The Use of Probiotics in the Primary Prevention of Atopic Dermatitis: A Systemic Review of the Literature in Light of the Hygiene Hypothesis

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INTRODUCTION:
Atopic dermatitis (eczema) is a type 1 hypersensitivity reaction that is common in infants and young children, with incidence increasing in the Industrialised world. Based on epidemiological evidence, the hygiene hypothesis proposes that reduced exposure to infective organisms is associated with immune dysfunction (Seroni *et al*., 2010). Caesarean sections, lack of breast feeding, lack of exposure to micro-organisms and parasites in early life, widespread use of antibiotics and a more hygienic or clean environment is closely associated with the development of atopic dermatitis. This is explained by type 2 helper T-lymphocyte (Th2) cell dominance and a reduction in T-regulatory (Treg) cell function due to lack of stimulation via infectious organisms (Boon *et al.,* 2006; Seroni *et al*., 2010) (Fig. 1). Furthermore, altered gut microbiota and dysbiosis due to similar risk factors has been implicated in the development of atopic dermatitis (Kranich *et al*, 2011). There has been recent interest in the use of probiotics in the prevention of atopic dermatitis. The terms atopic dermatitis and atopy are incorrectly used interchangeable in much of the literature, and this study will follow this protocol.

METHODS:
Electronic research databases were systematically searched using relevant keywords. Articles were limited to randomised, double blind placebo controlled papers that specify the probiotic strains, the dosages and protocols used.

RESULTS
In total, 12 studies were identified. Of these, 2 studies utilised pre-natal exposure only, 3 studies utilised post-natal administration to infants, and 7 studies that administered probiotics both pre- and post-natally. The probiotic strain, dosage and time of intervention varied greatly, as did the results. The results are summarised in table 1.

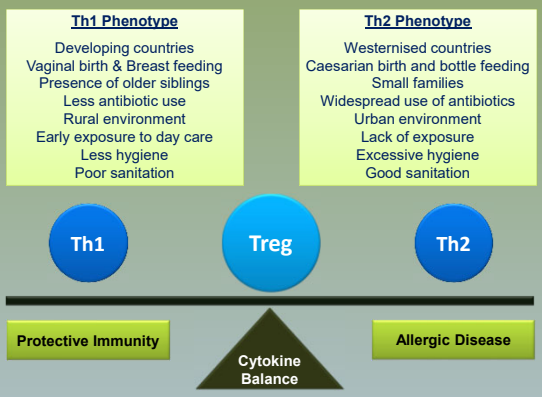

Figure 1: The hygiene hypothesis is based on the Th1/Th2 cytokine relationship. Infants are born with a dominant Th2 phenotype, and require interaction with beneficial (microbiota) and pathogeneic organisms in order to stimulate the Th1 immune response. Failure to do so is associated with a Th2 dominance, which may result in allergic disease, autoimmunity and cancers. Treg cells play a central role in regulation and immune suppression.

Table 1: A comparison of placebo controlled studies assessing the efficacy of probiotics in the prevention of atopic dermatitis (eczema). The studies identified show a high degree of variation in terms of strains used, dosages and results. CFU = colony forming units; n = number; wk = weeks; mo = months; yr = years.

Strains	Dosage (CFU/day)	n	Prenatal Duration	Postnatal Duration	Follow Up	Results	Reference
Lactobacillis rhamnosus	1.8×10^{10}	250	4 wk	Nil	1 yr	No beneficial effects in prevention of eczema	Boyle *et al.,* 2011
Bifidobacterium bifidum *Bifidobacterium lactis* *Lactobacillus acidophilus*	1.6×10^{9} 1.6×10^{9} 1.6×10^{9}	112	4-6 wk	6 mo. (mother)	1 yr	Some benefit in high risk infants; No difference in IgE levels of food allergen sensitisation	Kim *et al.,* 2009
Lactobacillus F19	1×10^{8}	179	Nil	13 mo. (infant)	13 mo.	Decreased incidence of eczema Increased Th1/Th2 ratio; No difference in serum IgE	West *et al.,* 2009
Lactobacillus acidophilus	3×10^{9}	231	Nil	6 mo. (infant)	2 yr	No benefit	Taylor *et al.,* 2007
Lactobacillus rhamnosus	5×10^{9}	154	Nil	1 mo.	1 mo.	Study showed improvement of IgE associated atopic eczema in a treatment design (not prevention)	Viljanen *et al.,* 2005
Lactobacillus reuteri	1×10^{8}	188	4 wk	12 mo. (infant)	2 yr	No difference in incidence or severity Reduced IgE associated eczema	Abrahamsson et al., 2007
Lactobacillus rhamnosus spp; *Lactobacillus rhamnosus LC;* *Bifidobacterium breva;* *Proprianum bacterium*	5×10^{9} 5×10^{9} 2×10^{8} 2×10^{9}	1223	2-4 wk	6 mo. (infant)	2 yr	Decreased incidence of atopic eczema and IgE associated disease No effect on all types of allergic disease Lacto- and bifidobacteria more frequently colonised infants	Kukkonen *et al.,* 2007
Bifidobacterium bifidum *Bifidobacterium lactis* *Lactococcus lactis*	1×10^{9} 1×10^{9} 1×10^{9}	156	6 wk	12 mo. (infant)	2 yr	Decreased incidence of eczema Lactococcus more frequently colonised infants	Niers *et al.,* 2009
Lactobacillus rhamnosus; or *Bifidobacterium animalis*	6×10^{9} 9×10^{9}	474	5 wk	24 mo. (infant)	2 yr	Decreased incidence with L. Rhamnosus, but not with B. Animalis for eczeman, but not atopy	Wickens *et al.,* 2008
Lactobacillus rhamnosus; *Bifidobacterium animalis;* *Lactobacillus acidophilus*	5×10^{10} 5×10^{10} 5×10^{9}	415	4 wk	3 mo.	2 yr	Decreased incidence of atopic eczema; No difference in atopic sensitisation or asthma	Dotterud *et al.,* 2010
Lactobacillus rhamnosus	2×10^{10}	159	2-4 wk	6 mo.	2, 4 & 7 yr	Decreased incidence with no difference in severity; No difference in atopic sensitisation	Kalliomaki *et al.,* 2007
Lactobacillus rhamnosus	1×10^{10}	105	4-6 wk	6 mo.	2 yr	No difference in incidence or severity; Associated with increased rates of bronchial wheezing	Kopp 2*et al.,* 2008

CONCLUSIONS:
Based on the studies identified, *Lactobacillus rhamnosus* supplemented to pregnant mothers and to infants from birth to 6 months in dosages from 5 to 10 billion colony forming units (cfu) per day has shown the most beneficial results in primary prevention of atopic dermatitis in infants. Pre-natal supplementation shows little benefit and should not be recommended. Numerous studies showed a reduction in incidence of eczema, but not necessarily atopy and IgE sensitisation. It is therefore difficult to determine if any positive impact is based on the hygiene hypothesis in terms of allergic disease, although West (2009) showed benefit based on this model. It is recommended that future studies focus on larger trials to refine a beneficial protocol for prevention. Furthermore, studies should include the impact of the supplementation on the microbiota of the infants, and the possible mechanisms of benefits based on the hygiene hypothesis model.