no complications. A small number of exacerbations occurred, but these responded swiftly to a course of amoxicillin–clavulanate.

To our knowledge, this is the first time that the effect of an antibiotic in adult patients presenting with acute purulent rhinorrhea (but with an otherwise unspecified diagnosis) has been investigated in a randomized, placebo-controlled trial. This trial is in line with a number of other family practice–based pragmatic trials in which patients were included on the basis of respiratory symptoms instead of by diagnosis \(^{10-12,37} \) and in which the emphasis was on practical relevance rather than on diagnostic accuracy.

Since 1995, 6 randomized clinical trials of high methodologic quality \(^{10-16} \) have studied the efficacy of antibiotics in general practice patients suffering from various acute infections of the nasal passages and usually presenting with purulent rhinorrhea. In 3 of these trials, no beneficial effect of antibiotics was found. Study populations consisted, respectively, of patients with a set of clinical symptoms (including purulent rhinorrhea) indicating rhinosinusitis \(^{10,15} \); patients with clinical suspicion of rhinosinusitis plus sinus abnormalities on conventional radiology \(^{11,13} \); and patients with clinical suspicion of sinusitis but without the radiologic signs. \(^{12} \) In the 3 other trials, treatment was (more or less) effective. Included were patients with clinical suspicion of sinusitis and abnormalities on CT scan, \(^{11} \) patients with unilateral facial pain and elevated C-reactive protein levels or erythrocyte sedimentation rate, \(^{15} \) and patients with rhinopharyngitis and positive bacteriologic cultures of nasopharyngeal secretions. \(^{15} \) These trials show that antibiotics are efficacious in some patients. In our trial, which probably included a mix of all these populations, we also found more patients in the amoxicillin group to be symptom free after 10 days. Despite a fairly large sample size, however, this difference was too small (less than 15%) to be statistically significant.

In this trial, as in daily practice, we did not know the precise diagnosis of included patients. Moreover, despite our frequent requests, participating FPs

### TABLE 3

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean Score Reduction</th>
<th>Amoxicillin n = 170</th>
<th>Placebo n = 164</th>
<th>( P ^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral facial pain</td>
<td>1</td>
<td>1.1</td>
<td>1.0</td>
<td>.56</td>
</tr>
<tr>
<td>Pain on bending forward</td>
<td>1.21</td>
<td>1.32</td>
<td>1.55</td>
<td>.55</td>
</tr>
<tr>
<td>Pain in upper teeth or chewing</td>
<td>0.72</td>
<td>0.93</td>
<td>1.11</td>
<td>.17</td>
</tr>
<tr>
<td>Need to blow nose</td>
<td>1.73</td>
<td>1.70</td>
<td>0.85</td>
<td>.85</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.13</td>
<td>1.05</td>
<td>0.83</td>
<td>.63</td>
</tr>
<tr>
<td>Runny nose</td>
<td>1.47</td>
<td>1.55</td>
<td>1.33</td>
<td>.33</td>
</tr>
<tr>
<td>Cough</td>
<td>1.0</td>
<td>1.11</td>
<td>0.83</td>
<td>.46</td>
</tr>
<tr>
<td>Thick nasal discharge</td>
<td>2.2</td>
<td>1.5</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>Postnasal discharge</td>
<td>1.29</td>
<td>1.09</td>
<td>0.83</td>
<td>.26</td>
</tr>
<tr>
<td>Ear fullness</td>
<td>1.13</td>
<td>1.31</td>
<td>1.32</td>
<td>.32</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.95</td>
<td>0.87</td>
<td>0.83</td>
<td>.63</td>
</tr>
<tr>
<td>Ear pain</td>
<td>0.64</td>
<td>0.77</td>
<td>0.56</td>
<td>.36</td>
</tr>
<tr>
<td>Facial pain or pressure</td>
<td>1.54</td>
<td>1.61</td>
<td>1.69</td>
<td></td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>1.14</td>
<td>1.23</td>
<td>1.32</td>
<td>.54</td>
</tr>
<tr>
<td>Wake up at night</td>
<td>1.39</td>
<td>1.44</td>
<td>1.44</td>
<td>.28</td>
</tr>
<tr>
<td>Lack of a good night’s sleep</td>
<td>1.24</td>
<td>1.44</td>
<td>1.44</td>
<td>.28</td>
</tr>
<tr>
<td>Wake up tired</td>
<td>1.34</td>
<td>1.65</td>
<td>1.65</td>
<td>.09</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.46</td>
<td>1.61</td>
<td>1.61</td>
<td>.38</td>
</tr>
<tr>
<td>Reduced productivity</td>
<td>1.45</td>
<td>1.63</td>
<td>1.63</td>
<td>.29</td>
</tr>
<tr>
<td>Reduced concentration</td>
<td>1.24</td>
<td>1.48</td>
<td>1.48</td>
<td>.19</td>
</tr>
<tr>
<td>Frustrated, restless, irritable</td>
<td>0.87</td>
<td>1.41</td>
<td>1.41</td>
<td>.91</td>
</tr>
<tr>
<td>Sad</td>
<td>0.38</td>
<td>0.52</td>
<td>0.52</td>
<td>.18</td>
</tr>
<tr>
<td>Embarrassed</td>
<td>0.36</td>
<td>0.76</td>
<td>0.76</td>
<td>.36</td>
</tr>
</tbody>
</table>

\( ^* \) Student’s t test.
included only a minority of eligible patients. Concern might arise that only patients with mild disease were studied. We made 3 efforts to verify that the population was truly representative. First, we determined that the personal characteristics and severity of symptoms of patients of low-recruiting FPs (who tend to include patients with worse symptoms\(^38\)) were no different from those of patients included by high recruiters. Second, an analysis of questionnaires from all eligible but excluded patients over a 6-week period showed that included and excluded patients were very much alike. The analysis also showed that in only 3\% of patients did the FP consider the subject too ill to be included. Third, the results obtained on plain radiography of the maxillary sinuses were in line with the imaging results of other family practice populations with clinical suspicion of rhinosinusitis.\(^11,19-21\)

With regard to the methodology, we wish to clarify certain choices. Amoxicillin was selected because it is recommended as the first-line drug for rhinosinusitis in several practice guidelines\(^39-41\) and the sensitivity of respiratory pathogens to it was sufficient in our geographic area at the start of the trial.\(^42\) To evaluate symptoms, we chose the 20 items of the SNOT-20 questionnaire (Table 1), an abbreviated version of the RSOM-31,\(^29\) a disease-specific quality-of-life test for sinusitis. These 20 items include not only all classic rhinosinusitis symptoms but also a number of more subjective symptoms, such as sleep disturbances and reduced productivity, which may also severely inconvenience patients. Any beneficial effect of amoxicillin on these symptoms would be just as important as an effect on the classic sinusitis symptoms.

Outcome measures were mainly self-assessed by patients, since in this kind of pathology, for which subjective inconvenience is often greater than objective signs might indicate, the patient is in our view the best and only judge of symptom improvement. The main outcome measure, disappearance of perceived worst symptoms, was designed to take into account the heterogeneity of clinical presentations.

**CONCLUSIONS**

Patients with an acute upper respiratory tract infection with purulent rhinorrhea (and without signs of complications of sinusitis) represent a large, clearly defined, clinically recognizable group. Our results show that amoxicillin pro-

* Streptococcus pneumoniae 97% sensitive and Haemophilus influenzae 87% sensitive: data from Ghent University Hospital, Laboratory of Bacteriology, De Pintelaan 185, B-9000 Ghent, Belgium. Director: Prof. G. Verschraege. Personal communication.
vides no clinically important benefits for this population. The implication for practice is that whatever treatment is chosen, symptoms can last for a long time. In the rare event that symptoms worsen, they should consult their FP for antibiotic therapy. If patients are clearly distressed by the purulent rhinorrhea itself, this trial suggests reasons for considering the use of amoxicillin, but potential patient benefits still probably do not outweigh the disadvantages.

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REFERENCES