Critical Review Form
Meta-analysis

Antibiotics for clinically diagnosed acute rhinosinusitis in adults. Cochrane Database Syst Rev. 2012 Oct 17;10:CD006089.

Objective: **To determine if, in patients with clinically diagnosed rhinosinusitis, antibiotics reduce the severity and duration of symptoms, influence outcomes, or affect the incidence of adverse outcomes.**

Methods: **One author searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2; www.thecochranelibrary.com (accessed 10 October 2012)), MEDLINE (January 1950 to February week 4, 2012) and EMBASE (January 1974 to February 2012) using a well-described search strategy (for MEDLINE and CENTRAL search strategy see Appendix 1, p. 82; for EMBASE search strategy see Appendix 2, p. 83). The reference lists of identified trials, systematic reviews, and guidelines were scrutinized for other relevant trials.**

The review included only trials in which adults (18 years or older) with clinically diagnosed rhinosinusitis were randomized to treatment with antibiotic or placebo. Trials were excluded if > 50% of patients were considered to have a "common cold"; if patients had symptoms for > 30 days; if rhinosinusitis was diagnosed based on radiologic (CT, x-ray), laboratory (C-reactive protein, erythrocyte sedimentation rate), or bacteriological or cytological investigations; if one antibiotic was compared to another antibiotic or active medication; if no placebo arm was included; or if the drop-out rate was over 35% or considerably different between intervention groups.

Two authors independently performed data extraction, with disagreement resolved by consensus. The two authors also assessed the chosen studies for methodological quality using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011, Part 2, Chapter 8), which include assessments of allocation, blinding, incomplete outcome data, selective reporting, and other sources of bias. Studies were categorized as low risk of bias (all criteria met), risk of bias (one or more criteria partially met), or high risk of bias (one or more criteria not met). There were no disagreements between the authors with respect to degree of bias.

The primary outcome was the proportion of patients cured at a specific time point. Secondary outcomes included:

1) Ratings of overall well-being

2) Severity or duration of clinical symptoms
3) Use of concomitant medications
4) Adverse effects of the antibiotic
5) Clinical failure and serious adverse events.

Ten trials met all inclusion criteria, with a total of 2450 participants (1239 in intervention groups, 1211 in placebo groups). The overall drop-out rate was 4.8%. The three most common inclusion criteria were nasal discharge, facial pain, and common cold or upper respiratory tract infection.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Antibiotic prescription rates remain high in patients with rhinosinusitis (McCaig 1998, Steinman 2003). If antibiotics are shown to provide no benefit, the resulting reduction in prescribing could potentially lead to decreased adverse drug reactions and decrease contributions to antibiotic resistance.
2.	Was the search for relevant studies detailed and exhaustive?	Yes. Cochrane Central Register of Controlled Trials (CENTRAL), MED- LINE, and EMBASE were searched using a well-described search strategy. The reference lists of identified trials, systematic reviews, and guidelines were scrutinized for other relevant trials.
3.	Were the primary studies of high methodological quality?	Yes. Risk of bias was assessed for 6 criteria (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias). For each criterion, each study was assigned a score of either low risk of bias, unclear risk of bias, or high risk of bias. Out of the ten studies, there were three studies with unclear risk of bias for random sequence generation and allocation concealment; there was one study with unclear risk of bias for blinding and incomplete outcome data; and there were two studies with high risk of bias in the category of selective reporting.
4.	Were the assessments of the included studies reproducible?	Yes. As noted above, a detailed description of the assessment of bias was provided, and can be found in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011, Part 2, Chapter 8),
II.	***What are the results?***	
1.	What are the overall results of the study?	Overall, 47% of participants were cured after one week, 49.5% after 10 days, and 71% after 14 days. For overall cure rate the authors of the meta-analysis considered participants who started other antibiotics as

		"treatment failures" rather than dropouts. • For the 8 studies in which "cure" was the primary outcome: OR for antibiotics relative to placebo was 1.25 (95% CI 1.02 to 1.53), for a number needed to treat (NNT) of 18.0 (95% CI 9.7 to 114.9). I^2 = 0%. • Excluding studies with an intention to treat (ITT) analysis resulted in an OR 1.06 (95% CI 0.76-1.47). • Pooling only studies with an ITT analysis resulted in an OR of 1.39 (95% 1.02-1.79). With regards to cure rate for different time frames, there were no significant differences between the treatment groups: • One week (4 studies): OR 1.07 (95% CI 0.81 to 1.41), I^2 = 0% • 10 days (3 studies): OR 1.18 (95% CI 0.92 to 1.52), I^2 = 0% • 14 days (4 studies): OR 1.48 (95% CI 0.99 to 2.23), I^2 = 6%. For resolution of purulent secretions, the OR was 1.58 (95% CI 1.13-2.22), NNT 10.8 (95% CI 6.1-50.8), I^2 = 0%. While the data could not be pooled, none of the studies showed a significant difference with regards to general feeling of illness, pain duration, illness duration, restriction of activities, or the use of nasal vasoconstrictors or antihistamines. Four of the included studies showed no effect of antibiotics on the use of analgesics, while one (Varonen 2003) revealed that more patients in the placebo group used analgesics than in the antibiotic group (43% vs. 23%, p = 0.03). Data was pooled from seven trials to determine the adverse effect rate: OR 2.10 (95% CI 1.60-2.77), number needed to harm (NNH) = 8.1 (95% CI 6.0-12.5), I^2 = 13%. Data was pooled from four trials evaluating the incidence of diarrhea: 15.9% of patients receiving antibiotics reported suffering from diarrhea and 10.4% of participants who received placebo suffered from diarrhea. This result was statistically significant (OR 1.81, 95% CI 1.18 to 2.78), NNH 18.1 (95% CI 9.9 to 108.7), I^2 = 0%. Data was pooled from seven trials to evaluate clinical failure, defined as the need to start antibiotic therapy due to an

		"abnormal course" of rhinosinusitis (exacerbation, ongoing symptoms, respiratory complications, treatment failure): OR 0.49 (95% CI 0.36-0.66), NNH 19.5 (95% CI 13.5-35.3), I^2 = 0%. In all of the studies, only one serious adverse event occurred, involving the development of a brain abscess in a patient receiving amoxicillin-clavulanic acid.
2.	How precise are the results?	See above.
3.	Were the results similar from study to study?	Yes. See I^2 values above.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	The study seems to show a small overall benefit in cure rate when all time frames are considered together; 18 patients would need to be treated to cure one patient whose symptoms would not otherwise have resolved. However, the incidence of adverse effects was also higher in the antibiotic group, with a number needed to harm of 8. It is possible that the adverse effects (nausea, vomiting, abdominal pain, diarrhea, rash, etc.) may be as distressing (or more) than the symptoms of sinusitis.
2.	Were all patient important outcomes considered?	Yes. A thorough assessment was made of important outcomes, including cure rate, adverse effect rate, complication rate, use of other medications, feeling of illness, pain duration, illness duration, and activity restriction.
3.	Are the benefits worth the costs and potential risks?	No. As noted above, the meta-analysis revealed a NNT of 18 to effect cure in 7-14 days, with a NNH of 8. Treating 72 patients with antibiotics (for example) would result in 4 fewer people with continued symptoms of sinusitis at 7-14 days, with 9 additional patients suffering side effects (nausea, diarrhea, abdominal pain, rash).

Limitations:

1) **Variability in criteria used to diagnose rhinosinusitis, with only two of the ten studies requiring symptoms be present for 10 or more days (IDSA guidelines).**

2) **Variability in definition of "cured" with a variation in cure rate between studies of 30% to 74%.**

3) **Use of different interventions in the form of various antibiotics (penicillin V, doxycycline, amoxicillin), while the IDSA guidelines recommend amoxicillin-**

clavulanate given 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) **The odds ratios were calculated using a fixed effect model. Given the significant clinical and methodological heterogeneity in the studies, a random effects model may have been more appropriate.**

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

Bottom Line:

This meta-analysis of studies on the effect of antibiotics on acute bacterial sinusitis revealed a small benefit in the rate of "cure" with a NNT of around 18. This benefit may be counterbalanced by the increased risk of adverse effects, with a number needed to harm of 8. The included studies varied a great deal in terms of clinical criteria used to diagnose bacterial sinusitis, the antibiotic used, and the definition and timing of "cure." Few of the studies used a duration of 10 days or more in diagnosis, and only one study compared amoxicillin-clavulanate to placebo, despite recommendations in the IDSA guidelines. The inclusion of many patients with likely viral upper respiratory infections, and the failure to use appropriate antibiotics may have led to an underestimation of the treatment effect of antibiotics for this condition.