Food Allergy and Atopic Dermatitis: Fellow Travelers or Triggers?

Wynnis L. Tom, MD*

Abstract

Many children with atopic dermatitis also have an allergy to one or more foods, but the presence of these two conditions in an individual does not necessarily indicate a causal link between them. Testing and interpretation, sometimes with specialist consultation, may be required to discern whether food allergy is present in a child with atopic dermatitis and—if it is present—whether the food is triggering or exacerbating signs and symptoms of atopic dermatitis. Recent milestone trials have demonstrated that early introduction of peanuts can reduce the development of peanut allergy in at-risk children. Parents may benefit from education about current revised guidelines that now recommend offering peanut-containing foods to most children at the time he or she is ready for solid food.

Semin Cutan Med Surg 36(supp4):S95-S97

Keywords

Atopic dermatitis; avoidance; food allergy; peanut

Food allergy is common among children with atopic dermatitis. About one-quarter to one-third of children with atopic dermatitis have immunoglobulin E (IgE)-mediated clinical reactivity to food proteins.[1,2] For comparison, about 5% of infants and young children and 2% of adults in the United States have food allergies.[3] Analysis of 18 population-based studies determined that the rate of food allergy was as much as 6 times higher in children 3 months of age with atopic dermatitis compared with healthy controls (odds ratio, 6-18; 95% confidence interval 2.94-12.98; $P<0.001$). Some data suggest that food allergy is linked to relatively severe atopic dermatitis.[4]

Conversely, atopic dermatitis is more common in those with food allergy than it is in the general population, with an estimated 35% to 71% of patients with food allergy also having atopic dermatitis.[5]

*Associate Clinical Professor of Dermatology and Pediatrics, University of California, San Diego School of Medicine, Rady Children's Hospital, San Diego, California

Publication of this CME/CE article was jointly provided by University of Louisville, Postgraduate Institute for Medicine, and Global Academy for Medical Education, LLC, and is supported by an educational grant from Pfizer Inc. Dr Tom has received an honorarium for her participation in this activity. She acknowledges the editorial assistance of Eileen McCaffrey, MA, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

Wynnis L. Tom, MD, *Consultant:* Pfizer. *Grant/Research:* Pfizer, Celgene Corporation, Pfizer, and Regeneron.

Address reprint requests to: Wynnis Tom, MD, Rady Children's Hospital, 8010 Frost Street, San Diego, CA 92123; wtom@rchsd.org

Food allergies may exacerbate atopic dermatitis through immune cell activation or by increasing pruritus but the two conditions also may simply coexist in the same patient. More commonly seen skin reactions with food allergy include urticaria (hives), facial swelling, and flushing (**Table**). Food allergy also may manifest in ways other than on the skin (eg, gastrointestinal symptoms).[5,6]

Pitfalls in Diagnosis of Food Allergy

Medical history and self-report are insufficient to make a diagnosis of food allergy, as 50% to 90% of self-reported allergic symptoms are not confirmed on testing.[5] The presence of IgE antibodies to a specific food also does not equate to allergy; rather, a clinical reaction to that food must occur. IgE reactivity does not correlate well to clinical allergic response. A population-based study of 562 children in Denmark identified food allergy in ~3.6%, but in 80% of cases (16/20), children actually tolerated food to which they had elevated IgE levels.[7] Specific IgE levels also are not clinically useful for predicting the later development of food allergies by infants and toddlers.[8]

Skin prick testing (SPT) for food allergy has a high negative predictive value but a low positive predictive value. Larger wheals are more predictive of clinically significant food allergies, but SPT is often insufficient for diagnosis.[5] Oral food challenges should be performed to confirm a true allergy.[5,7]

Negative blood and SPT results are more helpful as they exclude the possibility of food allergy, while positive findings require additional interpretation to determine if they result in clinical food hypersensitivity reactions, eczematous skin manifestations, and/or atopic dermatitis. Referral to an allergist may be required to interpret the results of allergy testing.[6]

When to Test for Food Allergy

The National Institute of Allergy and Infectious Diseases (NIAID) Food Allergy Expert Panel recommends considering testing for food allergy to milk, egg, peanut, wheat, and soy in infants and children <age 5 years with persistent, moderate to severe atopic dermatitis despite optimized management and topical therapy, and/or those with a reliable history of an immediate reaction after ingesting a specific food.[5]

TABLE Cutaneous Manifestations of Food Allergy: Not Only Atopic Dermatitis

IgE-mediated: Urticaria, angioedema, flushing, pruritus
Cell-mediated: Contact dermatitis, dermatitis herpetiformis
Mixed IgE- and cell-mediated: Atopic dermatitis

Source: Boyce JA, et al.[5]

1085-5629/13/$-see front matter
doi:10.12788/j.sder.2017.049

Should We Eliminate Elimination Diets?

Parents who suspect that one or more foods may be provoking atopic dermatitis flares in their child sometimes experiment with self-designed elimination diets. This approach poses a risk for malnutrition, especially if multiple common foods (eg, milk, egg, wheat, soy, peanuts) are eliminated for more than a brief interval.[9] Elimination or restriction, especially for prolonged periods, should be performed only under medical supervision.[6] Keeping a food diary and noting any symptoms may suggest foods to investigate as potential allergens.

A retrospective study examined was conducted of 125 children with atopic dermatitis who were following elimination diets based on sensitization tests (IgE or SPT). A total of 364 oral food challenges were performed on foods being avoided; 89% of those challenges were negative. Depending upon the reason for avoidance, 84% to 93% of the foods could be returned to the diet safely.[9]

Recent evidence indicates that avoiding a food actually may reduce oral tolerance to that food. A retrospective review of 132 patients whose atopic dermatitis was triggered by food allergy but who had no history of immediate reactions found that 19% developed new immediate food reactions after starting an elimination diet. More than two-thirds (70%) of these new reactions affected the skin, but anaphylaxis occurred in 30% of cases. In this analysis, avoiding a food was associated with significantly increased risk of developing an immediate reaction to it ($P<0.01$). The authors suggested at least annual IgE monitoring and re-introduction of the potential allergen in a monitored setting, and advised patients to carry injectable epinephrine in case of accidental consumption of an offending food.[10]

Can Food Allergy Be Prevented? Early Introduction vs Avoidance

In 2000, the American Academy of Pediatrics (AAP) advised delaying the introduction of peanut-containing foods to children at risk for atopic disease until the age of 3 years.[11] By 2008, this recommendation was rescinded for lack of evidence.[12] Shortly thereafter, observational studies reported that earlier introduction of peanuts, eggs, and cow's milk was associated with lower rates of allergy to these foods.[13-15]

A randomized, controlled trial (Learning Early About Peanut Allergy; LEAP, published in 2015) demonstrated that early introduction of peanut-containing food (ie, at 4 months to <11 months of age) in infants at high risk for peanut allergy (defined as presence of severe atopic dermatitis, egg allergy, or both) resulted in a significantly lower risk of developing peanut allergy by age 60 months compared with peanut avoidance. In infants negative for peanut allergy on SPT at randomization (n=530), the prevalence of peanut allergy at 60 months old (assessed by oral food challenge) was 13.7% in the consumption group and 1.9% in the avoidance group ($P<0.001$). The same trend was observed among those who were mildly positive on SPT at study entry ($P=0.004$; **Figure 1**).[16] The rate of serious adverse events did not differ significantly between groups but more overall adverse events were reported in the consumption group ($P=0.02$). It should be noted that infants with marked wheals on SPT at study entry were excluded from further participation and peanut consumption versus avoidance was not tested.

A follow-up study evaluated whether avoiding peanuts after a period of consumption would affect the development of allergy. Participants in the LEAP trial were directed to avoid peanuts for 12 months and then were assessed by oral peanut challenge. This sequence did not lead to an increase in the prevalence of peanut allergy (**Figure 2**). The rate of adverse events was higher in the peanut avoidance group (89.4% vs 80.7%). Atopic dermatitis, lower respiratory tract infections, myopia, and gastroenteritis also were reported more often in the avoidance group.[17]

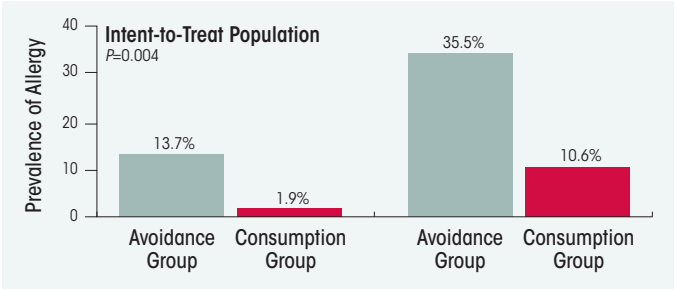

FIGURE 1 Prevalence of Peanut Allergy at 60 Months, by Consumption or Avoidance of Peanuts.

Data from the LEAP trial, combining results from both the SPT-negative (n=530) and the SPT-positive (n=98) cohorts. Infants age 4 to <11 months were evaluated by SPT for peanut allergy, stratified by SPT results, then randomized to consumption or avoidance of peanuts. Status of peanut allergy was reassessed at age 60 months.

SPT=skin prick test.

Source: Du Toit G, et al.[16]

Applying the LEAP Findings to Children With Atopic Dermatitis

Based on the LEAP study, the NIAID Expert Panel amended its guidelines to recommend the introduction of peanut-containing foods as early as 4 to 6 months of age for infants with severe atopic dermatitis, egg allergy, or both. Prior to offering peanut-containing food, strong consideration should be given to testing for peanut-specific IgE, SPT, or both (**Figure 3**). Those with IgE <0.35 kUa/L or 0-2mm wheal on SPT can

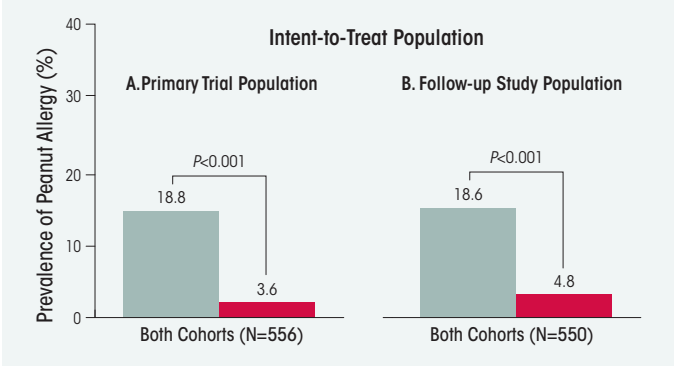

FIGURE 2 Prevalence of Peanut Allergy After Consumption Followed by 12 Months of Avoidance.

A. The rate of peanut allergy at the age of 60 months among participants in the LEAP study who also participated in the 12-month follow-up trial. Graph combines results from the SPT-negative (n=463) and SPT-positive (n=93) cohorts. **B.** The rate of food allergy at the age of 72 months in the LEAP follow-up study. Graph combines results from the SPT-negative (n=458) and SPT-positive (N=92) cohorts.

SPT status reflects the results of SPT for peanut allergy upon entry in the LEAP study.

SPT=skin prick test.

Source: Du Toit G, et al.[17]

proceed with consumption, although other solids foods should be introduced first to determine whether the infant is developmentally ready for this dietary change. Parents should be cautioned not to feed young children peanuts due to its choking hazard, but instead should offer peanut-containing foods such as peanut butter. The first introduction may be done at home or in a health provider's office. Referral to an allergist should be considered for specific IgE levels ≥0.35 kUa/L (ImmunoCAP; Thermo Fisher Scientific). SPT results of 3 mm to 7 mm suggest a moderate to high risk of reaction. A supervised feeding or oral food challenge in a specialized facility is advised. SPT results of ≥8 mm indicate a high probability of allergy and should prompt consultation with or referral to a specialist; avoidance might be necessary in this scenario.[18]

Children with mild to moderate atopic dermatitis have moderate risk for peanut allergy and can be offered peanut-containing food by age 6 months, after other solid foods have been introduced.[18] This may be done at home or in a provider office. Infants without atopic dermatitis or egg allergy are considered at low risk of developing peanut allergy. Peanut-containing foods can be freely introduced into their diet with other solid foods, according to the family's preferences and practices or also at around 6 months of age.

Summary

Food allergy is more common among children with atopic dermatitis,[4] but the presence of both conditions in an individual does not confer a relationship between them. Food allergy may be a trigger—exacerbating atopic dermatitis symptoms or causing cutaneous symptoms unrelated to atopic dermatitis—or it may be simply be a fellow traveler, coexisting with atopic dermatitis without affecting the skin.

Although avoidance of potential food allergens used to be recommended, a randomized, controlled study concluded that early introduction of peanut-containing foods in children with severe atopic dermatitis, egg allergy, or both (and no to mild reaction on SPT) was associated with significantly lower risk of allergy to peanuts.[16] There are now updated guidelines for prevention of peanut allergy based on three tiers of risk (high, moderate, low).[18] Data are not available to indicate that a similar approach of early consumption should be taken with other foods.

Consultation with a specialist may be needed to interpret results of food allergy testing and to distinguish if a food allergy has an effect on concomitant skin disease.[6]

References

1. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998;101(3):E8.
2. Mavroudi A, Karagiannidou A, Xinias I, et al. Assessment of IgE-mediated food allergies in children with atopic dermatitis. *Allergol Immunopathol (Madr)*. 2017;45(1):77-81.
3. FDA. Food Allergen Labeling and Consumer Protection Act of 2004. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106890.htm. Accessed October 23, 2017.
4. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137(4):1071-1078.
5. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-58.
6. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014;71(6):1218-1233.
7. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy*. 2009;64(7):1023-1029.
8. Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food allergy in infants with atopic dermatitis: limitations of food-specific IgE measurements. *Pediatrics*. 2015;136(6):e1530-1538.
9. Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr*. 2011;158(4):578-583.e571.
10. Chang A, Robison R, Cai M, Singh AM. Natural history of food-triggered atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract*. 2016;4(2):229-236.e221.
11. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.
12. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121(1):183-191.
13. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122(5):984-991.
14. Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol*. 2010;126(1):77-82.e71.
15. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol*. 2010;126(4):807-813.
16. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813.
17. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435-1443.
18. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *Ann Allergy Asthma Immunol*. 2017;118(2):166-173.e7.

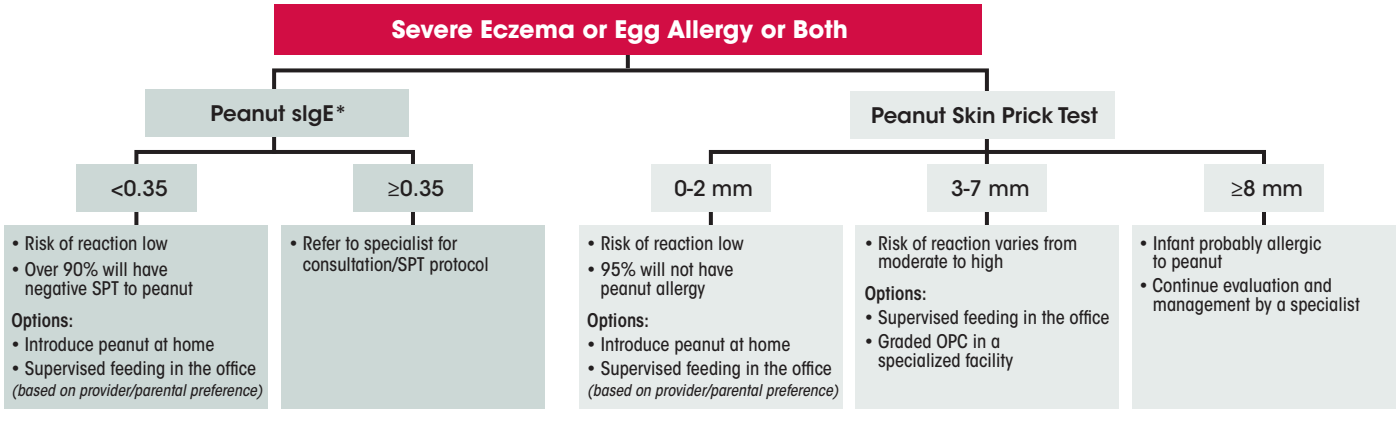

FIGURE 3 NIAID Expert Panel Recommended Approach to Evaluation of High-Risk Infants Prior to Introduction of Peanut-Containing Food.
*To minimize a delay in peanut introduction for children who may test negative, testing for peanut-specific 1gE may be the preferred initial approach in certain health care settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predicitve value.

NIAID=National Institute of Allergy and Infectious Diseases; OFC=oral food challenges; sIgE=specific immunoglobulin E; SPT=skin prick test.

Source: Togias A, et al.[18]

Infection and Atopic Dermatitis

Infection is a major complication of atopic dermatitis.[1,2] Factors that contribute to the higher frequency of infection include a defective skin barrier facilitating microbial entry, a compromised immune system impairing recognition of active infection, and reduced antimicrobial peptide production.[1-4] Genetic variants in the innate immune response may predispose patients with atopic dermatitis to an increased risk of skin infections.[5] Abnormalities in the cutaneous microbial environment have also been documented that may play a role.[6-9]

Increased *Staphylococcus aureus* (*S aureus*) Colonization

Colonization of atopic dermatitis lesions with *S aureus* is common, with as many as 80% to 100% of patients with atopic dermatitis demonstrating colonization compared to 5% to 30% of non-atopic individuals.[10] Rates of bacterial colonization are higher at more severely affected and inflamed sites, while overall microbial diversity is reduced.[6,10] Such findings suggest that the absence of beneficial organisms in the skin microbiome of patients with atopic dermatitis may facilitate colonization and infection. Adequate atopic dermatitis therapy is associated with greater bacterial diversity[7] and reduced rate of skin infection.[11] In one study, treatment with topical corticosteroids, alone or combined with bleach baths, restored microbial diversity to control skin levels and normalized bacterial composition on lesional skin to resemble that of nonlesional skin.[6]

A Cochrane review identified no benefit to routine antistaphylococcal therapy in individuals with atopic dermatitis in the absence of clinical infection.[12] Current guidelines recommend systemic antibiotics for overt secondary infection and bleach baths and intranasal mupirocin to reduce atopic dermatitis severity and infectious episodes.[3,13]

Viral and Fungal Infection

Infection with the herpes simplex virus can lead to eczema herpeticum (EH), which involves vesiculation and skin erosions, and, at times, fever and lymphadenopathy. EH is much less common than bacterial infection, affecting less than 3% of patients with atopic dermatitis, but it can cause significant illness and complications such as keratoconjunctivitis and meningitis.[1,3,14] Other viral infections observed in patients with atopic dermatitis include eczema coxsackium (infection with the coxsackievirus) and eczema molluscatum.[1]

Superficial fungal infection also may develop in patients with atopic dermatitis. This includes reports of infection with dermatophytes such as *Trichophyton* and *Epidermophyton*. Some patients may be sensitized to *Malassezia* yeast, the most common fungi on healthy human skin.[3,15] This appears to be associated with more severe atopic dermatitis disease, especially on the head and neck.[15]

Can Amplifying "Good" Bacteria Reduce *S aureus* Colonization?

A recent study showed most coagulase-negative *Staphylococcus* (CoNS) isolates from the skin of healthy controls were able to inhibit *S aureus* growth, but far fewer CoNS isolates from individuals with atopic dermatitis demonstrated antimicrobial activity. Individuals who were colonized with *S aureus* displayed even fewer CoNS with antimicrobial activity.[8]

Researchers then isolated CoNS strains with antimicrobial activity from the skin of each of 5 individuals with atopic dermatitis, cloned and expanded those isolates, and formulated them into a cream base. Applying a single dose of this cream to the skin of the 5 individuals as an autologous microbial transplant significantly reduced the presence of *S aureus* on the skin.[8] These findings, while preliminary, suggest the possibility of a new approach to the treatment of atopic dermatitis.

Preventing Infection in Atopic Dermatitis

Good control of atopic dermatitis itself is the best way to reduce the risk of infection. A meta-analysis of 8 randomized controlled trials (N=2,706; follow-up, 4 to 52 weeks) revealed a lower relative risk of skin infection and EH with dupilumab therapy, a monoclonal antibody that blocks interleukin (IL)-4 and IL-13 signaling. Authors postulate that reduced atopic dermatitis severity explains this observation.[11]

Summary

The pathology of atopic dermatitis predisposes patients to skin infections. Secondary bacterial infection is most common, although viral and fungal agents can also exacerbate disease. Recent research suggests that alterations in the skin microbiome, including an imbalance of beneficial and potentially pathogenic bacteria, may contribute to the frequent colonization and infection of atopic dermatitis lesions. Amplifying endogenous bacteria with antimicrobial activity and returning those bacteria to the skin of patients with atopic dermatitis has been shown to reduce *S aureus* colonization; larger trials are underway to test this therapeutic possibility.

– Wynnis L. Tom, MD

References

1. Sun D, Ong PY. Infectious complications in atopic dermatitis. *Immunol Allergy Clin North Am*. 2017;37(1):75-93.
2. David TJ, Cambridge GC. Bacterial infection and atopic eczema. *Arch Dis Child*. 1986;61(1):20-23.
3. Kim KH. Clinical pearls from atopic dermatitis and its infectious complications. *Br J Dermatol*. 2014;170(Suppl 1):25-30.
4. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014; 71(1):116-132.
5. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51(3):329-337.
6. Gonzalez ME, Schaffer JV, Orlow SJ, et al. Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis. *J Am Acad Dermatol*. 2016;75(3):481-493.e488.
7. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22(5):850-859.
8. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9(378).
9. Totte JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. 2016;175(4):687-695.
10. Gong JQ, Lin L, Lin T, et al. Skin colonization by *Staphylococcus aureus* in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. *Br J Dermatol*. 2006;155(4):680-687.
11. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: A meta-analysis of randomized controlled trials. *J Am Acad Dermatol*. 2017. [Epub ahead of print]
12. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol*. 2010;163(1):12-26.
13. Sidbury R, Davis DM, Cohen DE, et al. Guidelines for the management of atopic dermatitis: section 3. Management and treatment with polytherapy and systemic agents. *J Am Acad Dermatol*. 2014;712(2):327-349.
14. Leung DY. Why is eczema herpeticum unexpectedly rare? *Antiviral Res*. 2013;98(2):153-157.
15. Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The role of *Malassezia* spp. in atopic dermatitis. *J Clin Med*. 2015;4(6):1217-1228.