

The Interpretation section of the abstract in an article by Nicole Le Saux and associates<sup>1</sup> reads as follows: “Our results did not support the hypothesis that placebo was noninferior to amoxicillin (i.e., that the 14-day cure rates among children with clinically diagnosed acute otitis media would not be substantially worse in the placebo group than the treatment group).”

There seem to be several possible interpretations of what the authors might mean. Which is correct?

- Placebo is superior to amoxicillin.
- Placebo is equivalent to amoxicillin.
- Placebo is inferior to amoxicillin.
- Placebo is equivalent but not quite so.
- Our data are equivocal and more study is needed.

I not infrequently have difficulty divining the true meaning of sentences that contain double negatives.

#### Z. Kondziewski

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#### Reference

1. Le Saux N, Gaboury I, Baird M, Klassen TP, MacCormick J, Blanchard C, et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. *CMAJ* 2005;172(3):335-41.

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#### [Three of the authors respond:]

Barry Pless asks why a noninferiority trial was chosen over an equivalence trial for our study of the treatment of otitis media.<sup>1</sup> There are subtle but important differences between these types of trials in terms of both sample size requirements and interpretation. We were not aiming to demonstrate statistically significant superiority of amoxicillin over placebo, as this has already been well established. Our objective was to show that waiting to treat (which we simulated by using placebo) would not be substantially worse (within a 10% clinically acceptable difference in failure rates compared with amoxicillin) than giving amoxicillin to children present-

ing with acute otitis media. In recent terminology, this is known as a noninferiority trial. By contrast, an equivalence trial seeks to demonstrate that the outcomes of 2 interventions are not substantially different, without prespecifying which intervention will lead to better results. Hence, for our question, a noninferiority trial was appropriate.

In response to Mathieu Lemaire, we found the article by Gomberg-Maitland and associates<sup>2</sup> off the mark. The context of the Lemaire quotation was a 3-arm study (placebo, active control and experimental treatment), which was not the design of our study. Similarly, Lemaire's last remark (following the citation from Chen and colleagues<sup>3</sup>) is in reference to noninferiority trials with active control, which was not part of the design of our trial.

Brian Blakley brings up an important clinical point. Within the clinical definition for acute otitis media one has to meet the “time” criterion of abrupt onset of signs and symptoms of middle ear inflammation and middle ear effusion. This presentation is distinct from otitis media with effusion, which is a subacute or chronic problem, does not display inflammation and does not usually require antimicrobial therapy. We agree that potential overdiagnosis of acute otitis media is a common problem and must be addressed for each child. Even among children with clinically diagnosed acute otitis media, however, many (80% in this trial) will experience resolution of the problem without specific antimicrobial therapy.

Both Pless and Kondziewski found the double negatives in our interpretation baffling. We plead guilty to this charge, but note that equivalence and noninferiority trials are notoriously difficult to report. In our trial, for all children aged 6 months to 5 years, placebo was statistically inferior to amoxicillin. The CONSORT Group is presently working on a CONSORT extension for noninferiority trials.

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#### References

1. Le Saux N, Gaboury I, Baird M, Klassen TP, MacCormick J, Blanchard C, et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. *CMAJ* 2005;172(3):335-41.
2. Gomberg-Maitland M, Frison L, Halperin JL. Active-control clinical trials to establish equivalence or noninferiority: methodological and statistical concepts linked to quality. *Am Heart J* 2003;146(3):398-403.
3. Chen G, Wang YC, Chi GY. Hypotheses and type I error in active-control noninferiority trials. *J Biopharm Stat* 2004;14(2):301-13.

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## Guidelines for treating acute otitis media

In a recent commentary, R.A.M.J. Damoiseaux<sup>1</sup> misquotes the guideline for the treatment of otitis media that has been endorsed by the Guidelines Advisory Committee (GAC) of the Ontario Ministry of Health and Long-Term Care and the Ontario Medical Association.

The article states that the GAC “advises using antibiotics to treat any symptomatic episode of acute otitis media.” In fact, the GAC-endorsed guideline<sup>2</sup> also recommends watchful waiting, among other options. Furthermore, the GAC “guideline note” on this subject points to the degree to which clinicians underestimate the natural history of this condition and the marginal impact of antibiotics on outcomes.<sup>3</sup>

#### Dave Davis

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#### References

1. Damoiseaux RAMJ. Antibiotic treatment for acute otitis media: time to think again [commentary]. *CMAJ* 2005;172(5):657-8.
2. Linsk R, Blackwood A, Cooke J, Harrison V, Lesperance M, Hildebrandt HM. University of Michigan Health System. Guidelines for clinical care. Otitis media. Ann Arbor (MI): Regents of the University of Michigan; updated 2002 May. Available: <http://cme.med.umich.edu/pdf/guideline/om.pdf> (accessed 2005 Apr 28).
3. Otitis media: antibiotic therapy. Guideline notes. Toronto: Guidelines Advisory Committee.