

Letter to the editor

Probiotic research: learn from the evidence

Rigorous scientific thinking is required both in the assessment of current evidence, and in the search for future directions—and probiotic research is no exception. A recent editorial (1) showed some inaccuracies in assessment of the current knowledge of probiotics in allergic disease, which may hamper future research; the interested reader is advised to refer to the original reports (2–4).

For example, the editorial presented the first probiotic study in allergic disease as a double-blind placebo-controlled comparison between breastfed infants and those fed with hydrolyzed milk formula; such a design is impossible, even technically. In fact, this study was a randomised double-blind comparison of two groups; infants with atopic eczema, diagnosed according to criteria currently recommended for the eczema/dermatitis syndrome (AEDS) (5), and challenge-proven allergy to cows milk. These infants were fed either an extensively hydrolyzed formula or an extensively hydrolyzed formula containing *Lactobacillus rhamnosus* GG (ATCC 53103), while breastfed infants with AEDS and healthy infants were reported for reference. Picking out arbitrary SCORAD scores of mild eczema—without comparison to baseline—distracts the reader unnecessarily from the principal findings: the control of intestinal inflammation, as indirectly assessed by feces levels of tumor necrosis factor- α (pg/g at 0 and 1 months); 632 (126–1880) and 494 (147–1009) in the placebo group and 709 (91–1131) and 34 (19–103) in the probiotic group; and distinct alleviation of the subjective symptoms and extent of eczema achieved by probiotics, but not by placebo. Such distortion of SCORAD data was evidently not possible in the case of a second study (3) that evaluated exclusively breastfed infants at weaning; the median SCORAD score was 16 (7–25) at enrolment, and 13.4 (4.5–18.2) 2 months later in the placebo group, 1 (0.1–8.7) in infants receiving *Lactobacillus* GG, and 0 (0–3.8) in those receiving *Bifidobacterium lactis* Bb-12; as the paper in question (3) was not cited in the editorial (1).

The editorial states that a rationale for the use of probiotic preparations stems

from several in-vitro and in-vivo studies of immune effects, some of which diverge from those characteristic of the atopic constitution. Interestingly, some of these reports assess the *development* of expression of this condition, and some assess fully *established* allergic disease; there are significant overlaps in the responsiveness of type 2 T-helper cells (Th2) and the concentration of IgE antibodies at an early age in infants with and without later expression of atopy (6–8). In fact, an age-dependent decline in Th2 response during the early postnatal period in children not expressing atopy and a converse pattern in children expressing atopy has been suggested (7). Increased production of Th2 cytokines, and thereby IgE antibodies, could result from defective immune regulation associated with the development of allergic disease, rather than a direct cause of such a development; we simply have not yet identified the regulator.

The principal confusion, however, concerns the mode of documenting intestinal colonization by probiotics. First, the pattern of adherence and transient colonization for *Lactobacillus* GG has been extensively studied and documented. Transient colonization has been reported especially for infants (2, 9–11) with doses selected for clinical studies. Significantly, these studies (9) were carried out before the strain became available to the public; all controls were negative. Thus, compliance in the first studies could be assessed by determining the fecal recovery rates of *Lactobacillus* GG (2, 10). Second, colonization has not been proven mandatory for probiotic effect, and most studies only refer to fecal cultures or other fecal assays. The microbial populations in different parts of the gastrointestinal tract are not necessarily reflected in fecal analysis. Efficacy/inefficacy verified in human clinical studies is more important than plain “colonization”. This is acknowledged in the definition of probiotics as “a viable microbial food supplement which beneficially influences the health of the host”, as redefined by a multidisciplinary expert group of ILSI (International Life Sciences Institute) Europe (12). Unfortunately, the editorial in question employs an

outmoded definition of probiotics as “live microbial feed supplements which beneficially affect the host animal by improving the intestinal microbial balance” (13); this definition is misleading and neglects more than a decade of research that aimed to improve understanding of probiotic action.

Furthermore, it is simplistic to assume that the target of administering lactobacilli (such as *Lactobacillus* GG) is enhancement of *Lactobacillus* spp., as suggested by this editorial. Significant crosstalk prevails between bacteria, and no proof exists that lactobacilli *per se* are health-promoting. For example, although bifidobacteria appear to be important (14, 15), our recent data indicate that allergic infants have different species of bifidobacteria compared to healthy infants (16, 17), carrying a different immunoregulatory potential (18). Thus, the effect appears to be strain-specific, or at least species-specific—not genus-specific.

We recently (19) defined probiotics as “specific live or inactivated microbial cultures that have documented targets in reducing the risk of human disease or in their nutritional management”—the aim being to encourage further well-controlled studies in different populations. What have we learned on probiotic research in allergic disease so far? Bifidobacteria appear to be important in reversing the expression of atopy (14, 15); *Lactobacillus rhamnosus* GG are effective in prevention of AEDS (4), but not cows’ milk allergy (20); specific strains of *Lactobacillus* and *Bifidobacterium* are promising in the treatment of infants with AEDS and cows’ milk allergy (2, 3).

Further reports are in progress about probiotic-induced changes in the composition of gut microbiota; such reports will enhance our understanding of many unresolved issues in the development of allergic diseases (21).

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