Critical Review Form
Therapy

PGY-3

Amoxicillin for acute rhinosinusitis: a randomized controlled trial. JAMA. 2012 Feb 15;307(7):685-92.

Objective: **"to determine the incremental effect of amoxicillin treatment over symptomatic treatments on disease-specific quality of life in adults with clinically diagnosed acute bacterial rhinosinusitis." (p. 686)**

Methods: **This prospective, randomized, placebo-controlled trial was performed at 10 primary care offices in St. Louis, MO between November 1, 2006 and May 1, 2009. To be eligible, patients had to be between 18 and 70 years of age with moderate, severe, or very severe symptoms of acute bacterial rhinosinusitis based on the CDC diagnostic criteria (maxillary pain or tenderness in the face or teeth, purulent nasal secretions) for 7-28 days duration, or symptoms < 7 days that had significantly worsened despite treatment. Exclusion criteria included allergy to penicillin or amoxicillin, antibiotic use in the preceding 4 weeks, concomitant illness requiring antibiotics, the presence of complications of sinusitis, comorbid conditions that impair the immune response, cystic fibrosis, pregnancy, or very mild to mild symptoms. A research assessment at the primary care offices assessed patients for eligibility and consented patients.**

An investigational pharmacist, not involved in patient enrollment or outcome assessment, used computer-generated blocks of random numbers to determine how the 2 study drugs were allocated to consecutively numbered treatment packages. Patients were randomized to a treatment package by the research assistant. Study participants were given either amoxicillin (500 mg orally three times a day) or a placebo with similar taste and appearance. Unless contraindicated, subjects were also prescribed symptomatic medications to be taken as needed (including acetaminophen, guaifenesin, dextromethorphan, pseudoephedrine, and saline nasal spray).

The primary outcome was the effect of treatment on quality of life, measured using the Sinonasal Outcome Test-16 (SNOT-16) at day 3. The SNOT-16 assesses 16 sinus-related symptoms on a 3 -point scale (0 = no problem, 3 = severe problem), with the mean of all items lying between 0 and 3, and a minimally important difference of 0.5 units. Secondary outcomes included:

1) **A retrospective patient assessment of symptom change since enrollment (a lot or a little worse or better, the same, or no symptoms), with those reporting "a lot better" or "no symptoms" considered "significantly improved."**
2) **Number of days unable to perform usual activities and days missed from work**
3) **Recurrent sinusitis (defined as any patient with "no symptoms" at days 7 and 10 who reports "the same" or "worse" at day 28)**
4) **Level of agreement with the statement "The study medication that I received for my sinus problem helped a lot," assessed at day 10**
5) **Adverse effects were assessed at day 10 using the question "Have you had any side effects from the study medication?" as well as specific questions about potential adverse effects associated with amoxicillin treatment**
6) **Treatment adherence, assessed by patient self-reporting (defined as having missed less than 3 doses of study drug).**

The SNOT-16 was completed during an interview with the research assistant on day 0, and was repeated by telephone later that day, as well as on days 3, 7, 10, and 28. The in-person score was used only for 4 patients who missed the telephone interview on day 0. The telephone interviews were conducted using a standard questionnaire by research assistants blinded to group allocation.

The researchers calculated that a sample size of 100 patients per group would provide 83% power to detect a difference of 0.25 in SNOT-16 scores at day 3, with $\alpha = 0.05$. An intention to treat analysis was used for all participants. To account for missing data, the primary analyses were repeated 20 times, imputing the missing SNOT-16 data, with no change in the statistical significant pattern.

A total of 244 adult patients were screened, 174 were eligible, and 166 were randomized to amoxicillin (n = 85) or placebo (n = 81). All patients reported purulent nasal discharge and maxillary pain or tenderness in the face or teeth. There were 143 patients (88%) with rhinosinusitis symptoms for 7-28 days that were worsening (n=105) or not improving (n = 38); 23 (14%) reported symptoms for less than 7 days that worsened after initial improvement.

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 (presumably by study site) was conducted using computer-generated random sequences.

2.	Was randomization concealed (blinded)?	Yes. Treatment packages were assembled by the investigational pharmacist (who was not involved in patient enrollment or outcome assessment) using computer-generated random numbers.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. 23 subjects (11 in the amoxicillin group and 12 in the control group) did not complete the 10-day course of treatment. An intention to treat analysis was used primarily, although a per-protocol analysis was used for comparative purposes.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes and no. There was a higher rate of smoking in the control group (26% vs. 13%, p = 0.03). The groups were similar with respect to age, race, medical history, history of sinus disease, baseline SNOT-16 scores, symptom severity, duration of symptoms, and prior use of symptomatic treatment.
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 were blinded to treatment group. The placebo was similar in appearance and taste, and was distributed in a similar fashion to the amoxicillin.
2.	Were clinicians aware of group allocation?	No. Treatment packages were assembled by a pharmacist using computer-generated random numbers, and patients were randomized to treatment package by the research assistant. Clinicians were not aware of the randomization sequence.
3.	Were outcome assessors aware of group allocation?	No. Patients reported SNOT-16 scores, symptom change, satisfaction with treatment, and adverse effects. Patients were not aware of group allocation. While not specifically mentioned, it is safe to assume that those performing the telephone interviews were also not aware of group allocation.
4.	Was follow-up complete?	Mostly. There were 11 subjects with missing data (4 in the amoxicillin group, 7 in the control group). The authors repeated the primary analyses, imputing the missing data 20 times, and noted no change in the statistical significance pattern for these additional analyses compared with the unimputed data.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• The mean change in SNOT-16 scores was similar in both groups at days 3 and 10, but was greater in the amoxicillin

group at day 7 (Table 1).

Table 1. Mean changes in SNOT-16 scores

	Tx group mean Δ in SNOT-16 score (95% CI)	Control group mean Δ in SNOT-16 score (95% CI)	P value
Day 3	0.59 (0.47-0.71)	0.54 (0.41-0.67)	0.69
Day 7	1.06 (0.93-1.20)	0.86 (0.71-1.02)	0.02
Day 10	1.23 (1.08-1.37)	1.20 (1.07-1.32)	0.85

- The percent of subjects reporting symptoms as "a lot better" or "no symptoms" were similar at days 3 and 10, but were greater in the amoxicillin group at day 7 (Table 2), for a number needed to treat (NNT) of 6 (95% CI 3-34).

Table 2. Percent reporting symptoms significantly improved

	Reported symptom improvement: amoxicillin	Reported symptom improvement: control	P value
Day 3	37%	34%	0.67
Day 7	74%	56%	0.02
Day 10	78%	80%	0.71

- A per protocol analysis of patient who completed all 10 days of treatment (n = 143; 74 in the amoxicillin group, 69 in the control group) and an analysis of those patients with 7-28 days of treatment (n = 143; 73 in the amoxicillin group, 70 in the control group) were consistent with the primary analysis.

- Days missed from work or unable to perform usual activities, rates of disease recurrence by day 28, additional health care use, and satisfaction with treatment did not differ statistically between the groups (Table 3).

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Table 3. Secondary outcomes
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<tr><th></th><th>Amoxicillin</th><th>Control</th><th>P value</th></tr>
<tr><td>Days of missed work, mean (95% CI)</td><td>0.55 (0.28-0.82)</td><td>0.55 (0.22-0.87)</td><td>0.99)</td></tr>
<tr><td>Days unable to do usual activities, mean (95% CI)</td><td>1.15 (0.76-1.54)</td><td>1.67 (1.08-2.26)</td><td>0.14</td></tr>
<tr><td>Relapse rate, % (95% CI)</td><td>9 (3-16)</td><td>6 (1-11)</td><td>0.58</td></tr>
<tr><td>Recurrence rate, % (95% CI)</td><td>6 (1-11)</td><td>2 (0-6)</td><td>0.44</td></tr>
<tr><td>Satisfaction with treatment, % (95% CI)</td><td>53 (42-64)</td><td>41 (29-52)</td><td>0.13</td></tr>
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There were no reported serious adverse events. There was no difference in the percent of patients in the amoxicillin and control groups who reported one or more adverse effect: 48% (95% CI 37-59) vs. 52% (95% CI 39-62), p = 0.75.
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<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>Likely yes. These were patients selected from primary care offices, rather than the Emergency Department. 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,</td></tr>
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		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 antibiotic treatment.
2.	Were all clinically important outcomes considered?	Yes. The authors considered change in a validated scoring system (SNOT-16), subjective assessments of symptoms improvement, days of missed work and/or activity, recurrence rate, patient satisfaction with treatment, and adverse effects.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. While there were significant improvements in mean SNOT-16 scores and the percent of patients reporting significant improvement at day 7, there were no differences at days 3 or 10. While patients may improve somewhat faster (potentially 3 days earlier based on these findings), this did not result in improvements in patient satisfaction with treatment, days of missed work, days unable to do usual activities, recurrence rates, or adverse event rates. Moreover, the statistically significant difference in mean SNOT-16 scores at day 7 was small (1.06 vs. 0.86), and not likely to be clinically significant. This difference would not likely balance out the risk of increased bacterial resistance that would result from providing antibiotics to all patients with acute sinusitis.

Limitations:

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

2) **Patients with symptoms less than 7 days duration (whose symptoms were worsening despite treatment) were included. 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.**

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

4) **IDSA guidelines recommend amoxicillin-clavulanate rather than amoxicillin alone due to the risks of penicillin-resistant *Streptococcus pneumonia* and the prevalence of β-lactamase producing bacteria (typable *Haemophilus influenza*, or *Moraxella catarrhalis*) the prevalence of which have increased in upper respiratory infections (Block 2004, Casey 2010).**

Bottom Line:

This randomized controlled trial revealed a statistically significant (but likely clinically insignificant) improvement in symptom score at day 7, with no difference at days 3 and 10. There was a significant increased in the percent of patients reporting significant improvement in symptoms at day 7, again with no difference at days 3 or 10. Failure to follow IDSA guidelines for duration of symptoms and antibiotics selection may have resulted in an underestimate of the treatment benefit.