Acute Rhinosinusitis Treatment

To the Editor: Dr Garbutt and colleagues reported the results of a randomized, placebo-controlled trial of adults with rhinosinusitis comparing a 10-day course of amoxicillin (1500 mg/d) with placebo administered in 3 doses per day. They concluded that the 10-day course of amoxicillin did not reduce symptoms after day 3 of treatment compared with placebo. However, the study has methodological limitations.

First, the authors state that the inclusion criteria were based on the US Centers for Disease Control and Prevention’s expert panel diagnostic criteria for acute bacterial rhinosinusitis. The criterion “rhinosinusitis symptoms lasting for less than 7 days that had significantly worsened after initial improvement” was independently considered. However, in the original study by Lindbaek et al, this symptom was considered in combination with others to give a specificity of only 0.81 and a sensitivity of 0.66. Thus, selection bias may have occurred, with the enrollment of too many patients with less severe rhinosinusitis.

Second, the daily dose of amoxicillin in this study was 1500 mg. Although this same dose has been used in many studies, we consider this dose to possibly be inadequate according to clinical guidelines in Taiwan, which recommend a dose of 80 to 90 mg/kg/d in children and usually more than 2000 mg/d in adults. Higher doses of up to 90 mg/kg/d have been frequently used in pediatric studies. We are therefore concerned that this dose may have led to the insignificant differences.

Third, although there were no statistically significant differences at day 3 or at day 10, the modified Sinonasal Outcome Test-16 (SNOT-16) scores and reported symptom improvement did differ at day 7 (SNOT-16 score: 0.65 for amoxicillin group and 0.84 for control group; symptom improvement: 74% for amoxicillin group and 56% for control group; P = .02).

The results of the study by Garbutt et al may be applicable to some patients with acute rhinosinusitis, but we believe generalization of their study findings should be limited.

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To the Editor: Dr Garbutt and colleagues concluded based on a recent trial that treatment of patients with clinically diagnosed acute rhinosinusitis with amoxicillin for 10 days offered little clinical improvement over placebo. We have concerns that the study methods confound the conclusions.

First, the criteria used in diagnosing sinusitis, although promulgated by the Centers for Disease Control and Prevention, may be overly broad. Participants were diagnosed with sinusitis if they had maxillary pain or tenderness in the face or teeth, purulent nasal discharge, and rhinosinusitis symptoms lasting 7 days or more. It has been shown that the mean duration of an uncomplicated upper respiratory tract infection in young children is 6.6 to 8.9 days. Including patients who have symptoms for less than 10 days may result in including those who have an uncomplicated viral illness and are thus not likely to respond to antimicrobial agents.

Second, the antimicrobial used in this study was very low-dose amoxicillin (1500 mg/d). A maximum of 4.0 g in 2 divided doses was used for children. While the authors state that the prevalence of penicillin-resistant Streptococcus pneumoniae in their community is low, amoxicillin is not an effective therapy for non-typable Haemophilus influenzae that produce β-lactamase or for Moraxella catarrhalis (all of which produce β-lactamase). There is evidence that the role of nontypable H influenzae is increasing in upper respiratory infections since the...
introduction of conjugate pneumococcal vaccines. Based on this microbiology, the probability of a β-lactamase-producing bacteria in upper respiratory tract infections is high, which would result in amoxicillin failure.

Third, the decision to prescribe 3 or 4 different types of symptomatic treatments for all patients seems counterproductive to an effort to determine relief of symptoms during the early phase of clinical treatment and might mask a benefit of antibiotic.

Finally, this study was performed in adults. We have shown in a recent study that when children in the office setting are diagnosed with sinusitis using stringent clinical criteria, amoxicillin and clavulanate produce more clinical cures than placebo. Accordingly, the results are not generalizable to children.

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In Reply: Dr Sun and colleagues and Drs DeMuri and Wald raise concerns about our study: the diagnostic criteria may have failed to exclude those with a cold; the dose of amoxicillin may have been inadequate; a broader-spectrum antibiotic may have been indicated; and the use of symptomatic treatments was inappropriate.

Because our goal was to determine if the clinical guidelines for the management of acute rhinosinusitis effectively identified those who would benefit from antibiotic treatment, we used those diagnostic criteria. We think it is unlikely that most patients simply had a cold because the median symptom duration was 10 days (mean, 11.2 days) and all participants described their symptoms as moderate or severe, not improving, or worsening.

The dose of amoxicillin (1500 mg/d) was likely to be effective against S pneumoniae given the local prevalence of amoxicillin-resistant strains was less than 5%. The most recent US guidelines continue to recommend standard dosing of amoxicillin unless the endemic rate of amoxicillin-resistant S pneumoniae is unusually high (>10%).

We disagree with DeMuri and Wald’s assertion that the “probability of a β-lactamase-producing bacteria in upper respiratory tract infections is high.” First, most infections are viral. In a recent study, a bacterial pathogen was isolated from only 28% of adults with acute rhinosinusitis confirmed by x-ray. Second, the initial decrease in S pneumoniae and corresponding increase in nontypeable H influenzae and M catarrhalis associated with widespread use of the 7-valent conjugated vaccine for S pneumoniae quickly reversed with resurgence of serotypes of S pneumoniae not in the vaccine.

Concern about the increasing prevalence of β-lactamase-producing H influenza resulted in the recent recommendation to use amoxicillin and clavulanate over amoxicillin as empirical antimicrobial therapy for adults with acute rhinosinusitis, although it was acknowledged that the evidence to support this recommendation is weak. We believe careful use of the strict diagnostic criteria suggested in these new guidelines will be needed to avoid widespread and unnecessary use of amoxicillin and clavulanate.

We chose to evaluate the incremental benefit of antibiotics over symptomatic treatments because many patients would use these nonprescription products whether or not they were provided by the study (94% patients had used them before the index visit). We believe their use was unlikely to bias study findings because it was similar in both groups and there is little evidence of effectiveness. Although no children were included in our study, a prior study found no benefit from amoxicillin or amoxicillin and clavulanate for those with clinically diagnosed acute sinusitis.

The difference in disease-specific quality-of-life scores assessed at different time points is likely the most accurate way to assess meaningful clinical change. Using this approach, we found no statistically significant or clinically important change in SNOT-16 scores at days 3 and 10, but did identify a statistically significant difference of 0.19 units in SNOT-16 favoring amoxicillin at day 7. Because this difference in score was much less than the minimum change of 0.5 considered to be clinically significant, we disagree with Sun et al that this change was clinically important.

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1. Hickner JM, Bartlett JG, Besser RE, Gonzales R, Hoffman JR, Sande MA; American Academy of Family Physicians; American College of Physicians–American Society of Internal Medicine; Centers for Disease Control; Infectious Diseases Societies.
Exposure to Air Pollutants and Myocardial Infarction Risk

To the Editor: Dr Mustaﬁc and colleagues studied the association between exposure to air pollutants and the risk of myocardial infarction (MI) in a meta-analysis.1 It may not be appropriate to combine data from different studies because the increases in air pollutant concentrations and lag patterns differ in each study.

For increases in air pollutant concentrations, the authors selected 1 mg/m³ as a standard increase in pollutant concentration for carbon monoxide and 10 µg/m³ for other air pollutants when calculating relative risks.1 However, the studies used 0.9 mg/L, 0.1 mg/m³, and 0.23 mg/m³ for carbon monoxide and 7.5 µg/m³, 10 µg/m³, and 9.1 µg/m³ for particulate matter with an aerodynamic diameter of 10 µm (PM₁₀).1,2

For lag patterns, the authors selected single-day lags for ozone, carbon monoxide, and PM₁₀.1 However, the study by Bhaskaran et al3 used a lag of 19 to 24 hours. The authors should take into account all the different periods used in that study (1-6, 7-12, 13-18 and 19-24 hours) and the relative risks for single-day lags should be calculated by summing these 4 parameters.

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In Reply: We agree with Mr Huang and Dr Mao that there is heterogeneity among studies evaluating the effect of air pollutants on the risk of MI. The intent in performing a meta-analysis is, as far as possible, to reduce heterogeneity. We converted the pollutant concentrations from the various studies to the same units and chose the most frequently used values for the increase in pollutant concentrations: 10 µg/m³ for all pollutants except for carbon monoxide and 1 mg/m³ for carbon monoxide. This method is frequently used for meta-analyses.1

The studies were also heterogeneous in the lag patterns of exposure used. For the lag period for each pollutant, we chose the one used most frequently; most studies used lag exposures of 1 or multiple days. For carbon monoxide, the most frequently used lag pattern in selected studies was 0 days (0-24 hours). The study by Bhaskaran et al3 analyzed lags based on hours. We decided to choose the highest lag within 24 hours to remain as close as possible to the other studies with a lag of 0 days, which is the most conservative approach. Averaging relative risks using lag periods based on hours does not appear to be correct because many other parameters, such as distribution, are unknown. For PM₁₀, the most frequent lag periods were equally distributed between 0 and 1 day. Using 0 or 1 day did not change the overall results in terms of magnitude or significance.

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Trans-Fatty Acid Levels in White Adults

To the Editor: Dr Vesper and colleagues1 found that levels of plasma trans-fatty acids (TFAs) in a nationally representative sample of white adults studied in 2009 were lower than in a sample studied in 2000, which may be related to the US Food and Drug Administration’s requirements for TFA labeling in 2003. Some data in the study and their possible implications warrant further discussion.

The authors found a similar decrease in all 4 TFAs studied. Various TFA-containing foods have profiles with specific TFA content. For example, ruminant TFAs, derived from meat and dairy products, are mostly vaccenic acid and cis-9,trans-11 conjugated linoleic acid (C₉, T₁₁-CLA), while TFAs from industrial sources are mostly elaidic acid.2,3 Only 13% to 17% of vaccenic acid intake comes from hydrogenated plant oils.3 If the change in TFAs observed in the study is attributed solely to 2003 legislative changes, one would expect to have found decreases in all TFAs but with less alteration to vaccenic acid.

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