Critical Review Form
Therapy

Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial. J Fam Pract. 2005 Feb;54(2):144-51

Objectives: To study the effect of antibiotics on clinical improvement in patients with sinusitis seen in the primary care setting.

Methods: This prospective, randomized controlled trial was conducted in a suburban primary care office from October1, 2001 to March 31, 2003. Two physicians and one nurse practitioner enrolled and treated patients age > 18 years with at least one of the following features present for at least 7 days:

1) **Unilateral purulent nasal discharge**
2) **Unilateral localized facial pain**
3) **Bilateral purulent nasal discharge**
4) **Pus visible in the nasal cavity.**

Exclusion criteria included antibiotic treatment within the past month, penicillin allergy, prior sinus surgery, immune compromise, and concomitant pneumonia or streptococcal pharyngitis.

A block randomization scheme was used, stratified by clinician. Opaque sealed envelopes containing 40 capsules (either amoxicillin 500 mg or a placebo of identical appearance) were randomly assigned to patients. Patients were to take either 1000 mg (2 capsules) of amoxicillin twice a day for 10 days, or 2 capsules of placebo twice a day for 10 days. Clinicians were blinded to treatment assignment. On days 3, 7, and 14 following the initial visit, trained personnel, blinded to treatment assignment, conducted telephone interviews using 12 follow-up questions. A power analysis determined that 135 subjects (67 in the amoxicillin group and 68 in the placebo group) would be needed to have 80% power to detect a 25% rate of improvement based on a dichotomous outcome of either "improved" or "not improved" at the end of 2 weeks.

Over the study period, 308 patients were approached for enrollment. Of these 173 were excluded, leaving 135 subjects. Sixty-seven of these received amoxicillin and sixty-eight received placebo. Eleven subjects in the amoxicillin arm and eight in the placebo arm were lost to follow-up with only baseline data recorded. These patients were counted as "not improved" in the analysis.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. Block randomization (by clinician) was conducted.
2.	Was randomization concealed (blinded)?	Yes. Sealed, opaque envelopes were used. The method of sequence generation was not discussed.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was used. The authors do not state if they measured patient compliance with the assigned treatment. All patients lost to follow-up were included in the analysis, and considered as "not improved."
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients in the placebo and amoxicillin groups were similar with respect to mean age (32.6 vs. 35.1), percent female (49% vs. 44%), mean number of days of symptoms prior to enrollment (11.7 vs. 10.7), mean self-rating or health (3.1 vs. 3.1), mean self-rating of how sick the patients felt at enrollment (6.3 vs. 6.2), and presence of each of the four cardinal symptoms of sinusitis. P-values were > 0.05 for all baseline characteristics reported.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. Patients received envelopes containing either amoxicillin or a placebo of identical appearance.
2.	Were clinicians aware of group allocation?	No. The authors note that the clinicians were not aware of allocation. Opaque sealed envelopes containing the study drug were provided, though they do not detail how or where these were assembled or the method of random sequence generation.
3.	Were outcome assessors aware of group allocation?	No. Trained personnel who were blinded to group allocation conducted follow-up telephone interviews.
4.	Was follow-up complete?	No. There were 11 subjects in the amoxicillin arm (16%) and 8 subjects in the placebo arm (12%) with only baseline

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<tr><td></td><td></td><td>data. In the analysis, these patients were considered as “not improved.”</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>

For the primary outcome, number of patients “improved” at the end of 2 weeks, there was no statistically significant difference between the amoxicillin and placebo groups: 48% vs. 37% (p = 0.26), for a relative risk of treatment failure of 1.3 (95% CI 0.87-1.94).
Participants in the amoxicillin group did improve significantly earlier based on the Kaplan-Meier curve (p = 0.039). Median day to any improvement was day 8 in the amoxicillin group compared to day 12 in the placebo group (p = 0.005).
The average Likert score for the question “How sick do you feel today” was lower at each time point for the amoxocillin group vs. the placebo group, though the differences were not statistically significant (Table 1).

Table 1. Average Likert score for sickness
<table>
<tr><td>Time</td><td>Amoxicillin (n = 67)</td><td>Placebo (n = 68)</td></tr>
<tr><td>Day 0 (SD)</td><td>6.10 (2.0)</td><td>6.30 (1.9)</td></tr>
<tr><td>Day 3 (SD)</td><td>4.33 (1.8)</td><td>4.73 (1.9)</td></tr>
<tr><td>Day 7 (SD)</td><td>3.15 (2.1)</td><td>3.30 (2.0)</td></tr>
<tr><td>Day 10 (SD)</td><td>2.30 (1.9)</td><td>2.80 (2.5)</td></tr>
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The mean number of days to improvement was lower in the amoxicillin group than the placebo group, regardless of the number of cardinal signs and symptoms present at baseline (Table 2).

Table 2. Mean number of days to improvement by number of signs and symptoms
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<tr><td>Number of signs/symptoms</td><td>Amoxicillin (n = 32)</td><td>Placebo (n = 25)</td></tr>
<tr><td>One (n, SD)</td><td>7.8 days (16, 3.7)</td><td>11.0 days (10, 2.6)</td></tr>
<tr><td>Two (n, SD)</td><td>7.8 days (5, 3.7)</td><td>10.3 days (6, 3.2)</td></tr>
<tr><td>Three or four (n, SD)</td><td>8.6 days (11, 3.6)</td><td>10.6 days (9, 3.0)</td></tr>
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		• There was no significant difference in the number of patients reporting side effects: 13 patients in the placebo group compared to 7 in the amoxicillin group (p = 0.12).
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Likely yes. These were patients presenting to a primary care office with sinusitis diagnosed by clinical criteria. In our Emergency Department we might expect to see patients with more severe disease or those with less access to primary care and follow-up. We also do not know what co-morbidities these patients had, including potential immunocompromise (diabetes, renal failure, chemotherapy, immunomodulation therapy). In addition, we rarely use strict criteria to diagnose acute sinusitis. However, it is likely that the majority of patients with true sinusitis (whether diagnosed by Berg and Carenfelt criteria, CDC criteria, or other criteria) would be similar, whether seen in primary care or the ED, and would respond similarly to treatment with antibiotics and intranasal steroids.
2.	Were all clinically important outcomes considered?	No. While the authors assessed the number of patients "improved" and the average score for the question "how sick do you feel today," they did not assess any well-validated scoring tools, such as the SNOT-16 score. They also did not assess physician-reported outcomes or cure rates.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While the study showed no difference in the proportion of patients "improved" at 2 weeks, patients did improve significantly faster at all points in the study. While there were no differences in the number of patients with side effects, the study size was small and likely underpowered to detect a significant difference.

Limitations:

1) **Measures of agreement not assessed between physicians in diagnosing acute bacterial sinusitis.**

2) **Failure to identify the method of random sequence generation.**

3) **Failure to identify the method of clinical blinding.**

4) **IDSA guidelines require symptoms for at least 10 days prior to diagnosing acute bacterial sinusitis, while this study did not specify symptom duration. It is possible that many patients in this study had viral upper respiratory infections that would not be expected to respond to antibiotics.**

5) **No sensitivity analysis for the patients lost to follow-up.**

6) **Limited external validity: the results should not be applied to children, the immunocompromised, or the more severely ill.**

Bottom Line:

This small, randomized controlled trial to assess the efficacy of amoxicillin in acute bacterial sinusitis found no difference in the number of patients subjectively "improved" at the end of two weeks (RR of treatment failure 1.3, 95% CI 0.87-1.94). Patients did, however, improve significantly earlier, and scores on the question "how sick do you feel today?" were lower at all times points (though these differences were not statistically significant). The inclusion of patients with less than 10 days of symptoms and the use of amoxicillin could artificially deflate any treatment effect.