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Probiotics and Atopic Dermatitis

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1. Introduction

The term "probiotic" was only coined starting from 1953 and means "for life" ("pro = for" and "bios = life") as opposed to "antibiotics". Yet, the related concept dates back to the early 1900s when Tissier and Metchnikoff pioneered the notion that not all bacteria are detrimental and that some may even be ingested for benefit of health and longevity (Tissier, 1906; Metchnikoff, 1908). Since then, over 9000 articles and 700 clinical trials have been devoted to document and unravel the beneficial effects attributed to probiotic strains and the mechanisms of action that may be involved. The health benefits attributed to probiotics are numerous (Nomoto, 2005; Nova et al., 2007; O'Hara and Shanahan, 2007; Parvez et al., 2006; Salminen et al., 2005; Sanders, 2008; Santosa et al., 2006) but the level of proof supporting them is highly variable depending on the benefit and more importantly on the studied strain. In view of the large diversity and the high number of probiotic candidate strains it is important to stress that most observations are strictly strain specific which means that data obtained on a given strain may not be extrapolated to all strains belonging to the corresponding bacterial species and genus. This renders a global analysis of the field quite difficult and general conclusions often lack accuracy.

2. Human gut microbiota

The adult human gastro-intestinal tract (GIT) houses about 10^{14} microbial cells, that outnumber by a factor of 10 the number of cells that compose the human body. This complex microbiota contains over 1000 bacterial types whose number and composition vary along the GIT as a consequence of the different biochemical conditions in the intestine, nutrient availability, age and health status of the host. Of note, the corresponding pool of genes (microbiome) is 150 times larger than the human genome (Eckburg et al., 2005). For this reason, the gut microbiota is sometimes referred to as an organ by itself. It is well established today that this complex microbial community plays an essential role in health and well being. Research conducted with germ-free or gnotobiotic (*i.e.* germ-free animals that were colonized by known bacteria) rodents has unambiguously demonstrated that even if germ free animals are viable when housed in specific conditions and fed with a very nutritious diet, the gut microbiota plays a critical role for normal growth and development (Kelly et al., 2007; Sjogren et al., 2009).

The GIT of mammals is sterile at birth but it becomes rapidly colonized by maternal and environmental bacteria during the delivery. The successive installation of bacterial species

has been well studied (Fanaro et al., 2003; Salminen and Gueimonde, 2005) and was shown to be influenced by several factors such as the mode of delivery and the neonate's diet (Laubereau et al., 2004; Martindale et al., 2005; Negele et al., 2004; Sicherer and Burks, 2008; Zutavern et al., 2006). The next critical phase of bacterial colonization occurs around weaning, when new foods are progressively introduced in the infant's diet. A more complex microbiota is then established that evolves towards the typical adult one over the following years. The progressive bacterial population of the infant intestines has been shown to be of prime importance in the development of a mature gut ecosystem and a functional mucosal immune system. The GIT corresponds to a huge mucosal surface (close to 200 m² in the adult) that is constantly challenged by external factors such as food components, microbes, toxic compounds, chemicals *etc.* and as such is one of the principal point of entry of pathogens. The GIT thus developed into a sophisticated organ that is able to discriminate between harmful and harmless agents, with an immune system that rapidly mounts defensive responses against infectious microbes while being able to tolerate food or self antigens. This exquisite level of regulation is progressively established as a result of bacterial stimulus including gut microbial colonization in early stages of life. The "hygiene hypothesis" postulates that the lack of adequate microbial challenge linked to modern living conditions in westernized countries is at the origin of the increasing prevalence of chronic immune dysfunctions such as inflammatory bowel disease and allergy (Ege et al., 2008; Schaub et al., 2006; Waser et al., 2007). This postulate is the rationale behind the use of probiotic microorganisms to promote, restore or maintain a healthy status in humans and animals.

3. Probiotics and health related benefits

Probiotics have been defined by a FAO/WHO expert group as « live microorganisms which when administered in adequate amounts confer a health benefit on the host » (2001). This is the most widely accepted definition even if others - that are relatively similar- can be found in literature. This definition implies that the microorganisms are not restricted to bacteria, and yeasts such as *Saccharomyces boulardii/cerevisiae* for example have been studied for their health promoting properties. Typically *S. boulardii* probiotic preparations are commercialized as over the counter (OTC) products to fight diarrhea. Yet, most of the probiotic research has been conducted with lactobacilli and bifidobacteria, even though one strain of *Escherichia coli*, *E. coli Nissle* 1917, and a few strains of *Enterococcus* and *Bacillus* have also been well studied during the last decades. Today, the search for new health promoting microorganisms is extending beyond bacteria isolated from humans to strains originating from fermented food and feed products such as *Pediococcus, Propionobacterium* and *Lactococcus spp*. The bacterial genera *Lactobacillus, Enterococcus, Pedicoccus, Propionibacterium, Streptococcus* and *Lactococcus* belong to the family of lactic acid bacteria (LAB) which - as indicated by their name - are able to rapidly transform fermentable carbohydrates in substantial amounts of lactic acid, eventually accompanied by acetic and propionic acid, and butyrate. The capacity of lowering the environmental pH and thus creating an unfavorable milieu for specific pathogens is at the origin of the use of LAB for the preparation and preservation of fermented food and feed products since time immemorial. As a consequence, several LAB species have a "generally-recognised-as-safe" (GRAS) status in the food industry due to their long history of safe human consumption. Several species are also part on the endogenous mammal microbiota and can naturally be found in the oral, intestinal and urogenital tracts of healthy individuals. The number of specific genera of LAB

varies along the gastro-intestinal ecosystem and lactobacilli are typically dominant members of the human vaginal microbiota where they play a key protective role against infections (Falagas et al., 2007).

The health benefits addressed by probiotic research are ranging from their anti-microbial properties to the impact probiotics may have on the host immune system and gut barrier, and on the metabolism and composition of the endogenous microbiota, and as a consequence on the host physiology. The applications are nowadays extending to extra-intestinal sites such as the skin, the oral cavity, the urogenital tract and importantly the gut-brain axis. Targeted diseases include bacterial and viral infections, chronic immune disorders such as allergy, inflammatory bowel disease and autoimmune diseases, irritable bowel syndrome, energy and weight management, mood disorders, stress and even psychological disorders such as autism (Asahara et al., 2001; Bin-Nun et al., 2005; Brenner et al., 2009; Carroll et al., 2007; Chapat et al., 2004; Cryan and O'Mahony, 2011; Dani et al., 2002; Iovieno et al., 2008; Madsen et al., 2001; Zareie et al., 2006). From an experimental point of view, the major challenge is to select the most appropriate candidate probiotic strain(s) to reach the selected aim. Therefore, a series of *in vitro* and *ex vivo* assays are used before testing a limited number of strains in animal models mimicking the human disease. Even if time consuming this preclinical research is aiming at facilitating the clinical studies that are mandatory to support the health claim that may be attributed to a probiotic strain. In the past several selection criteria have been applied such as origin of the strain, acid and bile resistance, adhesion to epithelial cells *etc.*, which today rather serve for characterization of candidate probiotic strains (Mercenier et al., 2008). Nowadays, safety and stability of the strains are considered as the main criteria that may lead to exclusion of strains for further applications (Delgado et al., 2008; Grimoud et al., 2010; Gueimonde and Salminen, 2006; Kalliomaki et al., 2010; Niers et al., 2007).

4. Probiotics and immune modulation

Probiotics are able to interact at different levels with the host intestinal ecosystem. They may exert effects in the gut lumen via the release of soluble active compounds (metabolites, enzymes), by co-aggregation with pathogens and by intensive cross-talk with the endogenous microbiota (Ait-Belgnaoui et al., 2006; Boirivant and Strober, 2007; Ewaschuk et al., 2008; Haller et al., 2001). They are also known to interact with the intestinal epithelial barrier and its associated mucus, and to initiate immune signaling (Vesterlund et al., 2006; Ohland and MacNaughton, 2010). Specific probiotics are able to exert an effect beyond the gut, influencing the systemic immune system as well as other cell and organ systems, such as liver and brain. For example, certain strains were shown to interact with the enteric nervous system and as such to trigger the gut-brain axis (Cryan and O'Mahony, 2011; Duncker et al., 2008).

Even though we are far from having identified all active compounds that may mediate these interactions, it has been undoubtedly established that bacterial cell surface associated molecules are recognized by the gut immune system. The cell wall of gram-positive bacteria – to which most probiotic bacteria belong – differs from that of gram-negative bacteria by a higher content in peptidoglycan, by the absence of lipopolysaccharides (LPS) and presence of a variety of lipoteichoic acids (LTA) or wall teichoic acids (WTA) instead. In both gram-positive and gram-negative bacteria the cell surface may also be decorated by exopolysaccharides (EPS) and/or glycosylated proteins. Altogether these cell surface

components correspond to Microbial Associated Molecular Patterns or MAMPs (also named PAMPS for pathogenic microbes) that may differ substantially from one strain to another. MAMPS are known to bind to specific receptors, the pattern recognition receptors or PRRs, which are expressed by many immune cells and tissues such as the gut epithelium. The binding of MAMPs to PRRs explains how probiotic, commensal or pathogenic bacteria can elicit innate and adaptive immune responses in the host by triggering signaling cascades that in turn lead to the production of cytokines, chemokines and other innate effectors (Abreu, 2010; Kawai and Akira, 2010; Wells et al., 2010). The PRRs belong to three major families: the Toll-like receptors (TLRs), retinoic acid inducible gene I (RIG-I)-like receptors and nucleotide oligomerization domain-like (NOD) receptors (Kawai and Akira, 2010). The TLR and NOD receptors have been shown to play a role in immune activation by probiotics and commensals and so to influence skewing of naïve T cells, regulation of regulatory T cells (Tregs) and activation of antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages. Activated DCs produce different cytokines in response to different bacterial stimuli and this has consequences for the induction of different T cell subtypes (Baba et al., 2008; Mohamadzadeh et al., 2005). In this sense it is not surprising that different candidate probiotic strains exhibit different immune modulation specificities as they may carry varying MAMPs (Wells, 2011).

Several studies have demonstrated that *in vitro* cytokine profiles elicited from PBMCs, DCs or macrophages vary substantially depending on the species but importantly also on the strain (Wells et al., 2011). Typically, Meijerink *et al.* recently compared the DC response to stimulation by 42 *Lactobacillus plantarum* strains and amounts of IL-10 and IL-12 levels showed up to 39 and 600 fold differences, respectively (Meijerink et al., 2010). This indicates that multiple factors play a role in determining the immune phenotype of a strain. Using genome comparison of *L. plantarum* strains and gene deletion techniques, bacterial genetic loci involved in these specific immune properties could be identified (Marco et al., 2009; Meijerink et al., 2010).

The impact of the LTA has also been highlighted by genetic studies dealing with different *Lactobacillus* species, for example the composition of LTA in *L. plantarum* NCIMB8826 and *Lactobacillus rhamnosus* GG (Grangette et al., 2005; Perea et al., 2007), and presence/absence of LTA in *Lactobacillus acidophilus* NCK56 (Mohamadzadeh et al., 2011) was shown to influence the pro- or anti-inflammatory properties of the wild type and mutant strains. These are examples of studies that combined bacterial physiology and genetics with *in vitro* immune assays in order to generate a hypothesis that could be tested in animal models. They illustrate a nowadays quite active and rapidly evolving field of research. Recent reviews have captured the information that has been gathered on how probiotics can signal through TLR2, TLR2/6, TLR4, TLR9, NOD 1 & 2, and other signaling pathways (Lebeer et al., 2010; Wells et al., 2011).

Different lactobacilli and bifidobacteria have been reported to enhance or restore the barrier function (Resta-Lenert and Barrett, 2003; Ulluwishewa et al., 2011). *In vivo* data support these observations, which were recently reinforced in a human study showing that tight junction proteins of the gut epithelium (biopsies) were regulated upon perfusion of *L. plantarum* WCFS1 in the duodenum of healthy volunteers (Karczewski et al., 2010).

Even though a lot of research has been dedicated to identify which cell surface molecules are operational in the probiotic-host interaction, other molecules such as DNA (Rachmilewitz et al., 2002; Rachmilewitz et al., 2004), metabolites or secreted soluble factors have also been established to play a key role. For example, soluble factors of *Bifidobacterium breve* C50 were

demonstrated to participate to the anti-inflammatory properties of the strain and to impact on intestinal ion channels (Heuvelin et al., 2010).

While providing an exhaustive review of this area is beyond the scope of the chapter, it might be concluded that the use of a variety of *in vitro* and *in vivo* immune models linked to a good knowledge of bacterial physiology and genetics allowed progress in understanding the mechanisms of action of specific probiotic strains and identification of certain effector molecules. Nevertheless, efforts should be continued in this area while it will also be necessary to fill the major gap that remains between preclinical and clinical research.

5. Atopic dermatitis (AD): Physiopathology of AD

Atopic dermatitis or atopic eczema (AD/AE) is a chronic inflammatory disease of the skin, which usually occurs in the early years of life. The skin in AD is extremely dry and itchy and is inflamed - this leads to the characteristic redness, swelling, and scaling pattern often seen in the face and at flexural surfaces of the extremities of patients suffering from AD. AD has been divided in at least 2 different forms: (i) IgE associated or extrinsic dermatitis; (ii) non-IgE associated or intrinsic dermatitis.

Based on epidemiological and immunological studies, the natural history of AD seems to follow three phases: an initial non-atopic (non-IgE associated) form of eczema occurring in the early infancy followed in 60 to 80% of the cases by a sensitization to food and /or environmental allergens with the development of associated IgE (true AD). Finally, an IgE sensitization to self-proteins is observed in a high proportion of children and adults with AD due to molecular mimicry (Bieber, 2008).
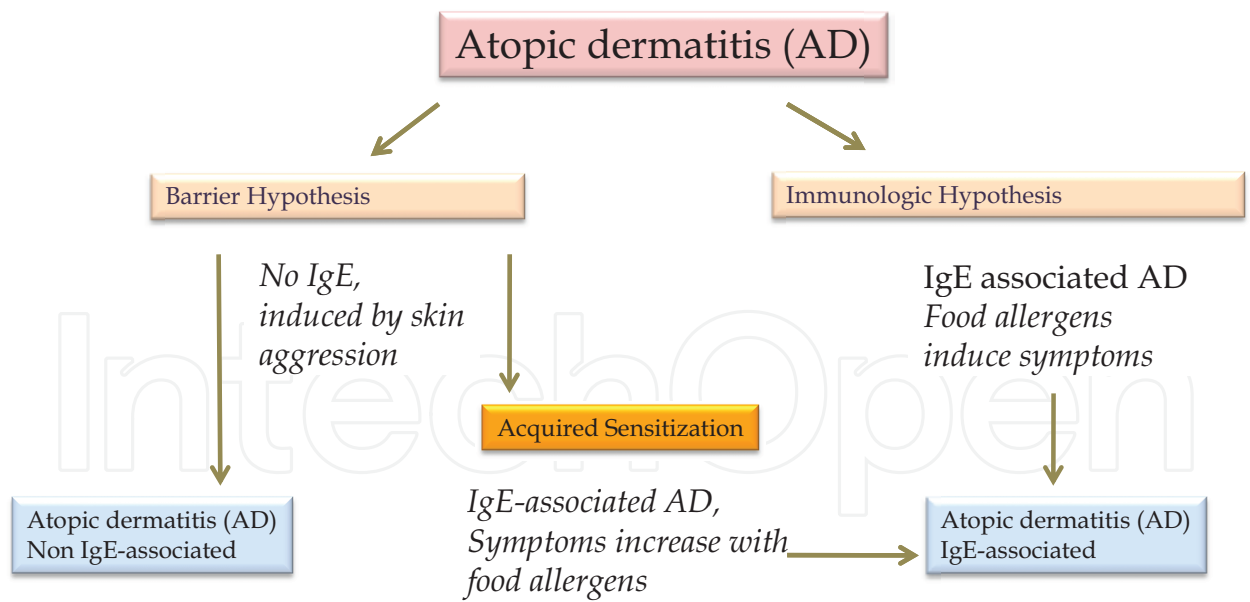

Fig. 1. AD classification (Bieber, 2008)

AD is often the first disorder to manifest in the relay of allergies, usually referred to as the Atopic March (Hahn and Bacharier, 2005; Illi et al., 2004; Spergel and Paller, 2003; Zheng et al., 2011). The prevalence of the disorder has increased dramatically in the last two decades similar to other allergies such as allergic rhinitis and asthma. AD affects mostly infants and young children and according to recent epidemiological studies, 5-20% of

children are affected in developed countries (Asher et al., 2006; Williams et al., 1999). The treatment of AD is mainly symptomatic and includes emollients to moisturize the skin, and topical corticosteroids along with a switch to an elimination diet (BuBmann et al., 2009; Peserico et al., 2008).

AD has a complex etiology. Recent investigations into mechanisms that drive the inflammatory response in AD have highlighted the crucial role of genetic predisposition. Many mutations have been associated to the development of AD. These mutations are located in two subsets of genes, in structural protein genes involved in the epidermal-barrier function or in genes involved in IgE production (Bieber, 2008; Demehri et al., 2009; Hsu et al., 2008; Suzuki et al., 2011). Also, environmental factors can contribute to the development of AD. As such, AD can be classified into IgE-mediated and non IgE-mediated subtypes (Fig. 1.).

As mentioned above, it has been postulated ("hygiene hypothesis") that the pattern of bacterial colonization of the gut during the early months after birth can contribute to the development of AD (Vael and Desager, 2009). During the first year of life the newborn immune system is still under development while exposure to novel dietary foods is increasing, especially around the weaning period. These multifactorial events in concert contribute to the establishment of oral tolerance, *i.e.* prevention or development of atopic sensitization to common foods such as cow's milk, eggs, wheat and nuts that predispose to the development of AD (Garcia et al., 2007; Gonzalez, I et al., 1971; Han et al., 2004; Heratizadeh et al., 2011).

6. Animal models of allergy and preclinical studies with probiotics

Even though animal models do not completely recapitulate all clinical, histological and immunological features of human AD, they can offer valuable tools (i) to evaluate candidate probiotic strains and their ability to prevent/alleviate AD and (ii) to elucidate their cellular and molecular mechanisms of action. Indeed, assessing the effect of probiotic candidate strains directly in human trials is expensive and time-consuming. Moreover, the number of candidate strains, the importance of their preparation/formulation, the dose, routes and possible administration regimens/schedules increase the number of parameters to be evaluated before to launch a clinical trial. Also, food and safety agencies recommend to better characterize the mechanism of action of potential probiotics. Since access to biological materials other than blood is limited and functional studies are difficult to perform in human trials, research on probiotics may benefit from preclinical animal models (Kalliomaki et al., 2010).

In the context of AD, several animal models are used nowadays (Jin et al., 2009) (table 1). The historical model of Nc/Nga mice that spontaneously develop AD-like features has been commonly used to evaluate the capacity of candidate strains to prevent/manage AD (Matsuda et al., 1997). In this model, Nc/Nga mice housed under specific pathogen free conditions are protected from AD. Once these mice are transferred to air-unregulated conventional environment, they exhibit AD-like lesions by 7-8 weeks. Feeding (heat-treated) *Lactobacillus rhamnosus* GG or live *Lactobacillus johnsonii* NCC533 around weaning period prevented or delayed the onset of AD (Sawada et al., 2007; Tanaka et al., 2008). Offsprings exhibited lower clinical scores with shorter scratching duration/frequency, a reduced total IgE serum titer and a decreased number of mast cells infiltrating skin lesions. One of the caveats of the model of Nc/Nga mice is that the allergen is unknown. To circumvent this

Animals	Models	Examples	Common features with human AD/rationale	Ref.
Rodents	Spontaneous dermatitis	Nc/Nga mice	Mice develop AD-like lesions when housed in non-sterile (conventional) environment. Closely mimics human AD features: scratching behavior, skin thickening,dermal infiltration of eosinophils and mononuclear cells, elevation of total IgE	Matsuda et al., 1997
		DS-Nh mice	AD develops in conventional conditions with elevation of total IgE. The skin is colonized with *Staphylococcus aureus*	Hikita et al., 2002
		Skin injury and epicutaneous sensitization with ovalbumin	Skin barrier disruption, mimics skin injury inflicted by scratching in patients with AD: epidermal and dermal thickening, infiltration of CD4+ T cells and eosinophils, upregulation of Th2 cytokines, production of specific IgE	Spergel et al., 1998
		Epicutaneous sensitization with aero-allergens (house dust mite, *Aspergillus fumigatus*)	Majority of patients with allergic rhinitis have pre-existing atopic disease. Mimics skin hyperplasia, infiltration of CD4+ T cells and eosinophils, upregulation of Th2 cytokines, elevation of total IgE	Huang et al., 2003b; Akei et al., 2005
		Epicutaneous sensitization with Th2-inducing hapten (oxazolone, trinitrochlorobenzene)	Mimics exposure to allergen via a breach in the skin barrier: epidermal hyperplasia, elevation of transepidermal water loss, infiltration of CD4+ T cells, mast cells and eosinophils, upregulation of Th2 cytokines	Matsumoto et al., 2004; Man et al., 2008
	Epicutaneous sensitization	Food hypersensitivity-induced AD (allergen + cholera toxin)	Supports the role of food allergy in a subset of patients with AD: scratching is one of the possible clinical symptoms	Li et al., 2001
		Superantigen-induced AD	Mimics the exacerbation of AD by *S. aureus*	Laouini et al., 2003
		Mice overexpressing IL-4	IL-4 Tg mice develop dermatitis with infiltration of mononuclear cells, mast cells, and eosinophils	Chan et al., 2001
		Mice overexpressing TSLP, Retinoid X Receptor RXRαβ^{ep}−/− mice	Mice overexpress the cytokine thymic stromal lymphopoietin (TSLP), known to be produced in epidermal keratinocytes of AD patients, and develop AD-like skin and systemic abnormalities	Yoo et al., 2005; Li et al., 2005

Animals	Models	Examples	Common features with human AD/rationale	Ref.
		IL-31 transgenic mice	IL-31 overexpression reproduces skin histological lesions with no IgE increase or systemic Th2 cytokines	Dillon et al., 2004
		Stratum corneum (SC) chymotripic enzyme overexpresssing transgenic mice	The SC chymotrypic enzyme, a serine protease has been shown to be overexpressed in chronic lesion of AD. The SC chymotrypic enzyme transgenic mice develop AD-like skin lesions	Hansson et al., 2002
	Genetically modified mice	Cathepsin E-deficient mice	The cathepsin E (Cat E) proteinase is preferentially expressed in the antigen-presenting cells. The Cat E°/° mice develop pruritic and skin lesions, infiltration of CD4+ T cells and eosinophils, upregulation of Th2 cytokines, elevation of total IgE	Tsukuba et al., 2003
		Caspase-1 or IL-18 transgenic mice	IL-18 precursor becomes active after cleavage with capase-1 (CASP1). Its expression is increased in human AD skin lesions and IL-18 and CASP1 transgenic mice develop AD-like skin inflammation with scratching behavior. They have a spontaneous Th2-bias, elevated seric IgG1and IgE and histamine levels, and an increased number of skin mast cells	Konishi et al., 2002
		APOC1 transgenic mice	APOC1 (Apolipoprotein C1) is expressed in the skin and involved in lipoprotein metabolism. In the APOC1 the transgenic mice there is an impairment of the skin barrier function that leads to increased total IgE and dermatitis. Both can be suppressed by topical corticoid treatment	Nagelkerken et al., 2008
Dogs	Spontaneous dermatitis	Beagles	This model reproduces human AD clinically, histologically with an epidermal barrier dysfunction. Immunologically, AD dogs' PBMC exhibit a Th2 cytokine profile	Marsella and Girolomoni, 2009

Table 1. Common preclinical models of AD (adapted from (Jin et al., 2009))

drawback, modified models have been set up. Repeated application of house dust mite *Dermatophagoides farina* extract induces human-like atopic skin lesions (Huang et al., 2003a). In this model, oral administration of live *Lactobacillus plantarum* from Kimchi, a traditional Korean fermented food (Won et al., 2011), or of live *L. johnsonii* NCC533 alleviated AD symptoms (Inoue et al., 2007). In another Nc/Nga-derived model, mice were sensitized by epicutaneous application of the hapten picryl chloride, and oral administration of heat-treated *Lactobacillus breve* SBC8803 delayed the development of AD (Segawa et al., 2008). It is noteworthy that most of these experiments have been performed in young mice with administration of probiotics around weaning. However recent papers started to investigate the impact of different intervention periods. In this respect, a protective effect of live *L. rhamnosus* LPR was observed when the strain was fed to pregnant dams and their pups for 12 weeks. Protection was equally seen when probiotic treatment started at weaning but not when it was initiated one week after the onset of the disease (Tanaka et al., 2009).

The general hypothesis evoked to explain the beneficial effect of specific probiotic strains in allergy mouse models is their capacity to establish or restore the Th1/Th2 balance. Indeed, allergic disorders such as AD are characterized by an immune response that is Th2-biased with increased production of cytokines IL-4, IL-5 and IL-13. Investigators working in the probiotic field thus started to screen strains according to their ability to polarize T cells responses into Th1 responses (with IL-12 and INFγ production) (Mohamadzadeh et al., 2005) and to induce regulatory T cells (Hacini-Rachinel et al., 2009).

Alternative models such as the canine model of AD might be of interest as the latter, for ex., displays features similar to human AD. Of note, Marsella et al. evaluated the efficacy of *L. rhamnosus* GG in the prevention of canine AD but no significant decrease in clinical symptoms was observed (Marsella, 2009).

7. Probiotics and allergy: Clinical studies

Studies have been conducted comparing the gut microbiota of infants with AD or food allergy to non-allergic infants and in these studies it was observed that allergic infants had reduced numbers of lactobacilli and bifidobacteria species in their gut (Adlerberth et al., 2007; Kirjavainen et al., 2002; Penders et al., 2007). A little more than a decade ago the first studies were published testing the hypothesis that probiotic intervention either in the pre- or post- natal period (pregnant women, offsprings or both) could influence the incidence of AD in the early years of life. Over 25 published studies have investigated similar hypotheses since then. However, these studies have largely differed in the choice of probiotic strain investigated, duration of administration of the strain, the population treated (mothers vs. newborns vs. both mothers and newborns) and in selecting the primary outcome addressing the efficacy of the trial. We have grouped the studies into 2 types- those in which the probiotic is given as a prevention strategy *i.e.* in at risk population (history of atopy in the family) and the others in which probiotics are administered as a therapeutic entity in subjects diagnosed with AD to better manage their symptoms.

7.1 Prevention of AD
Around 15 clinical trials have investigated the efficacy of probiotic in prevention of AD (summarized in Table 2). We highlight some of the more relevant well designed trials that raised key questions in the field of probiotics. Kalliomaki *et al.* conducted the first long-term preventive study on probiotics in AD and found that supplementation with the *L. rhamnosus*

Ref.	Study design	Probiotic daily dose	Intervention	Population	Biological effect
Kim et al., 2010	R, DB, PC	1) B. bifidum BGN4, B. lactis AD011, L. acidophilus AD030 each at 1.6e9 cfu/day in powder 2) Placebo powder (maltodextrin and alpha-corn)	Given to mothers from 8 weeks before delivery until 3 months post-delivery, then to infants from 4 until 6 months	68 Infants at high risk of eczema; Korea	The cumulative incidence of eczema during the first 12 months was reduced significantly in probiotic group
Morisset et al., 2011	R, DB, PC	1) Infant formula fermented with B. breve C50 (4.2e9 cfu/100g)+ S. thermophilus 065 (3.8e7 cfu/100g) 2) Placebo: infant formula	1 year from birth	129 Infants and children at high risk of atopy (0-24 months), France	No effect between the groups
Niers et al., 2009	R, DB, PC	1) B. bifidum W23, B lactis W52, L lactis W58 (Ecologic® Panda) 3e9 cfu/day (1e9 of each); freeze dried powder; in sachet 2) Placebo: rice starch + maltodextran in sachet	During last 6 weeks of pregnancy and postnatally for 12 months to infant	98 Pregnant women with history of allergy, Netherland	Severity of atopic dermatitis decreased in probiotic treated-group during first 3 months
Taylor et al., 2007	R, DB, PC	1) L. acidophilus, LAVRI-A1 3e9 cfu/day lyophilised 2) Placebo: maltodextrin	6 months	178 Infants (< 6 months) with allergic disease history, Australia	No effect on incidence of atopic dermatitis
Ortiz-Andrellucchi et al., 2008	R, DB, PC	1) L. casei DN-114001 in milk (fermentation, dose not given) 2) Placebo (the same fermented milk b-irradiated)	45 days post delivery to mother	104 Prenatal, mother (18-40 y), Spain	No difference in the incidence of infant atopic dermatitis at 6 months
West et al., 2009	R; DB, PC	1) L. paracasei F19 lyophilised in cereals (rice and wheat based + milk proteins) 1e8 cfu/day 2) Placebo: cereals	9 months	171 Infants (subpopulation of at risk), Sweden	The cumulative incidence of atopic dermatitis was lower in probiotic treated-group
Abrahamsson et al., 2007	R, DB, PC	1) L. reuteri ATCC55730 1e8 cfu/day in coconut and peanut oil 2) Placebo: Same oil	4 weeks before delivery, 1 year mother and infant, 1 year follow up	188 Prenatal with allergic disease history, Sweden	Less IgE associated eczema at 2 years. Less skin prick test reactivity
Kopp et al., 2008	R, DB, PC	1) L. rhamnosus GG 1e10 cfu/day lyophilised in capsules 2) Placebo: microcrystalline cellulose in capsules	4-6 weeks before delivery + 6 months postnatally (first 3 months through the mothers/breastfeeding)	94 Pregnant women/ babies with familial atopic disease, Germany	No effect on the severity of atopic dermatitis

Ref.	Study design	Probiotic daily dose	Intervention	Population	Biological effect
Kalliomaki et al., 2001; Kalliomaki et al., 2003; Kalliomaki et al., 2007	R, DB, PC	1) *L. rhamnosus* GG 1e10 cfu/day lyophilised in capsules 2) Placebo: microcrystalline cellulose in capsules	2-4 weeks before delivery 6 months post natal	132 Prenatal with history of atopic disease, Finland	Incidence of eczema decreased during first 2, 4 and 7 years of life, respectively
Rautava et al., 2002	R, DB, PC	1) *L. rhamnosus* GG (Valio) 2e10 cfu/day lyophilised 2) Placebo: microcrystalline cellulose	4 weeks before giving birth and during breastfeeding	62 Mother/ Infant with history of atopic disease, Finland	Significant reduction in development of atopic eczema during first 2 years in probiotic treated-group
Huurre et al., 2008	R, DB, PC	1) *L. rhamnosus* GG, *B lactis* Bb12 1e10 cfu/day lyophilised (to the mother) 2) Placebo: crystalline cellulose	Middle pregnancy to end, breastfeeding	171 Prenatal with allergic history, Finland	Reduction of sensitization at 12 months in probiotic treated-group
Soh et al., 2009	R, DB, PC	1) *B. longum* BL999 1e8, *L. rhamnosus* LPR 2e8 cfu/day in formula 2) Placebo: formula	6 months	253 Infants (<6m) with history of allergic disease, Singapore	No effect on atopic senistisation and eczema at 1 year
Wickens et al., 2008	R, DB, PC	1) *L. rhamnosus* HN001, 6e9 cfu/day freeze-dried in capsules 2) *B. lactis* HN019 (Fonterra), 9e9 cfu/day freeze-dried in capsules 3) Placebo: capsules (dextran, salt, yeast extract)	Mothers: from 35 weeks gestation to 6 months postpartum. Infants: from birth to 2 years	446 Pregnant women with familial atopic disease, New Zealand	Reduction of eczema and of developing SCORAD by 2 years for *L. rhamnosus*, no effect on atopy; no effect of *B. lactis* HN019
Kuitunen et al., 2009	R, DB, PC	1) *L. rhamnosus* GG and LC705, *B breve* Bb99, *P. freudenreichii* JS 1e10, 4e8, 4e9 cfu/day resp lyophilised (Valio mix 1) + GOS 2) Placebo: Microcrystalline cellulose	4 weeks before delivery 6 months to infant	891 Pregnant women/ babies with familial atopic disease, Finland	Reduction of IgE-associated allergic disease in cesarean-delivered infants only as secondary outcome
Kukkonen et al., 2007; Kukkonen et al., 2008; Kukkonen et al., 2010	R, DB, PC	1) *L. rhamnosus* GG 1e10, *L. rhamnosus* LC705 1e10, *B. breve* Bb99 4e8, *P. freudenreichii* 4e9 cfu/day + GOS lyophilised in capsules (Valio mix 1) 2) placebo: microcrystalline cellulose in capsules	2-4 wks before delivery 6 months to the infant	1223 Pregnant women with familial atopic disease, Finland	Probiotic treatment showed no effect on the incidence of all allergic diseases by age 2 years but prevented atopic eczema

Table 2. Prevention Studies in AD with Probiotics (R= randomized; DB= double blinded; PC= placebo controlled)

GG strain both to mothers (history of atopic diseases) prenatally in the last 2-4 weeks of pregnancy and subsequently to infants from birth to 6 months significantly reduced the incidence of AD at 2 years of age, *i.e.* 15/64 subjects were confirmed AD patients in the probiotic group compared to 31/68 in the placebo control group. Interestingly enough, IgE levels and skin prick test (SPT) reactivity to common food- and aero-allergens were not different between the groups at 2 years (Kalliomaki et al., 2001). The same authors conducted a follow-up of the subjects till 4 and 7 years of age and documented the incidence of other allergic disorders (allergic rhinitis, asthma) in addition to the long term effect of probiotic treatment on AD incidence. At both the follow up time-points, *i.e.* 4 and 7 years, the incidence of AD was lower in the probiotic treated group compared to the placebo group (Kalliomaki et al., 2003; Kalliomaki et al., 2007). Yet, the incidence of respiratory allergies at the follow-up time periods seemed to be higher in the probiotic treated group. The link between probiotic administration early on in life and the development of later onset of allergies deserves to be further investigated. A subsequent study evaluating the *L. rhamnosus* GG strain in similar clinical trial settings reported no preventive effect on the development of AD at 2 years of age (Kopp et al., 2008). Possibly the beneficial effects of probiotic strains are influenced by variants such as diet and genetic heterogeneity in the target population or the strain preparation/formulation.

With the increasing interest in the field of probiotics, various strains were reported to display established or potential benefit for allergy management. In this scope, it may become important to compare the efficacy of different strains in the same clinical trial. Wickens *et al.* did exactly that and compared the efficacy of *L. rhamnosus* HN001 and *B. lactis* HN109 to a placebo; reduction in the incidence of AD at 2 years of age was observed with *L. rhamnosus* HN001 but not with *B. lactis* HN109 in comparison to the placebo, which constitutes a quite convincing result (Wickens et al., 2008). Combinations of multiple strains have also been attempted in AD clinical trials; Soh *et al.* combined two strains *B. longum* BL999 and *L. rhamnosus* GG (LPR), and found that in comparison to the placebo there was no significant effect in the reduction of AD incidence at 1 year of age (Soh et al., 2009). It should be emphasized that combination of different probiotic candidates or increasing the probiotic dose does not necessarily lead to an increased beneficial effect.

7.2 Therapy: Management of AD symptoms

Compared to prevention studies, probiotic trials in management of AD are relatively of shorter duration (typically 4-12 weeks) and aim at reducing the severity of AD. The primary outcome selected is often a change in SCORAD index which is a validated clinical scoring system that evaluates the intensity, severity of disease and quality of life parameters associated with AD symptoms. AD usually manifests at around 3-4 months of age and resolves in about 50% of the AD subjects by 2-3 years of age. As such it is often a challenge to demonstrate superiority of treatment compared to the placebo in these trials, as the baseline parameters improve spontaneously in part of the enrolled subjects since they are already on eviction diet and standardized treatments. Current data with probiotics in the management of AD is limited even though the first studies were reported almost 15 years ago (Majamaa and Isolauri, 1997).

Most studies supplement infant formulas that are extensively hydrolyzed with their choice of probiotic strains to demonstrate efficacy of probiotics over placebo (non supplemented formula). Extensively hydrolyzed formulas are a common dietary recommendation for

Ref.	Study design	Probiotic daily dose	Intervention	Population	Biological effect
Miniello et al., 2010	R, DB, PC	1) *L. reuteri* ATCC 55730 1e8 cfu/day in a chewable tablet 2) Placebo: identical table without probiotics	8 weeks	51 Children with atopic or non atopic eczema (4-10y), Italy	No improvement in SCORAD index by the probiotic treatment
van der Aa et al., 2010	R, DB, PC	1) *B. breve* M-16V 1.3e9 cfu/100ml + GOS/FOS mixture (Immunofortis) in an extensively hydrolyzed formula 2) Placebo: extensively hydrolyzed formula	12 weeks	90 Infants with atopic dermatitis, Netherlands	Synbiotic-treatment lowered the SCORAD index only in the IgE-positive subgroup
Isolauri et al., 2000	R, DB, PC	1) *L. rhamnosus* GG 3e8 2) *B lactis* Bb12 1e9 cfu/g in hydrolyzed formula 3) Placebo: hydrolyzed formula	2 months	27 Infants (mean 4.6m) exclusively breast fed with atopic eczema, Finland	Severity of atopic eczema, decreased in both probiotic treated-groups
Hol et al., 2008	R, DB, PC	1) *L. casei* CRL431, *B lactis* Bb12 1e9-1e10 cfu/day in formula 2) Placebo: formula	12 months	119 Infants with cow's milk allergy, Netherlands	No difference in cumulative percent of tolerance to cow's milk
Weston et al., 2005	R, DB, PC	1) *L. fermentum* VRI-033 PCC 2e9 cfu/day lyophilised 2) Placebo: maltodextrin	8 weeks treatment 8 weeks follow up	56 Infant (6-18m) with atopic dermatitis, Australia	Reduction in SCORAD index by the probiotic treatment
Rosenfeldt et al., 2003	R, DB, PC CO	1) *L. rhamnosus* 19070, *L reuteri* DSM12246, 1e10 cfu/day lyophilised in bags 2) Placebo: skim mlik protein and dextrose anhydrate in bags	6 weeks treatment with 6 weeks wash out between	41 Children (1-13y) with moderate to severe atopic dermatitis, Denmark	No change in SCORAD index but improvement in patients's subjective evaluation of eczema in probiotic treated-group
Kirjavainen et al., 2003	R, DB, PC	1) *L. rhamnosus* GG 3e10 cfu/day/kg body weight in an extensively hydrolysed milk formula, 2) Heat-killed LGG in the same formula 3) Placebo: same formula	Mean duration 7.5 weeks	35 Infants (mean age 5.5 mths) with atopic eczema and cow's milk allergy, Finland	All treatments including placebo caused a reduction in SCORAD index. Heat-inactivated GG caused adverse GIT symptoms. Study stopped because of adverse effects

Ref.	Study design	Probiotic daily dose	Intervention	Population	Biological effect
Brouwer et al., 2006	R, DB, PC	1) *L. rhamnosus* GG 5e8 cfu in an extensively hydrolysed milk formula 2) *L. rhamnosus* Lrh 5e8 cfu in an extensively hydrolysed milk formula 3) Placebo: extensively hydrolysed milk formula	3 months	50 formula-fed Infants (<5months) with atopic dermatitis, suspected with cow's milk allergy, Netherlands	No effect on SCORAD index
Folster-Holst et al., 2006	R, DB, PC	1) *L. rhamnosus* GG 1e10 cfu/day lyophilised in capsules 2) Placebo: cristalline cellulose	8 weeks	54 Infants (1-55 months) with moderate to severe atopic dermatitis, Germany	No difference for the clinical symptoms of atopic dermatitis (SCORAD, pruritus, sleep loss)
Gruber et al., 2007	R, DB, PC	1) *L. rhamnosus* GG 1e10 cfu/day lyophilised in capsules 2) Placebo: cellulose + saccharose + magnesium	12 weeks	102 Infants (3-12m) with atopic dermatitis , Germany	No effect on atopic dermatitis symptoms, consumption of rescue medication, seric IgE and the quality of life
Majamaa and Isolauri, 1997	R, DB, PC	1) *L. rhamnosus* GG, 5e8 cfu/g of hydrolysed formula 2) Placebo: hydrolysed formula 3) *L. rhamnosus* GG 2e10 cfu/day given to nursing mother	1 month	37 Infants (2-16 months) with atopic dermatitis, CMA suspected, Finland	Severity of atopic dermatitis, decreased in probiotic treated-infants
Sistek et al., 2006	R, DB, PC	1) *L. rhamnosus* and *B. lactis* HN019 (Fonterra) 2e10 cfu/day lyophilised in capsules 2) Placebo: microcrystalline cellulose in capsules	12 weeks	59 Children (1-10 years) with atopic dermatitis, UK	Severity of atopic dermatitis decreased only among children sensitized to foods in probiotic treated-group
Passeron et al., 2006	R, DB, PC	1) *L. rhamnosus* Lcr 35/ 3e9 cfu/day + prebiotic + fermentation broth lyophilised 2) Placebo: prebiotic	3 months	39 Children (2-12 years) with atopic dermatitis, France	No difference in SCORAD scores
Woo et al., 2010	R, DB, PC	1) *L. sakei* KCTC 10755BP/ 1e10 cfu/day freeze-dried in a sachet 2) Placebo: microcrystalline cellulose in a sachet	12 weeks	88 Children with atopic dermatitis(2-10 years), Korea	Severity of atopic dermatitis decreased in probiotic treated-group

Ref.	Study design	Probiotic daily dose	Intervention	Population	Biological effect
Viljanen et al., 2005	R, DB, PC	1) *L. rhamnosus* GG 1e10 2) MIX: GG + *L. rhamnosus* LC705 1e10, *B. breve* BBi99 4e8, *P. freudenreichii* 4e9 cfu/day lyophilised 3) Placebo: microcrystalline cellulose	4 weeks	230 Infants (<12 months) with suspected cow's milk allergy, Finland	Severity of atopic dermatitis decreased in IgE-sensitized infants with LGG treatment
Roessler et al., 2008	R, DB, PC CO	1) *L paracasei* Lpc-37 8e10, *L. acidophilus* 74-2 6e6, *B. lactis* DGCC420 1e7 cfu/day in yoghurt drink 2) Placebo: yoghurt drink (fermented with *S. thermophilus*)	8 weeks treatment with 2weeks wash out between	15 Adults with atopic dermatitis, Germany	No difference in SCORAD scores
Torii et al., 2011	R, DB, PC	1) Heat-killed *L. acidophilus* L92 1.5e11 Eq cfu/day+dextrin 2) Placebo: dextrin	8 weeks	60 Children (1-12 yrs) with atopic dermatitis, Japan	Improvement of symptom-medication-score in probiotic treated-group
Moroi et al., 2011	Prospective, R, DB, PC	1) Heat-killed *L. paracasei* K71 2e11 Eq cfu/day+dextrin 2) Placebo: dextrin	12 weeks	33 Adult atopic dermatitis patients managed with topical corticosteroid and tacrolimus treatment; Japan	Probiotic but not the placebo significantly decreases the skin severity score from baseline. However there was no intergroup (probiotic vs placebo) difference
Nermes et al., 2011	R, DB, PC	1) LGG 3.4e9 cfu/day + extensively hydrolysed milk formula 2) Placebo: extensively hydrolysed milk formula	3 months	39 Children with atopic dermatitis, Finland	No effect on SCORAD severity

Table 3. Management studies in AD with probiotics (R= randomized; DB= double blinded; PC= placebo controlled)

infants with AD manifestations linked to cow's milk allergy and are largely effective in reducing the severity of AD. To demonstrate an improvement with probiotic supplementation is by itself a challenging primary outcome. Different strains have been evaluated in pilot clinical trials (Table 3) with mixed results. Isolauri *et al.* showed that both *L. rhamnosus* LGG and *B. lactis* Bb12 were effective in reducing the severity of AD (Isolauri et al., 2000). Interestingly, in a recent publication LGG was however shown to have no effect on AD severity (Nermes et al., 2011).

The selection of the target population also plays a major role in the success of these trials. Weston *et al.* demonstrated the efficacy of *L. fermentum* PCC in a cohort of subjects with moderate to severe AD while other studies have typically selected mild to moderate AD subjects and have not succeeded in showing the efficacy of the probiotic strains (Weston et al., 2005). Combinations, with other strains or with prebiotics have been attempted with a variable success. For example, van der Aa *et al.* evaluated a combination of *B. breve* M-16V with a prebiotic mixture. After 12 weeks, the severity of atopic dermatitis (AD) did not differ between the two groups, indicating no superiority of the synbiotic combination of (pro- and pre-biotic) over placebo (van der Aa et al., 2010).

8. Conclusion

Probiotics in general are widely available and advertised for numerous health benefits ranging from infectious and inflammatory disorders - including allergy -, gut health to cognitive performance and skin health. However, the level of available or supporting scientific evidence varies widely depending on the studied probiotic strain and its proposed health benefit. Since numerous pre-clinical studies and clinical trials have examined the efficacy of candidate strains in different models and target populations, it is not possible to make the general conclusion that "probiotics" work at large for this or that purpose. As discussed in the chapter, health benefits or immune effects are strikingly strain specific, which means that observations made on one strain cannot be extrapolated, unless proven, to any other strain. As reviewed recently by Kalliomäki *et al.* (Kalliomaki et al., 2010), particularly for AD, taking into account the pre-clinical studies and clinical trials done, it is too early for the scientific community to recommend a general use of probiotics in routine clinical practice, even though specific strains have been developed with success. The meta-analyses that have been performed on probiotics and health benefits often include results of clinical trials conducted with different strains in different formats (probiotic powders or strains included in a fermented food), in different settings (prevention or treatment) targeting different populations (at risk or diseased people, varying age populations) and relying on different administration regimes (dose, timing, length of the treatment). Yet, a beneficial effect has been reported typically in the case of necrotizing enterocolitis or antibiotic-associated diarrheas. For allergy, the situation is complicated by the fact that this disease corresponds to a syndrome covering multiple manifestations that are influenced by several factors -including environmental ones- that may impact on the onset or the perpetuation of the disease (Prescott and Bjorksten, 2007). The meta-analyses conducted so far diverge somewhat in their conclusions even if they agree on the fact that the evidence is better for allergy prevention than for treatment (Doege et al., 2011; Kalliomaki et al., 2010). In 2008, ILSI Europe organized an expert meeting to establish guidance for assessing the probiotic beneficial effects and to propose how to fill the gap in the areas of digestive system metabolism, chronic intestinal disorders, infections and

allergic diseases and the conclusions of this work have been published (The journal of Nutrition, 140, Number 3S-I, supplement). Potential avenues for optimizing clinical trials in the field of probiotics and allergy, and caveats that may lead to misinterpretation of overall results were outlined (Kalliomaki et al., 2010).

A few studies point to the fact that probiotics may work only on IgE-mediated AD. These results although are based on (often retrospective) sub-grouping of the target population into IgE vs. non-IgE groups. Clinical trials are needed in the future specifically in large enough cohorts of IgE-mediated AD to substantiate this hypothesis.

Even though several probiotic candidate strains have been tested *in vitro* and in preclinical models of AD, it remains difficult to discuss the predictive value of these preclinical studies. Indeed there has not been sufficient alignment between the strains used for clinical trials and the ones used for preclinical studies. However, the preclinical models can certainly serve the purpose of (i) further understanding the mechanisms of action of specific strains that have been found to be beneficial in AD clinical trials, (ii) evaluating the best intervention window(s) (prenatal, perinatal, weaning, later in life), (iii) performing dose-response curves and (iv) analyzing the impact of probiotic preparation/formulation or inclusion in a final product, to assess combinations of anti-allergy ingredients, and (v) supporting the dossier to submit for approval by ethical committees for human trials.

In conclusion, when analyzing the results of past and ongoing clinical trials performed with probiotics and allergy, it should be kept in mind that AD is a complex multifactorial disease whose onset or outcome may strongly depend on the complex interplay between the host, in particular its genetic background, the status of the immune system and intestinal microbiota, and environmental factors. Nevertheless, additional efforts in the area deserve to be pursued as nutritional interventions remain by themselves an interesting approach to manage allergic manifestations.

9. Acknowledgements

10. References

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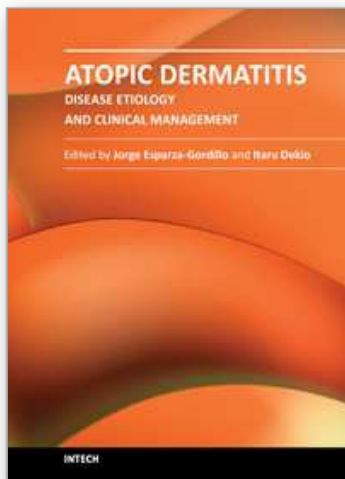
Atopic Dermatitis - Disease Etiology and Clinical Management
Edited by Dr. Jorge Esparza-Gordillo

Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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