

# CORRESPONDENCE

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## Flawed Australian CD Study Does Not End MAP Controversy

Dear Sir:

Although the paper by Selby et al<sup>1</sup> appears legitimate in its empirical reporting, its conclusions go far beyond its data. No attempt was made to culture or do polymerase chain reaction testing for MAP, either before or after treatment, so no conclusion can be drawn about the effect of their protocol on putative *Mycobacterium avium* paratuberculosis (MAP) infection. The MAP hypothesis of Crohn's disease is not tested by this study, nor resolved in anything except the author's assertions.

More troubling is the accompanying editorial, "Antimycobacterial therapy in Crohn's disease: game over?"<sup>2</sup> that at least has the good grace to include a question mark. The editorial itself acknowledges that "Subtherapeutic doses of rifabutin (450 mg), clarithromycin (750 mg), and clofazimine (50 mg) per day were used, whereas the optimal dose of rifabutin, clarithromycin, and clofazimine for treatment of *M avium* complex infections is 600 mg/d, 1000–2000 mg/d, and 100 mg/d, respectively." Not only were the doses low, but the clofazimine was delivered in a double encapsulated form that may well have hampered bioavailability. The fact that neither patients nor researchers could detect the effects of the antibiotics on skin, urine, tears, and teeth color also suggests suboptimal dosing; both clofazimine and rifabutin cause marked color changes at therapeutic doses.

The editorial lauds the work by Selby et al as a "landmark study" because it is "the largest randomized placebo-controlled antibiotic trial ever performed in [Crohn's disease]." Although both large sample size and placebo controls are always desirable, they cannot compensate for an inadequate treatment regime; one can hardly expect to test a possible medicine by giving it in insufficient quantities, but to large numbers of patients! The editorial goes on to note, as well, that "low-dose antibiotics may fail in the long run owing to the development of drug resistance." Thus, the Selby et al research has not only failed to demonstrate irrelevance of antimycobacterial therapy in the treatment of Crohn's disease, it may also have been bad clinical medicine.

If, 20 years ago, a research article purported to evaluate antibiotic treatment for *Helicobacter pylori*-induced gastric ulcer using doses widely known to be subtherapeutic, and then reported no significant effect, would—and should—GASTROENTEROLOGY have then editorialized "Antibiotic therapy in gastric ulcer: game over?" No way.

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1. Selby W, Pavli P, Crotty B, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology* 2007;132:2313–2319.
2. Peyrin-Biroulet L, Neut C, Columbel JF. Antimycobacterial therapy in Crohn's disease: game over? *Gastroenterology* 2007;132:2594–2598.

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## The Australian Antibiotic Trial in Crohn's Disease: Alternative Conclusions From the Same Study

Dear Sir:

I wish to comment on the recent article by Warwick Selby and others entitled, "Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease." In the conclusion of the abstract, the authors claim that the findings of their study do not support a significant role for *Mycobacterium avium* paratuberculosis (MAP). Had the authors identified which patients were infected with MAP, provided evidence of eradication of MAP infection, and shown that patients were still symptomatic, they could more convincingly claim that their study does not support a significant role for MAP in Crohn's disease.

The results of the Selby trial are encouraging (significantly better short-term remission rate in the treatment arm than the control arm) and suggest modifications of the current trial for future studies, which may lead to better outcomes. A blood culture method is now available to detect MAP infection in Crohn's patients<sup>1</sup> and could be used to assess MAP eradication in a properly designed controlled trial with more appropriate doses of the same drugs. The treatment of other nontuberculous mycobacterial infections such as *Mycobacterium avium* complex typically requires higher doses of clarithromycin, rifabutin, and clofazimine than were used in this trial.<sup>2</sup> Ciprofloxacin could be added to the current regimen as well.

The study design required an unrealistically high response rate for a positive outcome. Most of the current Crohn's therapies including infliximab would probably fail to show a positive outcome by this measure.

The Selby et al study was not designed to exclude the possibility of MAP reinfection following or during the course of therapy. MAP is present in viable form in pasteurized milk<sup>3</sup> and many of the study patients most likely encountered repeated challenges with the organism