

Probiotics for cow's milk allergy: Classification after intervention

To the Editor:

With interest we read the article by Pohjavuori et al¹ reporting on an increase in IFN- γ production by PBMCs derived from infants with cow's milk allergy (CMA) who were given *Lactobacillus rhamnosus* GG (LGG) in a randomized, double-blind study.¹ In this study, the infants with dermatitis were given LGG, a mixture of probiotics, or a placebo for a period of 4 weeks. Before the start of the intervention, serum IgE concentration (IgE) was measured, and skin prick tests were performed. A cow's milk (CM) challenge was performed 4 weeks after the intervention study to allocate the infants to 4 groups: CMA⁺atopy⁺, CMA⁺atopy⁻, CMA⁻atopy⁺, and CMA⁻atopy⁻. The main finding of this study was that IFN- γ production by PBMCs (IFN- γ) before treatment in the CMA⁺ children was significantly lower compared with the CMA-IgE⁺ children (Pohjavuori et al,¹ Fig 1). Furthermore, IFN- γ significantly increased in the CMA⁺ infants (highest increase) and in infants with IgE-associated dermatitis after 4 weeks of treatment with LGG only, but not after treatment with other probiotics (Pohjavuori et al,¹ Table I). The authors conclude first that the deficiency in IFN- γ in CMA⁺ infants is in line with a reduced IFN- γ secretion capacity found in infants who later develop atopic disease, as reported by others²; and second that LGG may provide beneficial T_H1-modulatory signals in infants with atopic disease.

Reading and discussing the study, an important question was raised that may be answered by the authors of this study. It is not clear to us why the CM challenge was performed after the participants were allocated to different treatment groups by randomization. It seems logical to perform CM provocation before allocation, and in our opinion, this is vital for a correct interpretation of the data shown in Table I (in Pohjavuori et al¹). The main reason for randomization is that the treatment groups are really different with respect to 1 factor only—namely, the treatment—and that other possible confounding factors are equally present in all groups. Proof of this may always be found in the baseline characteristics table, which was not shown in the article by Pohjavuori et al.¹ If participants are allocated to different groups after randomization is performed (as in this study with respect to CM challenge and IgE), it can no longer be assumed that different groups (the 4 groups mentioned) differ only with respect to treatment. Hence, in our opinion, it is questionable whether groups can be compared with respect to the outcome variable (ie, production of IFN- γ). Consistent with this line of reasoning, differences in baseline IFN- γ (Pohjavuori et al,¹ Table I: CMA-LGG vs CMA-placebo) may be a result of the fact the 3 groups may not have been equal at the start of the study. In our opinion, this may be a serious methodological error that may hamper interpretation of the data. If the aim of the study is to compare IFN-

γ before and after probiotic treatment between CMA⁺ and CMA⁻ infants, allocation of infants to different treatments by randomization must be performed within CMA⁺ and within CMA⁻ infants—ie, the correct procedure is first to establish disease categories and second to randomize for treatment within these categories.

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Reply

To the Editor:

Niers et al¹ argue that, when studying the immunological effects of probiotic bacteria, cow's milk challenge should have been performed before the infants were randomized to different treatment groups.² The main purpose of our study was to find out whether treatment with probiotic bacteria could improve the skin symptoms of infants with atopic eczema/dermatitis syndrome and cow's milk allergy (CMA). We took the opportunity to measure immunologic parameters of the patients during the planned clinical study. This randomized, double-blind, placebo-controlled study was performed between November 1999 and March 2002 in the Skin and Allergy Hospital of Helsinki University Central Hospital, Helsinki, Finland. Inclusion criteria were age younger than 12 months on entering the study; symptoms of CMA, with the obligatory symptom atopic eczema/dermatitis syndrome; and no regular use of probiotic bacteria (within 6 weeks before entering the study, longer than 1 week).³ In a clinical study, according to ethical guidelines, it was obligatory to eliminate the suspected allergen (cow's milk) and start a proper elimination diet and skin treatment. Niers et al¹ suspect that the 3 treatment groups (*Lactobacillus* GG, a mixture of 4 probiotics, or a placebo) may not have been equal at the start of the study. However, of 230 infants who completed the study, 80 received *Lactobacillus* GG,