Critical Review Form
Therapy

Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. *JAMA*. 2007 Dec 5;298(21):2487-96.

Objectives: To determine the effectiveness of an antibiotic and a nasal steroid, alone or in combination, in patients presenting in primary care with acute bacterial sinusitis.

Methods: This was a prospective study conducted in multiple primary care practices utilizing block randomization from November 2001 to November 2005. Each practice was informally trained in the appropriate use of the entry criteria and the performance of involved physical examination techniques. The treatment regimens studied were amoxicillin, 500 mg orally 3 times per day for 7 days, and budesonide, 200 µg in each nostril once per day for 10 days. Patients were included if they were older than 15 years with acute illness (symptoms < 28 days in duration) and positive for a minimum of two Berg and Carenfelt criteria (Table 1). Exclusion criteria included a history of recurrent sinusitis (≥ 2 episodes in the previous 12 months), poorly controlled diabetes or heart failure, pregnancy, breastfeeding, a history of allergies or adverse reactions to either of the study medications, or previous use of antibiotics or steroids in the previous month.

Table 1. Berg and Carenfelt Criteria for Acute Bacterial Sinusitis

1. Purulent nasal discharge with unilateral predominance
2. Local pain with unilateral predominance
3. Purulent nasal discharge bilaterally
4. Intranasal pus on inspection
A minimum of 2 of the above required for diagnosis of acute bacterial sinusitis

Block randomization was employed, such that sealed, opaque numbered packages containing either active or placebo drugs were distributed in randomized blocks of 4 to participating practices. Each pack of 4 consisted of the 4 possible combinations of study drug (active antibiotic and active steroid, placebo antibiotic and active steroid, active antibiotic and placebo steroid, and placebo antibiotic and placebo steroid). The packs were assembled by a person independent of the study team using random number tables. Neither the antibiotic nor the nasal steroid could be discerned from their respective placebos by taste or appearance.

Based on a prior Cochrane meta-analysis (Williams 2003), the authors calculated that in order to have an 80-90% chance (β of 0.10 to 0.20) of detecting a standard deviation (SD) difference of 0.4 (if such a difference truly existed) in the Total

Symptoms Severity (TSS) score, with an α of 0.05, they would need to recruit 208-290 patients (Day 1989).

After randomization and written consent, physicians completed a questionnaire including clinical signs, examination findings, symptom duration and severity, and baseline demographic data. Patients were then instructed in the completion of a 14-day symptom diary and provided with written and pictorial instructions on the correct method to take the medications. The patient diaries consisted of 11 symptoms variables measured on 7-point Likert scales (the TSS score). When patient scores reached all zeros, or at the end of 2 weeks, they were asked to return the diaries and all medication supplies by mail. Patients who did not respond were contact again by phone, and some patient study data was collected by telephone interview (n = 14, 5.8% of the randomized population).

In total, 117 practices were visited, with 230 family physicians expressing interest in the study; only 74 of these physicians, in 40 different practices, were willing to participate. Out of 388 patients assessed for eligibility, 240 were randomized; of these, 33 were lost to follow-up, leaving 207 patients in the final analysis. The median age was 44 years, and the female to male ratio was 4:1.

Patients were analyzed by factorial analysis. Combined analysis considered the following two comparisons: 1) antibiotic (active antibiotic and active steroid, active antibiotic and placebo steroid) vs. no antibiotic (placebo antibiotic and active steroid, placebo antibiotic and placebo steroid) (controlling for the effects of steroid in the model) and 2) topical steroid (active antibiotic and active steroid, placebo antibiotic and active steroid) vs. no topical steroid (active antibiotic and placebo steroid, placebo antibiotic and placebo steroid) (controlling for the effects of antibiotics in the model). The primary outcome was proportion cured by 10 days (determined by resolution of symptoms), and was assessed using logistic regression and Cox regression.

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 was employed with blocks of 4 allocated per physician.
2.	Was randomization concealed (blinded)?	Yes. The packs of 4 were assembled using random number tables by an individual independent of the study group.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. All patients were assessed using an **intention to treat analysis,** regardless of compliance.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. In Table 1 in the paper, patients were evaluated with respect to age, sex, smoking history, history of asthma, history of prior sinusitis, presence of pus on nasal inspection, initial temperature, number of days symptomatic, and the number of positive Berg and Carenfelt criteria. The only significant difference was observed with regards to median initial temperature between the antibiotic (36.5, IQR 36.0-36.8) and no antibiotic groups (36.5, IQR 36.3-37.0) ($p = 0.05$).
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 assigned treatment or placebo for each of the 2 medications beings studied. The treatments and placebo were "identical in taste and appearance." (p. 2489) Concealment was assessed by determining patients' beliefs in the effectiveness of the treatment allocated using a 0-5 scale: no difference was observed for the antibiotic vs. placebo ($p = 0.07$) or steroid spray vs. placebo ($p = 0.25$).
2.	Were clinicians aware of group allocation?	No. Each clinician received a randomized pack of 4 combinations of therapy that was assembled by an individual independent of the study group. The numbered packages were sealed and opaque. The code break for the packs "was kept in a sealed envelope in a locked filing cabinet at the university throughout the study period." (p. 2489)
3.	Were outcome assessors aware	Yes. Outcome assessments were recorded in a central

	of group allocation?	database and checked and verified by a research fellow blinded to group allocation.
4.	Was follow-up complete?	No. Of 240 patients randomized, 207 were followed to study completion, for an attrition rate of 13.7%. A larger percentage of subjects were lost to follow-up in the placebo/placebo group (19.0%) than in the antibiotic/steroid (13.2%), antibiotic/placebo (10.0%), and placebo/steroid (12.5%) groups. However, the authors report that sensitivity analyses performed by imputing data that assumed those lost to follow-up were still symptomatic at day 14 showed no difference in the results. The authors also note that patients with pus on nasal examination (AOR 1.50, 95% CI 0.66-3.40) and those who were male (AOR 3.75, 95% CI 1.66-8.48) were more likely to be lost to follow-up.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Primary outcome: the number of patients with symptoms lasting 10 or more days was 29/100 (29%) for amoxicillin vs. 36/107 (33.6%) for no amoxicillin (AOR 0.99, 95% CI 0.57-1.73), and 32/102 (31.4%) for budesonide vs. 33/105 (31.4%) for no budesonide (AOR 0.93, 95% CI 0.54-1.62). • Cox regression revealed similar findings for the primary outcome for amoxicillin (hazard ratio for resolution 1.08, 95% CI 0.79-1.48) and budesonide (hazard ratio 1.08, 95% CI 0.77-1.44). • There was no significant difference in the median TSS scores at day 10 for amoxicillin vs. no amoxicillin (median difference 0, 95% CI, −0.70 to 0.70; $p = 0.99$) or for budesonide vs. no budesonide (median difference 0, 95% CI, −0.70 to 0.70; $P = 0.99$). • The sensitivity analysis using imputation of data for patients lost to follow-up revealed no significant difference in the primary outcome for amoxicillin (AOR 0.90, 95% CI 0.54-1.50) or budesonide (AOR 0.90, 95% CI 0.54-1.50). • There was no appreciable difference in the time to cure for any group (defined as scores of 0 or 1 for each item in the TSS score); 40% of patients were

		cured within one week. • A significant interaction between increased severity at baseline and the nasal steroid was found for the unwell group of symptoms. The effect of steroids 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; the interaction coefficient was 0.28 (95% CI, 0.10 to 0.45; *P* = .003), i.e. the effect of the nasal steroid is reduced by 0.28 for each 1 point increase in baseline severity of sinusitis.
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 British patients presenting to a primary care office with sinusitis diagnosed by Berg and Carenfelt 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. The authors considered an array of subjective patient-reported outcomes based on TSS score and symptoms resolution. They did not reported on the rates of adverse effects or serious adverse outcomes, nor did they assess physician assessment of “cure.”
3.	Are the likely treatment benefits worth the potential harm and costs?	No. Based on these results, there was no difference in the proportion of patients symptom-free at the end of 2 weeks, median TSS score, or time to cure with either amoxicillin or nasal budesonide.

Limitations:

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

2) **Loss to follow-up was significantly higher in the placebo/placebo group than the other 3 groups (attrition bias).**

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

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

Bottom Line:

This randomized controlled trial performed in primary care offices evaluated the effectiveness of amoxicillin and nasal budesonide in the treatment of acute bacterial sinusitis. For the primary outcome, the number of patients with symptoms lasting 10 or more days, there was no significant improvement with either amoxicillin (AOR 0.99, 95% CI 0.57-1.73) or budesonide (AOR 0.93, 95% CI 0.54-1.62). The inclusion of patients with symptoms less than 10 days, and the use of amoxicillin alone may have falsely deflated the treatment benefit of antibiotics and nasal steroids.