Management of Atopic Dermatitis with Synbiotics

Melanie Rolfe, PharmD Candidate

Atopic dermatitis (AD), also known as eczema, is the most common chronic inflammatory skin condition, affecting 15-30% of children with increases in incidence seen annually. With hallmark symptoms including redness, inflammation, and itching, AD can be a burden to children both physically and psychologically, persisting into adulthood in 40-60% of cases. The increasing rate in the development of AD has often been attributed to the hygiene hypothesis which proposes that increased sanitation, vaccination, and decreased exposure to antigens reduces maturity of a child’s immune system, creating a higher propensity for development of allergic disorders. As part of the atopic triad along with allergic rhinoconjunctivitis and asthma, AD is typically the first manifestation in the development of future allergic disorders.

AD results from complex gene-gene and gene-environment interactions with an increased risk of development seen in patients who have a family history of allergic disorders. The disorder is characterized by decreased skin barriers, altered microbiome, and activation of inflammatory pathways. Current research suggests that the barrier dysfunction goes further beyond the skin and may be modulated in part by decreased barrier function of the intestinal mucosa. Based on this new theory of the pathophysiology of AD, the alteration in the intestinal mucosa may serve as a new target for therapy of this chronic disorder.

Current management of AD consists of both pharmacological and non-pharmacological interventions. Non-pharmacological management consists mainly of allergen avoidance, proper hygiene and skin hydration with moisturizers. Topical corticosteroids are the mainstay of pharmacological treatment with topical calcineurin inhibitors and phototherapy as second line options. Side effects from these treatments are minimal and consist mainly of skin irritations. Systemic side effects such as adrenal suppression, while rare, can be of concern with long term topical steroid use in children. The effectiveness of AD treatment can be evaluated by looking at the decreases in the severity score using the SCORAD (Scoring Atopic Dermatitis) as well as the Dermatology Life Quality Index (DLQI). The SCORAD is a clinical tool that evaluates AD symptoms based on extent and intensity as well as subjective symptoms of itching and sleep loss. The DLQI focuses on the impact of dermatological disorders on patient’s quality of life, taking into account impact on daily activities, work, and social life. These indices are further described in tables 1 and 2.

While topical corticosteroids are effective in relieving itching and inflammation by improving diminished skin barriers, targeting the deficiencies in the intestinal mucosa through the administration of probiotics could potentially be a new treatment option to further decrease AD symptoms and overall SCORAD values. This article will discuss the potential use of probiotics, in particular synbiotics, for the management of atopic dermatitis in adults and children.

What are Probiotics/Prebiotics?

Probiotics as defined by the World Health Organization are “Live microorganisms which when administered in adequate amounts confer a health benefit on the host.” Many different strains are available with some of the most common being Lactobacillus spp., Bifidobacterium spp., and the yeast Saccharomyces boulardii. These strains of bacteria are common to the normal flora of the gastrointestinal (GI) tract and are non-pathogenic upon administration. Probiotics are commonly used for the treatment or prevention of diarrhea and for the management of GI disorders such as Crohn’s and irritable bowel disease. Prebiotics, another supplement used for digestive health, are non-living organisms thought to promote the growth of healthy bacteria within the gastrointestinal tract.

Table 1 | Scoring Atopic Dermatitis (SCORAD)

<table>
<thead>
<tr>
<th>A</th>
<th>Surface Affected</th>
<th>0—100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Intensity of Symptoms</td>
<td></td>
</tr>
<tr>
<td>Dryness</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Oozing/Scabs</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Scratch Marks</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Thickening of Skin</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Subjective Symptoms</td>
<td></td>
</tr>
<tr>
<td>Trouble Sleeping</td>
<td>0-10</td>
<td></td>
</tr>
<tr>
<td>Itchin</td>
<td>0-10</td>
<td></td>
</tr>
</tbody>
</table>

A/5 + 7B/2 + C = SCORAD total

Mild <20, Moderate 20-40, Severe >40
the colon. Combinations of pre and probiotics together are known as synbiotics. When used together, a synergistic effect is seen to promote the growth of beneficial bacteria in the GI tract.9

While conclusive scientific data on efficacy is lacking in many areas, probiotics are increasingly being used as supplemental treatment of several disorders due to their various proposed beneficial effects. The colonization of the GI tract with healthy bacteria contained within the supplements helps to prevent the growth of harmful pathogens that may invade. The lactic acid production of the commonly used species helps to further acidify the GI tract and prevent the adherence of pathogenic bacteria. Probiotics are also thought to support the development of gut-associated lymphoid tissue (GALT), produce vitamin K and folate, modulate inflammation through regulation of inflammatory cytokines, and downregulate T-helper type 2 (Th2) cells.9 The immune modulating and barrier stabilization effects are the basis for their use in atopic dermatitis.

**Proposed MOA in Atopic Dermatitis**

The immune modulating effects of probiotics are thought to play the most important role in the potential treatment of AD. Children with AD have an increased propensity for a Th2 biased immune response. Th2 cytokines favor isotype class switching to IgE which promotes inflammation and the development of allergic disorders. Probiotics are thought to suppress the Th2 response by inhibiting the maturation of dendritic cells which are responsible for the differentiation of naïve T-cells into the Th2 class. This can help to bring back the balance between Th1 and Th2 cells, causing a decrease in the acute phase of AD.2 Administration of probiotics may also help to normalize regulatory T-cells which play a role in the induction of oral tolerance to orally ingested antigens.10

The intestinal microflora is proving to play an important role in the development of allergic disorders such as AD. Several studies have shown a significant difference in the intestinal colonization patterns of AD patients as compared to non-AD patients, those with atopy having a higher prevalence of clostridia and lower bifidobacteria.10,11 With the administration of probiotics containing bifidobacteria or lactobacillus, there is the potential for these beneficial species to recolonize the patient and alter the intestinal flora. Studies using these bacterial strains for the treatment of AD have shown a change in the fecal content of AD patients, reflecting a change in the intestinal colonization and possible benefits of AD symptom management.12

**Probiotic Use in Atopic Dermatitis**

A 2015 update to the World Allergy Organization guidelines for the prevention of atopic dermatitis added a low-level recommendation for the use of probiotics in pregnant women who are at high risk for allergy development in their children.13 While no concrete recommendations have been established for the use of probiotics in the treatment of AD, new evidence is emerging showing the potential benefit of the use of probiotics or synbiotics to decrease symptoms of AD. Studies date back to the early 1990s with the most recent meta-analysis published in late 2016. Some of the more recent data in support of their use is discussed further in the following section.

### Table 2 | Dermatology Quality of Life Index (DQLI)

<table>
<thead>
<tr>
<th>Over the last week:</th>
<th>Very much (3)</th>
<th>A lot (2)</th>
<th>A little (1)</th>
<th>Not at all (0)</th>
<th>Very much (3)</th>
<th>A lot (2)</th>
<th>A little (1)</th>
<th>Not at all (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>how itchy, sore, painful, or stinging has your skin been?</td>
<td>how much has your skin made it difficult for you to do any sport?</td>
<td>how much has your skin prevented you from working or studying?</td>
<td>how much has your skin been a problem at work or studying?</td>
<td>how much has your skin interfered with you going shopping or looking after your home or garden?</td>
<td>how much has your skin created problems with your partner or any of your close friends or relatives?</td>
<td>how much has your skin caused any sexual difficulties?</td>
<td>how much of a problem has the treatment for your skin been?</td>
<td></td>
</tr>
<tr>
<td>how embarrassed or self-conscious have you been because of your skin?</td>
<td>Very much (3)</td>
<td>A lot (2)</td>
<td>A little (1)</td>
<td>Not at all (0)</td>
<td>Yes (3)</td>
<td>No (0)</td>
<td>A lot (2)</td>
<td>A little (1)</td>
</tr>
<tr>
<td>how much has your skin interfered with you going shopping or looking after your home or garden?</td>
<td>how much has your skin caused any sexual difficulties?</td>
<td>how much of a problem has the treatment for your skin been?</td>
<td>Very much (3)</td>
<td>A lot (2)</td>
<td>A little (1)</td>
<td>Not at all (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>how much has your skin affected any social or leisure activities?</td>
<td>Very much (3)</td>
<td>A lot (2)</td>
<td>A little (1)</td>
<td>Not at all (0)</td>
<td>Very much (3)</td>
<td>A lot (2)</td>
<td>A little (1)</td>
<td>Not at all (0)</td>
</tr>
</tbody>
</table>

Score: 0-1 = No effect on patient’s life, 2-5 = Small effect, 6-10 = Moderate effect, 11-20 = Very large effect, 21-30 = Extremely large effect. A decrease in the DQLI indicates quality of life improvement.

http://pharmacy.ufl.edu/pharmanote/ 2

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Gerasimov et al. conducted a randomized, double blind, placebo controlled clinical trial at the Lviv City Children’s Community Hospital in Lviv, Ukraine. They compared probiotics containing L. acidophilus DDS-1, Bifidobacterium lactis UABLA-12 and fructo-oligosaccharide to a probiotic placebo of rice maltodextrin in 96 children aged 12-36 months with moderate to severe AD. Both formulations were identical powders, administered twice daily for eight weeks. Exclusion criteria included: mild AD, symptoms requiring use of systemic corticosteroids, infected skin lesions, food allergy other than to eggs or cow’s milk, any form of cancer or immunodeficiency, or use of immunosuppressants or antibiotics during the trial period. Patients were allowed to continue use of emollients and steroid creams (hydrocortisone 1% or mometasone 0.1%) for the management of symptoms during the trial period. The SCORAD index, Infant Dermatitis Quality of Life (IDQOL) questionnaire, and the Dermatitis Family Impact (DFI) questionnaire were used in assessing clinical response to treatment with the SCORAD index as the primary outcome. While decreases in SCORAD were seen in both probiotic and control group, greater and more rapid reductions were seen in the intervention group. At weeks 2, 4, and 8 in the probiotic group, decreases in mean (SD) SCORAD values of -4.7 (8.1), -8.7 (9.0), and -14.2 (9.9) were seen, respectively, whereas reductions of only -2.5 (7.3), -5.1 (8.2), and -7.8 (7.7) were seen at the same intervals with placebo. Results showed an overall reduction in mean SCORAD and topical steroid use of 33.7% vs. 19.4% (p=0.001) and 33.3g vs. 25.6g (p=0.006) in the probiotic group compared to control. Quality of life improvements were also seen in both groups with a decrease in IDQOL and DFI of 33.0% and 35.2% in the probiotic group, and 19.0% and 23.8% in the placebo group (p<0.05), respectively. No differences in adverse events were seen between probiotic and control groups. The study concluded that the administration of this particular probiotic combination significantly reduced the severity of AD symptoms in children with further investigation needed into the use of probiotics for AD in the adult population.

Another study published in 2011 by Drago et al. investigated the effects of probiotic supplementation with L. salivarius LSOI in maltodextrin compared to a matched maltodextrin placebo twice daily for 16 weeks on the severity of AD in an adult population. The double blind, placebo controlled study was performed from January to May 2009 on 38 patients from the Allergy and Clinical Immunology Unit of the L. Sacco Hospital of Milan. Patients in the study were between 18 and 46 years of age with moderate to severe AD. Exclusion criteria were chronic or infectious diseases, active respiratory allergic disease, probiotics, antibiotics, or immunosuppressant use six months prior to study, and pregnancy or breastfeeding. Only emollient creams and oral antihistamines were allowed to be used during the study period. Effectiveness of treatment was assessed by change in SCORAD index, Dermatology Life Quality Index (DLQI) improvement, cytokine production, and changes to the fecal microbiota. After only four weeks of the study, significant decreases in SCORAD were seen in the probiotic group (from 27.57 ± 3.4 to 13.14 ± 0.27, p<0.001) with no significant change seen in the control group (from 24.28 ± 2.15 to 20.14 ± 0.27). Neither group reported any adverse effects. There was also a significant improvement in quality of life, as measured by decrease in DLQI, from baseline after 16 weeks of the study in the probiotic group of 8.28 ± 1.79 to 4.42 ± 0.27 (p=0.04). There was no significant change in DLQI scores with the control group. Changes to the colonization of the intestines as shown in the fecal flora were significant in the probiotic group, showing a decrease in colonization from staphylococci. Clinical and fecal flora changes were maintained upon follow up one month after discontinuation of treatment. Contrary to current theory, changes to inflammatory cytokine production were shown to be non-significant in the probiotic group, while significant decreases were seen in the control group. Ratio of Th1 to Th2 were also decreased in both groups, however, only significantly in control. These last two results suggest that the clinical effect seen with probiotic may not be related to changes in Th1 cytokine production but rather more likely associated with the overall balance of Th1/Th2.12

Kim et al. conducted a meta-analysis in 2014 at Seoul National University in South Korea which analyzed 1,599 patients in 25 randomized controlled trials to determine the effect of probiotics in the treatment of AD. Subgroup analyses were performed to evaluate clinical effect by age group, the use of synbiotics, type of bacterial species used, treatment duration, and baseline severity of AD. All studies looked at weighted mean differences (WMD) in SCORAD and were categorized into three age groups: infants (<1 year), children (1-18 years), and adults (>18 years). Significant reductions in mean SCORAD values were seen in both the children and adult age groups, however, were not seen in infants. Analysis of synbiotic treatment showed greater reductions in SCORAD values than probiotics alone (WMD -7.02 vs -5.56, p< 0.001). Analysis by probiotic bacterial species showed significant positive effects from administration of mixed strain probiotics (WMD -6.60, 95% CI -10.42 to -2.79, P < .001) and lactobacillus spp. (WMD -3.81, 95% CI -6.42 to -1.21, P= 0.004) but negative results were seen with bifidobacterium spp. alone (WMD 1.75, 95% CI 1.10 to 2.40, P< 0.001). Other findings from subgroup
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study Design</th>
<th>Participant Age</th>
<th>Treatment Used/Dose</th>
<th>Control Used</th>
<th>Duration</th>
<th>Main Result/Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Gerasimov et. al (2010)</td>
<td>RCT</td>
<td>12—36 months</td>
<td>L. acidophilus DDS-1 (5x10⁹ CFU), Bifidobacterium lactis UABLA-12 (5x10⁹ CFU), fructooligosaccharide (50 mg)</td>
<td>Rice maltodextrin (prebiotic)</td>
<td>8 weeks</td>
<td>Overall decrease in SCORAD and improvement in quality of life in children treated with synbiotic as compared to placebo.¹³</td>
</tr>
<tr>
<td>Drago et. al (2011)</td>
<td>RCT</td>
<td>18—46 years</td>
<td>L. salivarius LSOI (1x10⁹ CFU), maltodextrin</td>
<td>Maltodextrin (prebiotic)</td>
<td>16 weeks</td>
<td>Overall decrease in SCORAD, improvement in quality of life, and decrease in colonization of gut microbiota with staphylococcus in adults treated with probiotic as compared to placebo.¹¹</td>
</tr>
<tr>
<td>Kim et. al (2014)</td>
<td>Meta-analysis</td>
<td>0—65 years</td>
<td>Multiple probiotics/synbiotics</td>
<td>Multiple probiotics/prebiotics</td>
<td>4—12 weeks</td>
<td>Probiotics may be an effective treatment option for patients &gt;1 year of age with moderate to severe AD. No benefit was seen with single strain Bifidobacterium species.¹²</td>
</tr>
<tr>
<td>Chang et. al (2016)</td>
<td>Meta-Analysis</td>
<td>0—14 years</td>
<td>Multiple synbiotics</td>
<td>Multiple probiotics/prebiotics</td>
<td>8—24 weeks</td>
<td>Evidence supports the use of mixed strain probiotics for the treatment of moderate to severe AD in patients &gt;1 year of age.⁷</td>
</tr>
</tbody>
</table>

RCT = Randomized controlled trial
analysis included significant improvements in SCORAD only after 8 weeks or more of treatment, and efficacy of treatment in only those with moderate to severe AD rather than mild. The overall clinical effect from the study showed a significant decrease in SCORAD index in the probiotic treatment groups as compared to placebo (WMD -4.51, 95% CI -6.78 to -2.24, P<.001), however, significant heterogeneity was seen (I²=87%). Heterogeneity was mostly attributed to differences in bacterial strain used. Adverse events reported were mostly GI in nature (eg, diarrhea, vomiting) but no difference was seen between probiotic and control groups. Overall the results of the analysis suggested that probiotics, particularly mixed strain or synbiotics, may be an option for treatment of adults and children aged greater than one year with moderate to severe AD.18

A more recent meta-analysis was conducted in 2016 by Chang et al. which specifically analyzed trials using synbiotics for treatment and prevention of AD in children. Eight studies including a total of 1,689 patients were included, 6 being treatment studies and 2 being preventive for patients at high risk of developing AD. Primary outcome for treatment studies were change in mean and standard deviation in SCORAD index with subgroup analyses based on type of control used (placebo or prebiotic), age and probiotic strain used. Primary outcome for prevention studies was incidence of AD. For the overall clinical effect, a significant decrease in WMD of SCORAD of -6.56 (95% CI, -11.43 to -1.68; P=.008, I²=77.1%) was seen in the synbiotic group compared to control with no adverse events reported. Upon subgroup analysis, it was found that duration of treatment of at least 4 weeks was necessary for beneficial effect, but no additional benefit was seen in treating for longer than 8 weeks. Mixed strain bacterial species showed significant improvements in SCORAD (WMD, -7.32; 95% CI, -13.98 to -0.66; p= 0.03) while single strain species showed no change. When compared with non-prebiotic placebo, synbiotics significantly decreased SCORAD whereas those studies with prebiotics as control showed no significant improvements. The authors concluded that the current evidence supports the use of mixed strains of synbiotics in patients older than one year of age for the treatment of AD, however, no strong evidence was found in support of synbiotics for AD prevention.8

**Discussion**

While much of the currently available literature on the use of probiotics in AD shows statistically significant reductions in SCORAD and improvements in quality of life, clinical significance of the findings have been questionable. However, many of the studies use prebiotics as placebo. As described by Michail et al. and Shibata et al., administration of prebiotics alone has shown increased bifidobacterial gut concentrations and improvements in clinical symptoms of AD.16,17 The use of prebiotics such as maltodextrin as placebo as seen in the studies by Gerasimov et al. and Drago et al. makes the studies more conservative and harder to show a clinically significant effect of the synbiotic intervention. Prebiotics as placebo may also explain the improvements in SCORAD observed in the study control groups. Future studies should employ the use of control other than compounds considered as prebiotics in order to show the true clinical impact of synbiotics on improving symptoms and quality of life in AD.

**Side Effects and Safety**

As seen from clinical trials, the adverse effect profile of probiotics is relatively mild with little to no side effects reported in the average patient. Most common side effects are GI in nature and may include upset stomach, flatulence, or diarrhea. However, side effects may be underreported as many recent probiotic studies do not mention adverse events associated with the treatments and instead claim side effects were minimal. Serious adverse effects such as systemic infection have been reported, however, these are extremely rare and only in patients with underlying immunocompromising conditions. Probiotics are generally considered to be safe for consumption in both children and adults. Caution is advised in immunocompromised patients.18

**Dosing and Administration**

Definitive dosing regimens for probiotics in the treatment of AD have not yet been established. Studies have reported various doses ranging from 500 million to 10 billion CFU with treatments lasting anywhere from 4 to 12 weeks. While synbiotic regimens have proven to be most effective in AD treatment, improvements in AD symptoms have also been shown with single strain probiotics alone. Further investigations need to be made to discover the most appropriate and effective dosing regimen in terms of strain, dose, and length of administration of probiotics for the treatment of AD.

**Conclusion**

Increasing data is being discovered in support of probiotics as a treatment for atopic dermatitis. Current evidence shows that supplementation with probiotics can modestly decrease symptoms of AD and improve quality of life while conferring minimal side effects. Probiotic supplementation may also help to decrease the use of topical corticosteroids. However, current study sizes and uncertain dosing requirements limit the effectiveness of probiotic use in AD. The use of probiotic, in particular synbiotic, supplementation in patients older than one year of age with AD is a promising treatment option that will need to be further investigated in high quality trials before definitive recommendations on their use can be made.

**References**


7. Food and Agriculture Organization of the United Nations. FAO


EDITOR’S CORNER

Rates of Hypoglycemia and Insulin Degludec: Updates from Clinical Trials

Insulin degludec is a relatively new “ultra long acting” insulin with a duration of action of approximately 42 hours. Since its time on the market, there have been concerns about increased risk of hypoglycemia with the extended duration of action and limited clinician experience. In June 2017 Wysham et al. published results from a randomized controlled trial (SWITCH 1) comparing the hypoglycemia risk with insulin degludec and insulin glargine over 32 weeks in type 2 diabetes patients. A similar trial by Lane et al. (SWITCH 1) published at the same time that enrolled type 1 diabetes mellitus patients. Both trials aimed to determine whether insulin degludec was superior or noninferior to insulin glargine when comparing the rate of symptomatic hypoglycemia.

The SWITCH 2 trial enrolled 721 type 2 diabetic patients and 580 of these patients completed the trial. Patients were randomized 1:1 to insulin degludec or insulin glargine U100 once daily in the morning or evening. The primary end point was the rate of overall symptomatic hypoglycemic episodes (severe or blood glucose confirmed [56 mg/dL]) during the maintenance period of 32 weeks. The rates of symptomatic hypoglycemia were 185.6 episodes for insulin degludec vs 265.4 episodes per 100 patient-years of exposure (PYE) (rate ratio = 0.70 [95% CI, 0.61-0.80]; P <0.001; difference, -23.66 episodes/100 PYE [95% CI, -33.98 to -13.33]). The proportions of patients with hypoglycemic episodes were reported in 22.5% of insulin degludec patients and 31.6% of insulin glargine patients (difference, -9.1% [95% CI, -13.1% to 5.0%]). No difference was seen in A1C between groups (P < 0.001 for noninferiority).

The SWITCH 1 trial enrolled 501 type 1 diabetic patients, 395 patients completed the trial. Similarly to the SWITCH 2 trial, patients were randomized 1:1 to either insulin degludec or insulin glargine U100 once daily in the morning or evening. The primary endpoint was the same as the SWITCH 2 trial. Overall symptomatic hypoglycemic events were 2200.9 episodes/100 PYE in the insulin degludec group and 2462.7 episodes/100 PYE in the insulin glargine group (rate ratio = 0.89 [95% CI, 0.85-0.94]; P < 0.001 for noninferiority; P < 0.001 for superiority). The proportion of patients with hypoglycemic episodes was 10.3% for the insulin degludec group compared to 17.1% in the insulin glargine group (risk difference, -6.8% [95% CI, -10.8% to -2.7%]).

Results of both SWITCH 1 and SWITCH 2 indicate that insulin degludec is a reasonable option for type 1 and type 2 diabetes without additional risk of hypoglycemia. Insulin degludec may even be associated with a decreased risk of hypoglycemia compared to insulin glargine. The study results support use of both insulins as no difference in antihyperglycemic efficacy was seen between the insulin agents.

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