Food allergy is associated with *Staphylococcus aureus* colonization in children with atopic dermatitis

To the Editor:

Atopic dermatitis (AD) commonly precedes the development of food allergy.[1] The reasons for this close association are not well characterized. Recent studies in patients with AD found that peanut allergy was associated with filaggrin *(FLG)* mutations.[1,2] This finding suggests that skin barrier dysfunction contributes to the development of food allergy by promoting epicutaneous allergen absorption and sensitization. However, *FLG* mutations are absent in most patients with AD,[1] and a recent study conducted in the United States did not demonstrate the close relationship between peanut allergy and *FLG* mutations in children with AD.[3] This lack of association suggests there are other important factors contributing to an impaired skin barrier in these patients.

Staphylococcus aureus can cause significant skin barrier dysfunction and might thereby promote food allergy in patients with AD through epicutaneous entry of antigen. Atopic skin is predisposed to colonization or infection by *S aureus*, with approximately 50% of patients with AD demonstrating *S aureus* colonization.[1] Additionally, *S aureus* is known to cause skin breakdown through the production of exotoxins, proteases, and lipases. In murine models topical application of *S aureus* enterotoxin promoted T_H2-associated skin inflammation.[4] Cutaneous exposure to peanut in the presence of *S aureus* enterotoxin greatly enhances $CD4^+$ T_H2 responses in mice,[5] further supporting the role of *S aureus* in the development of food allergy.

The aim of this study was to investigate the relationship between *S aureus* colonization and food allergy in children with AD. We hypothesized that children with AD would have an increased prevalence of food allergy when colonized with *S aureus*. The National Jewish Health Research Database was queried for patients aged 0 to 18 years with AD and *S aureus* culture from March 2008 to March 2015. Data analysis was performed with SAS (SAS Institute, Cary, NC) and R software. Permutation methods were used to compare outcomes among groups.

The study included 718 patients: 139 (19.4%) patients with methicillin-resistant *Staphylococcus aureus* (MRSA), 411 (57.2%) patients with methicillin-sensitive *Staphylococcus aureus* (MSSA), and 168 (23.4%) patients with no *S aureus*. Food allergy determined by means of ImmunoCAP was defined as food allergen–specific IgE (sIgE) levels that correlate to a greater than 95% positive predictive value of oral food challenge reaction in patients (peanut, 14 kilounits of allergen [kU_A]/L; egg white, 7 kU_A/L; and cow's milk, 15 kU_A/L).[6]

sIgE values correlating to clinical food allergy for peanut, egg white, and cow's milk were associated with *S aureus* colonization (Fig 1). Additionally, median IgE levels to peanut were significantly higher in the MRSA versus MSSA groups (77.7 vs 38.9 kU_A/L, $P = .02$). Age did not affect the level of IgE to peanut in any of these groups ($P = .20$). No difference between patients with MRSA and patients with MSSA was seen in food sIgE levels to egg white or cow's milk.

There were higher total serum IgE (tIgE) levels in patients with versus those without *S aureus* colonization (MRSA: 4498 kU/L vs MSSA: 2709 kU/L vs no *S aureus*: 217 kU/L, $P < .0001$; see Fig E1 in this article's Online Repository at www.jacionline.org). It has been suggested that a total serum IgE level of greater than 1000 kU/L is associated with nonspecific binding to allergens.[7] Therefore, we assessed an alternative approach to determine whether peanut allergy is associated with *S aureus* colonization.

Skin prick test data were analyzed for peanut allergy. Peanut allergy determined based on skin prick test responses was defined as a wheal size of 8 mm or greater, which is associated with a 95% to 100% positive predictive value for positive oral peanut challenge results.[8] *S aureus* colonization was associated with a significantly higher percentage of patients with a positive predictive value for peanut allergy determined by means of skin testing compared with no *S aureus* colonization (59% vs 47%, $P = .01$, Table I). There are no well-accepted positive predictive values for allergy by using skin prick tests to other foods,[6] and therefore egg white and cow's milk were not analyzed. The cohort was also evaluated for food allergy diagnostic codes, anaphylaxis diagnostic codes, and prescription for an epinephrine autoinjector. Food allergy diagnostic codes were found to be significantly more prevalent in patients with *S aureus* colonization versus

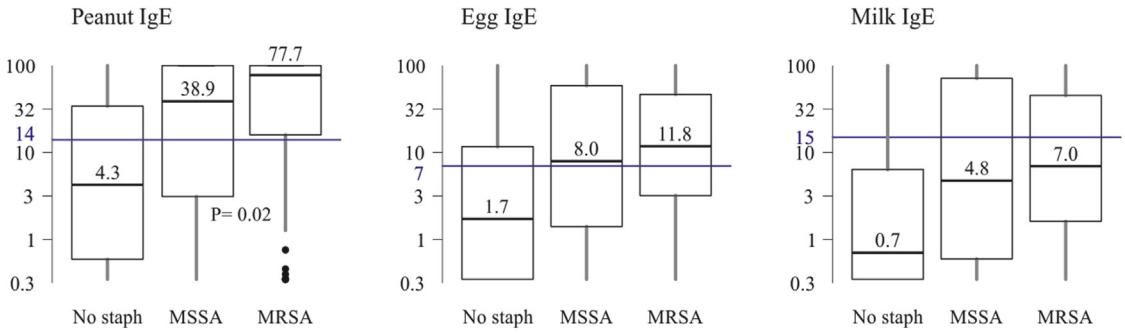

FIG 1. Comparison of sIgE levels to peanut, egg white, and cow's milk based on *S aureus* colonization status. Staph refers to *S aureus*. *Blue lines* represent the sIgE values associated with greater than 95% positive predictive value of oral food challenge reaction. Patients with *S aureus* colonization have significantly higher sIgE levels to peanut, egg, and milk compared with those with no *S aureus* colonization ($P < .0001$). Median IgE levels to peanut were significantly higher in the MRSA versus MSSA groups (77.7 vs 38.9 kU_A/L, $P = .02$).

TABLE I. Peanut skin prick test results

	<8 mm	≥8 mm	*P* value
S aureus colonization	227 (41%)	322 (59%)	.01
No *S aureus* colonization	89 (53%)	79 (47%)	

Peanut allergy determined by using skin prick tests was defined as a wheal size of 8 mm or greater, which is associated with a 95% to 100% positive predictive value for peanut allergy.[8] *P* values were determined by using the Fisher exact test.

those without *S aureus* colonization (70% vs 48%, $P < .0001$). Diagnostic code for anaphylaxis, prescription for an epinephrine autoinjector, or both were also found to be significantly more prevalent in patients with *S aureus* colonization versus those without *S aureus* colonization (53% vs 44%, $P = .04$; see Tables E1 and E2 in this article's Online Repository at www.jacionline.org).

These data suggest there is an association between *S aureus* colonization and food allergy to peanut, egg white, and cow's milk in patients with AD. *S aureus* is a pathogenic microbe that produces multiple virulence factors (eg, superantigens, cytolysins, proteases, lipases, protein A, and microbial surface components recognizing adhesive matrix molecules) that can lead to break down of the epithelial barrier.[9] Additionally, exposure of murine models to *S aureus* toxin leads to increased T_H2-mediated responses[4,5] and decreased regulatory T-cell function,[4] both of which are described in patients with food allergy.[10] We propose that the skin microbiome plays an important role in skin barrier function and directs immune responses. Aberrancies in the skin microbiome, including *S aureus* colonization, lead to skin barrier dysfunction and immune dysregulation, ultimately contributing to the development of food allergy through topical exposure of antigen.

Furthermore, these findings show a unique association between peanut allergy and MRSA because peanut sIgE levels were higher in patients with MRSA colonization compared with those with MSSA. These findings support the theory that *S aureus* causes skin breakdown, leading to epicutaneous absorption of peanut. MRSA produces more superantigens than MSSA[9] and might be contributing to more significant skin barrier breakdown. Additionally, studies have demonstrated that peanut allergy, in particular, occurs through epicutaneous allergen absorption.[2,3]

These results are of particular relevance to the events that predispose subjects to food allergy. Recent studies have demonstrated that environmental peanut drives sensitization and peanut allergy in patients with AD.[2] Further studies looking at peanut protein and *S aureus* in house dust could shed new light on the effect of *S aureus* and food allergy. The clinical relevance to our findings are suggested by increased diagnostic codes for anaphylaxis, epinephrine autoinjector prescription, or both in patients with *S aureus* colonization, indicating there was physician concern for clinically relevant food allergy.

In the future, studies are needed to assess the association between *S aureus* skin colonization and food allergy in patients with AD. Confirmation of our current observations open up the possibility that therapy directed at eradicating *S aureus* colonization will be important in the prevention of food allergen sensitization and possibly food allergy in patients with AD.

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Household almond and peanut consumption is related to the development of sensitization in young children

To the Editor:

Nut allergy is one of the most common and severe food allergies in children. Therefore understanding the causes of nut allergy is essential to establishing primary preventive measures to avoid the onset of this condition.

The most significant risk factor for children in terms of having food allergy is atopic dermatitis (AD). Food allergy has also been associated with genetic, molecular, dietary, and environmental factors.[1] The early introduction of allergenic foods in children's diets appears to prevent the development of allergy.[2-4] Moreover, in recent years, several studies have shown that there is a clear relationship between household peanut consumption and allergy, especially in children with eczema or other skin barrier function disorders, which supports the concept of a transcutaneous sensitization pathway.[5-7]

The aim of this study was to assess the association between consumption of various types of nuts (almonds, walnuts, and peanuts) in domestic settings by family members who live with the children and sensitization to these foods in children younger than 18 months who had not yet had the foods introduced to their diets.