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In a nutshell

Probiotic organisms can enhance immune function and help prevent or treat allergic disease, such as eczema. Clinical evidence is not definitive, but sufficient to warrant active consideration of its clinical use.

Probiotics may be particularly effective for atopy in infancy, or when given to the mother during a pregnancy with high risk for producing an atopic infant.

Probiotics, immunity and allergy

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NUTRITION RESEARCH REVIEW

Study 1: Probiotics, eczema and immune function

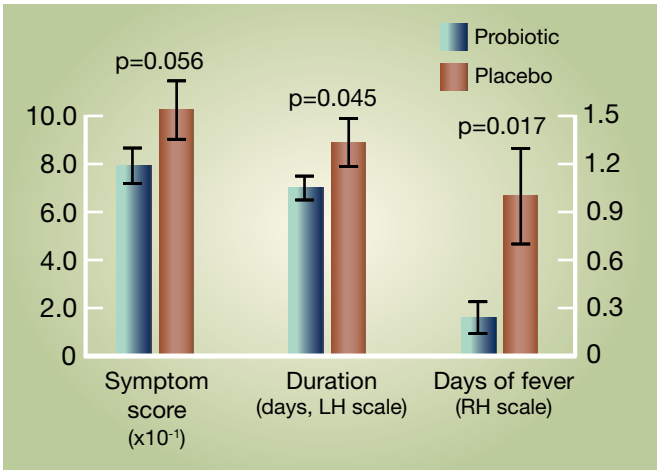
A new Australian trial has looked at the effect of probiotics in children with eczema.

Subjects and method: RCT of 56 toddlers (mean age 11 months) with moderate to severe atopic dermatitis given placebo or probiotic (10^9 *Lactobacillus fermentum* twice daily for 8 weeks) and followed up for a further 8 weeks after treatment. Interferon responses to common allergens were tested in peripheral blood mononuclear cells of 53 of the subjects.

Results: The probiotic but not the placebo group had significant improvement in median severity (fall in SCORAD score of 18.2 points at 8/52 and 17 points at 16/52, p=0.03). Comparison between groups did not quite reach statistical significance (p=0.06), and parents were no more likely to report improvement in the probiotic than placebo group. However, significantly more children in the probiotic than the placebo group had a better score at the end than the beginning of the study (92% vs 63%, p=0.01).

There were statistically significant increases in IFN-γ response to both *Staphylococcal* SEB toxin and mitogen (PHA) in probiotic but not in placebo group at 16 weeks (p<0.05). Whilst the difference between groups was not significant in either case, the increase was correlated with clinical improvement (in SCORAD scores, r=0.445, p=0.026). There was a significant difference between groups in regard to TNF-α responses to heat-killed bacteria (p<0.05). There were no differences in any of the other interferon or cytokine responses tested nor for any of the common specific allergens (other than a fall at 8 weeks in IL-13 response to egg ovalbumin in the probiotic group only, p=0.008).

Graph: Common cold outcomes: probiotic vs placebo (Study 2)



Refs.: Weston S. et al. Effects of probiotics on atopic dermatitis: a randomised controlled trial. Arch Dis Child. 2005 Sep;90(9):892-7. and
Prescott SL. et al. Clinical effects of probiotics are associated with increased interferon-gamma responses in very young children with atopic dermatitis. Clin Exp Allergy. 2005 Dec;35(12):1557-64.

Study 2: Probiotics and the common cold

A recent German trial assessed the impact of probiotics on the common cold.

Subjects and method: RCT of 479 healthy adults all supplemented with multivitamins and minerals plus either placebo or probiotic (*Lactobacillus gasseri* and

Bifidobacterium longum) for at least 3 months during two winter/spring seasons.

Results: The probiotic group compared with placebo had significantly less days with the cold, less days with fever and lower symptoms - **see Graph**. In a sub-set of subjects those on probiotics had significantly greater enhancement of cytotoxic plus T- suppressor cells (CD8+).

Ref.: de Vrese M. et al. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. Clin Nutr. 2005 Aug;24(4):481-91.

Comments

These two new Studies are only a small sample of many trials that have been conducted on probiotics over the last 18 months. This has become a `hot topic' !

This issue focuses on immune and allergy applications. **Tables 1 and 2** (page 3) summarise some relevant human clinical trials [1-35]. As can be readily seen, quite a few are recent and, although some have small subject numbers and negative or equivocal outcomes, the trend is clearly towards positive outcomes. Probiotics can reduce allergic disease severity and this is associated with positive changes in immune function and/or inflammatory mediators.

The potential clinical benefits of such immune-stimulating and anti-inflammatory effects are not restricted to atopic disorders. A new Australian trial, for example, found that probiotics reversed a defect in interferon-γ secretion found in fatigued athletes [36]. Probiotics can reduce the negative impact of the pro-inflammatory cytokines TNF-α and IFN-γ, something which may well be relevant to inflammatory bowel disorders [37, 38] (covered in our next issue #247) . Enhancing gut immunity could also help prevent bacterial translocation, something which can lead to systemic infection, for example after gut surgery [25].

New Study 2 found a positive effect of probiotics in lowering morbidity from the common cold, along with evidence of immune stimulation. Immune effects may explain the results of another recent trial in which workers at a Finnish factory given probiotics had significantly less days off work from respiratory and gastrointestinal illnesses [39]. (Although giving probiotics to children in Israeli child care centres resulted in less diarrhoeal but no difference in respiratory illnesses [40]).

How might this work? There are a number of possible mechanisms. One is that, by altering the balance of bowel flora, probiotics both reduce the load of other potentially allergy-provoking pathogenic organisms and increase the degradation of allergens in the gut [41, 42].

Another possible mechanism is through probiotics enhancing gut intestinal defences and decreasing abnormal gut permeability. This would lessen the likelihood of food allergy [43, 44], and there is evidence that this occurs clinically [21, 37], although probiotics may not be sufficient to correct abnormal gut permeability in more extreme situations such as burns or trauma [45, 46].

A more likely explanation involves what has sometimes been called the `hygiene hypothesis'. Clinicians used to advise parents to maintain infants at risk of atopic disease in a `clean' allergen-free environment from as early in life as possible. But we now realise that a certain amount of allergen exposure is essential for the paediatric immune system to `learn how to live in the real world' [47]. Early life allergen exposure helps the immune system in pattern recognition and to create a balance of T-helper cells [47-49]. There is evidence that infants who suffer from (or will develop) allergic disease have imbalanced bowel flora [47]. Probiotics can affect T-helper cell balance and responsiveness [42, 50, 51] and may influence the so called `toll receptors' involved in allergen pattern recognition [47, 52]. As Table 2 shows, probiotics can also influence a number of parameters of cytokine release and balance, which are involved in immune response and allergy.

Some technical details of probiotic supplementation need further clarification. The organisms are not all alike in their clinical effects. Whilst a majority of published trials have used various *Lactobacillus* species, only around 10% of these species so far tested have proven to have strong immunosupportive effects [53] and it may be that other organisms (such as certain *Bifidobacteria*) or combinations of organisms will be equally or more effective in certain situations [54]. We certainly do not yet have anything like a `probiotic pharmacopeia' for specific clinical indications [55].

Survival of the organisms to their site of action is obviously crucial, and whilst evidence on this point has so far been reasonably encouraging (e.g. [56]) good manufacturing and labelling standards are essential [57, 58], particularly as use of probiotics in infant formula and `nutraceutical' foods for allergy increases [58]. We will be addressing the question of probiotic safety in next week's issue (#247).

Overall, we think the evidence supporting the use of probiotics to prevent and treat atopic disease, whilst not definitive, is good enough to warrant active consideration of its use by clinicians. Probiotics may be particularly effective in infancy, or even given to the mother during a pregnancy at high risk for producing an atopic infant.

Table 1: Randomised human trials on probiotics for allergic disease

Year	Condition	n=	Subjects	Design	Organism		Result	Ref.
2005	Eczema	48	Children	RCDBT	Prebiotic ± *Lactobacillus*	SCORAD	Decrease of 39% with synbiotic and 47% with probiotic (both p<0.001)	1
2005	Pollen allergy	23	Patients	RCSBT	*Lactob.*	Various	Isolated decreases	2
2005	Allergic rhinitis	90	Patients	RCDBT	Live or heat-killed *Lactob.*	Frequency and level of bother	Decrease (p< 0.0001, p = 0.004)	3
2005	Eczema and CMA	235	Infants	RCDBT	*Lactob.* Or probiotic mix	Inflammatory indices	Increase in low-grade inflammation	4
		230				SCORAD	Decrease in IgE-sensitized infants only, p=0.036	5
		230				Faecal immune markers	IgA higher (p=0.014), TNF-α lower (NS)	6
2005	Allergic rhinitis	10	Adults	Open	*Bacillus clausii* spores	Cytokines	Decrease in IL4, increase in IFNγ TGF-ß	7
2005	Allergic rhinitis	49	Adults	RCDBT	*Lactob.*	Symptoms, blood parameters	Nasal symptoms decreased (p<0.05), blood parameters: NS	8
2004	Eczema	41	Children	RCDBT	*Lactob.*	GIT symptoms	28% decrease (p=.002)	9
2004	Allergic rhinitis	80	Patients	RCDBT	*Lactob.*	Frequency and level of bother	Decreased (p=0.037 and p=0.022)	10
2003	Eczema		Children	RCDBT	*Lactob.* Mixture	SCORAD	Improvement, esp. in those with +ve prick test and elevated IgE	11
2003	Eczema and CMA	35	Infants	RCDBT	Live or heat-killed *Lactob.*	SCORAD	Improvement only from live organisms	12
2002	Allergic rhinitis	13	Patients	RCT	Yoghurt	Symptoms, mucociliary transport, immune parameters	Improvement, less IL-4, more IFN-γ	13
2002	Eczema	21	Infants	RCT		IgE, E.coli count	Serum IgE correlated with E.coli count, which decreased with probiotics	14
2002	Pollen allergy	36	Patients	RCDBT	*Lactob.*	Symptoms	No effect	15
2002	Eczema	62	Mother-breast-fed infant pairs	RCDBT	*Lactob.*	Risk of infant eczema in first 2 yrs, anti-inflamm. TGF in breast milk	29% less risk (p<0.01), more TGF-ß2	16
2001	Eczema	132	Children (of mothers with F/H of atopy, both mothers and children given intervention	RCDBT	*Lactob.*	Risk of eczema	Risk halved (p<0.05)	17
2000	Eczema	9	Children	RCDBT	*Lactob.*	IL-10 production	Increased (p< 0.001)	18
2000	Eczema	27	Infants	RCDBT	*Bifidob.* or *Lactob.*	SCORAD and inflammatory mediators	Clinically better (p=0.002), reduced mediators	19
1997	Asthma	15	Adults with mild asthma	RCDBT	*Lactob.*	Immune indices, symptoms	No signif.changes	20
1997	Eczema with CMA	27	Infants (formula weaned	RCDBT	*Whey formula* ± *Lactob.*	Clinical score, α1-antitrypsin and fecal TNF-α levels	Improved (p<0.05). Inflamm.mediator levels decreased, (p≤0.03).	21

Eczema=atopic dermatitis | CMA=cows milk allergy | DB= double blind, SB=single blind, RCT=randomised controlled trial, | NS= not signif.

Table 2: Randomised human trials on probiotics and immune function

Year	n=	Subjects	Design	Organism	Outcome parameters	Result	Ref.
2006	33	Young women	RCDBT	Yoghurt ± probiotic	T-lymphocyte ratios, mononuclear cytotoxicity	CD3+, CD16+, CD56+ increased (all p<0.002) in probiotic only, but NS comparison with control	22
2005	99	Smokers	RCDBT	*Lactob.* In fermented milk	Natural killer cell activity	Significantly increased	23
2004	54		RCT	*Lactob.* In fermented milk	Immune cell function	Increased monocyte oxidative burst capacity and NK cell tumoricidal activity	24
2004	22	GIT elective surgery patients		*Lactob.*	GIT mucosal Ig's	Higher mucosal IgM (p=0.02)	25
2004	136	Students under exam stress	RCDBT	*Lactob.*	CD cell numbers	Increase in CD56 in probiotic group, c.f. fall in controls (p<0.05)	26
2004		Children with CMA and IgE-associated dermatitis	RCDBT	*Lactob.*+ mixture	IFN-γ, IL-4, and IL-5 production on CD4 lymphocytes	Increased IFN-γ production (p<0.05)	27
2002	43	Healthy elderly	RCDBT	Nutritional supplement + *Lactob.*	Immune response to vaccination	No treatment effect	28
2001	33	Healthy elderly	RCDBT	*Bifidobacterium lactis*	Immune cell activity	Increased CD4+, CD25+ and natural killer cell activity	29
2001	52	Healthy middle aged	RCDBT	*Lactob.*	Immune cell activity	Increased natural killer cell activity	30
2000	25	Healthy women	RCT	Yoghurt	Immune cell activity	No treatment effect	31
1999	30	Malnourished children	RCT	*Lactob.*	Lymphocyte function and proliferation		32
2000	25	Healthy elderly	RCDBT	*B. lactis*	Immune cell activity	Increased (p<0.05)	33
1998	20	Healthy men	RCDBT	*Lactob.*	Immune cell activity	No treatment effect	34
1997	20	Atopic adults	RCT	Yoghurt	Immune cell activity	No treatment effect	35

DB= double blind, SB=single blind,
RCT=randomised controlled trial,

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