



Bacterial colonization, overgrowth, and superinfection in atopic dermatitis

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Abstract *Staphylococcus aureus* infection is a major burden for individuals with moderate-to-severe atopic dermatitis and a known inducer of disease exacerbation. This increased susceptibility to staphylococcal infections has been attributed to abnormalities in the innate immune system of atopic dermatitis (AD) skin, including deficits in barrier proteins and lipids, and a muted response in generating antimicrobial peptides, all of which is further impaired by the activation of Th2 and Th22 immune pathways, which characterizes AD. Skewing of the immune response with a reduced Th1:Th2 ratio and increased adherence of bacteria to AD skin are also thought to contribute. Bacterial species diversity is reduced with flares, concomitant with increases in *S. aureus* and sometimes clinical infection, which has recently been linked to the finding that commensal bacteria produce anti-*S. aureus* factors that contribute to the endogenous response. *S. aureus* produces several virulence factors affecting the skin barrier and immune system, including promoting Th2 cell activation. Best practices for the management of staphylococcal infections include systemic antibiotics, initiation of antiseptics (particularly dilute bleach baths), and sometimes periodic intranasal mupirocin. Newer evidence suggests the possibility that treatment of the skin with commensal bacterial species could also reduce *S. aureus* growth and increase diversity.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects 10–20% of children^{1–3} and 7–10% of adults.^{4,5} Approximately one of every three children with AD have moderate-to-severe disease,⁶ and the percentage with moderate-to-severe disease increases with advancing age. The risk of cutaneous staphylococcal infections is well recognized to be increased in AD, and especially in pediatric and adults AD patients with moderate-to-severe disease.^{7–11} Staphylococcal infection is usually limited to the skin and characterized as impetigo, but staphylococcal pustulosis, folliculitis, abscesses (especially with methicillin-resistant strains

of *S. aureus*), and cellulitis may occur (Figures 1 and 2). Rarely, AD is associated with bacteremia, sepsis, septic arthritis, osteomyelitis, endocarditis, pneumonia, and/or ocular infection.^{12,13}

While this review focuses on *Staphylococcus aureus* infection, *Streptococcus spp.* may be found in addition to *S. aureus*. In one study, both organisms were present in cultures of 70–80% of AD patients with infected lesions.¹⁴ Streptococcal pharyngitis may be found in association with streptococcal pyoderma. Cutaneous dissemination of the herpes simplex virus (HSV), particularly at lesional sites (eczema herpeticum), occurs overall in less than 3% of AD patients; however, as with *S. aureus* infections, its occurrence is greatest in patients with more severe AD, heightened Th2 responses, and decreased skin expression of filaggrin and antimicrobial peptides.^{15,16}

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Fig. 1 Impetigo with erythema, swelling, and serosanguineous to honey-colored crusting on the foot.

Molluscum contagiosum¹⁷ and coxsackie infections (especially coxsackie A6; eczema coxsackium)^{18,19} are often more disseminated in children with AD, manifesting most prominently at sites of active dermatitis.

Individuals with AD are more susceptible to *S. aureus* colonization and infection

S. aureus (SA) is not typically a colonizer of the skin, nose, or respiratory tract; in healthy individuals only about 3% have skin colonization²⁰ and 23% have nasal colonization.²¹ In a recent systematic review and meta-analysis of 95 studies, the pooled prevalence of *S. aureus* colonization in AD was 70% for lesional skin, 39% for nonlesional skin, and 62% for the



Fig. 2 Inflammation, pustules, and purulent draining on a background of dermatitis. Note the tense edema and increased redness of the helical rim.

nose,²¹ demonstrating the markedly increased likelihood of being colonized on lesional skin (OR 19.74, 95% CI 10.88-35.81, $P < 0.001$), nonlesional skin (OR 7.77, 95% CI 3.82-15.82, $P < 0.001$), and nares (OR 4.50, 95% CI 3.00-6.75, $P < 0.001$). The rates of colonization increased with greater severity¹¹ and age.²¹ *S. aureus* density on lesional and nonlesional skin has also been shown to correlate with disease severity.²² Colonization on lesional skin occurs in 43% of mildly affected patients and 83% with severe AD.²¹ Colonization has been associated with the generation of IgE antibodies against staphylococcal superantigens, especially in more severe AD, and has recently been correlated with having specific IgE antibodies against multiple foods in children with AD.²³⁻²⁵

S. aureus and *S. epidermidis* bacteria are now known to be able to penetrate skin to the dermis,²⁶ providing additional evidence that bacteria can affect cutaneous immune homeostasis. *S. aureus* has been detected by qPCR in the epidermis and dermis of lesional AD skin at levels of 5×10^3 to 1×10^4 *S. aureus* DNA rCFU/mm³, but not in nonlesional AD skin, whereas *S. epidermidis* is found in the epidermis (1×10^2 to 2×10^3 DNA rCFU/mm³) and, to a lesser extent, the dermis (4×10^1 to 1×10^3 DNA rCFU/mm³) in lesional and nonlesional AD skin, as well as healthy control skin.²⁶

Colonization with methicillin-resistant strains of *S. aureus* (MRSA) has been increasing, and MRSA skin infections are much more challenging to treat than methicillin-sensitive *S. aureus* (MSSA). An Australian longitudinal study of colonization identified a tripling of the percentage of MRSA versus MSSA from 2003 to 2006 with a 13-fold increase from 2007 to 2010 and a 24-fold increase from 2011 to 2014, although MRSA still represented only 10% of all *S. aureus* at peak.²⁷ In contrast, another recent study found no significant changes in antimicrobial susceptibility of *S. aureus* strains isolated from adolescent AD patients during a 10-year period.²⁸

Regional variation in MRSA prevalence and antibiotic prescribing trends have been shown to affect colonization and may explain discrepancies. *S. aureus* is known to adhere well to AD skin, in part because of the increased exposure of fibronectin and fibrinogen from barrier dysfunction and excoriation. The presence of the *mec* genomic element, which encodes for methicillin resistance in *S. aureus*, is linked to expression of fewer functional fibronectin and fibrinogen adhesion proteins on the bacterial outer surface.²⁹ The relatively low percentage of AD patients with MRSA colonization may be attributable to the better adherence of MSSA strains to AD skin and the need for MRSA to compete with MSSA in AD skin and nares.³⁰

Defects in innate immunity may predispose to *S. aureus* infection

Several defects in the cutaneous innate immune system of individuals with AD increase the susceptibility to cutaneous infection, particularly disruption of the epidermal barrier,

diminished antimicrobial peptide production in response to immune stimulation, and reduced recruitment of innate immune cells to the skin.³¹

The integrity of the epidermal barrier depends on the presence and proper function of several proteins of differentiation, junctional proteins, and epidermal lipids. Impairment of the barrier in AD has been blamed on deficiency of proteins, especially filaggrin (only with chronic AD and not in the first 6 months after onset)³²; poor function of junctional regions, especially tight junctions; and abnormalities in lipids, especially reduction of long-chain fatty acids and ceramide. Increased activity of proteases and lipases further depletes proteins and lipids, and worsens the barrier. Barrier function can be measured as transepidermal water loss. Poor barrier function results in water loss (manifesting in skin dryness), as well as the easier penetration of organisms³³ and antigens.

The most common genetic defect is mutations in *FLG*, leading to filaggrin haploinsufficiency, which occurs in approximately 10% of individuals of Northern European descent and accounts for 20–30% of patients with AD; *FLG* mutations (most commonly null mutations) have been linked to greater AD severity and persistence, higher skin pH (increasing protease activity), and a greater risk of staphylococcal infection.³⁴ Although the majority with AD do not have a genetic mutation in *FLG*, filaggrin mRNA and protein expression has been shown to be reduced in the skin of adults with AD, likely reflecting their disease chronicity and the recognized diminution of filaggrin expression in the presence of Th2 cytokines interleukin (IL)-4 and IL-13³⁵ and by exposure to *S. aureus*.³⁶

Indeed, a measurement of transepidermal water loss in the upper quartile for neonates at 2 days of age has recently been found to increase the risk of having AD at 1 year of age by 7.1-fold, reiterating the importance of the barrier impairment early in the development of AD³⁷; however, the lesional skin from young children with AD in the first 6 months after onset has no deficiency of filaggrin mRNA or protein, detracting from the focus on filaggrin deficiency and emphasizing that deficiency or dysfunction of other barrier proteins and lipids may be more important in early AD.^{32,38}

In addition to their production of a physical epidermal barrier, keratinocytes also play a critical role in innate immunity through their recognition of microbes and elaboration of antimicrobial peptides. Keratinocytes express pattern recognition receptors, which, when activated, lead to the production of inflammatory cytokines and chemokines that promote neutrophil recruitment for microbe clearance. In AD patients, there are polymorphisms in several pattern recognition receptors (TLR2, NOD1, CD14), which are associated with severe disease and increased susceptibility to infection and allergic sensitization.^{39–42} In adult AD skin, there is an inadequate response in generating antimicrobial peptides, particularly cathelicidins and beta-defensins,⁴³ cationic polypeptides that lyse anionic bacterial membranes.⁴⁴ The Th2 cytokines that drive AD are also able to reduce expression of antimicrobial peptides. Children with moderate-to-severe AD and adults with more severe AD have low numbers of circulating skin-

homing Th1 lymphocytes in comparison to healthy controls,⁴⁵ which may contribute to the increased risk of infection. In addition, the Th1/Th2 ratio is particularly low due to Th2 skewing in AD, and Th2-produced IL-4 has been shown to suppress the production of antimicrobial peptides.³⁹

***S. aureus* is pro-inflammatory and can exacerbate AD**

S. aureus secretes several exotoxins, particularly superantigens,⁴⁶ which have been shown to worsen the epidermal barrier and/or increase inflammation (Table 1). MRSA strains are associated with a heightened production of superantigens, which has been thought to lead to more enhancement of skin inflammation than MSSA infection. In fact, the recently demonstrated correlation of heightened food sensitization with IgE responses to *S. aureus*, and particularly MRSA infection, may reflect more percutaneous absorption of antigen in association with *S. aureus* damage to skin.^{24,25} Among these various products are the superantigens (staphylococcal enterotoxins and toxic shock syndrome toxin-1), exfoliatin, V8 serine protease, alpha- and delta-toxin, staphylococcal protein A, and phenol-soluble modulins (Table 1). Superantigens bind to the non-peptide groove of the major histocompatibility complex class II on antigen-presenting cells and to the T cell receptor beta-chains, leading to nonspecific activation of T cells and the expression of TNF-alpha and IL-1-beta pro-inflammatory cytokines (superantigens, protein A). Toxins produced by *S. aureus* cause cell lysis and death of keratinocytes (alpha-toxin), as well as degranulation of mast cells (delta-toxin). Proteases from the staphylococcus, such as V8 serine protease and exfoliatin, cause damage to the epidermis, but *S. aureus* also has been shown to induce keratinocyte kallikreins,⁴⁷ further increasing protease activity and barrier deterioration.

The microbiome and *S. aureus*

Studies of the AD microbiota have shown that AD flares are associated with microbial dysbiosis that is dominated by *S. aureus* and, to a lesser extent, *S. epidermidis*.^{48–50} With appropriate treatment and response, diversity is restored, including with increases in *Streptococcus*, *Propionibacterium*, and *Corynebacterium* species. Topical steroids,⁴⁸ topical steroids plus dilute bleach baths,⁵¹ and even emollients alone^{52,53} have been shown to alter the lesional skin microbiota toward that of nonlesional skin. Whether the gut microbiome plays a role in AD remains controversial, but some reports suggest that increased diversity of organisms in the gut may also reduce the risk of development or severity of AD.^{54–58} Regardless, alteration of gut flora through the use of probiotics or prebiotics has largely had no impact on AD.

Table 1 *S. aureus* virulence factors that exacerbate AD

Factors	Mechanism of action
Superantigens	T cell activation, inducing cytokine production by keratinocytes
Staphylococcal exotoxin A	
Staphylococcal exotoxin B	
Toxic shock syndrome toxin-1	
Exfoliatins A, B	Protease causing desmoglein-1 cleavage and leads to desquamation at stratum granulosum level
V8 protease	Protease causing increased epidermal desquamation and barrier damage
Alpha-toxin	TNF-alpha production; keratinocyte lysis
Delta-toxin	Mast cell degranulation and inflammation
Protein A	Production of TNF-alpha by keratinocytes
Phenol-soluble modulins (PSM)	Epidermal inflammation

The role of commensal organisms in protecting against AD and infection

Recent studies have aimed to understand the interplay between *S. aureus* infections in AD patients and colonization from other commensal bacteria, such as *S. epidermidis*.⁵⁹ *S. epidermidis*, which is highly abundant in skin, has been shown to suppress toll-like receptor-mediated inflammation, increase T cell and mast cell recruitment to skin, promote regulatory T cell activity,⁶⁰ increase tight junctions, and amplify endogenous expression of antimicrobial peptides.⁶¹⁻⁶³ *S. epidermidis* produces phenol-soluble modulins (PSMs) and proteases that prevent *S. aureus* biofilm formation and organism growth.⁶⁴ A prospective study found that infants with AD by 12 months of age had fewer commensal staphylococci on the antecubital fossa at 2 months of age than healthy 12-month-olds; there was no evidence of dysbiosis or *S. aureus* colonization at 2 months in the babies with AD.⁶⁵ However, another prospective birth cohort study found more *S. aureus* on the skin at 3 months of age in those who developed AD.⁶⁶

Treatment with nonpathogenic bacterium *Vitreoscilla filiformis* significantly reduced inflammation in the NC/Nga murine model of AD.⁶⁷ More recently, two early phase open-label human trials with commensals that show toxicity against *S. aureus* in vitro have been reported. In one, topical application of autologous coagulate-negative staphylococcus (CoNS) reduced skin *S. aureus* colonization;⁶⁸ in the other, topically applied *Roseomonas mucosa* improved the dermatitis, reduced topical steroid use, and decrease skin *S. aureus* burden in 15 AD patients.⁶⁹ These studies suggest that increasing commensal organisms on the skin could improve AD. Fecal microbiota therapy has also become a method for correcting dysbiosis of the gut microbiome, especially for clostridial infection.

Management of staphylococcal infections

In general, staphylococcal infections are best managed by a course of systemic antibiotic (usually an early-generation cephalosporin or amoxicillin-clavulanate), unless so localized and mild that

they might respond to a topical antibiotic. Culture of lesional skin is likely to grow *S. aureus*, whether clinically infected or not, so that culture should be reserved for patients suspected of having MRSA infection (eg, if not responding well or having a history of MRSA), which, unless leading to abscess formation, is indistinguishable clinically from MSSA infection. MRSA infections may require treatment with clindamycin or trimethoprim-sulfamethoxazole, and therapy should be guided by culture results if MRSA. Antibiotics should not be administered in the absence of infection, as indiscriminate use may increase the risk of resistant organisms, and reduction in inflammation has not been demonstrated in the absence of infection.⁷⁰ That said, it is commonly recognized by practitioners that the severity of AD in infected patients improves while on the antibiotic and can flare after the course of antibiotic is completed despite maintenance of antiinflammatory topical therapy.

Dilute bleach baths are the most frequently used antiseptic routine and have been shown in double-blind trials to maintain disease control after treating infection in moderate-to-severe AD.^{71,72} Twice-daily baths with 0.005% hypochlorite (1/2 cup per full tub, 3.8 cc per gallon, or 1 cc per liter using standard 5-6% bleach) led to significantly greater mean reductions in Eczema Area and Severity Index scores and reduction in body surface area at 1 and 3 months after initiation compared with the placebo group. Although subjects also applied mupirocin (or vehicle) intranasally, the improved AD severity of only submerged areas implicated the bath rather than intranasal mupirocin as the effective component of the regimen. Other studies have confirmed the benefit of dilute bleach baths,^{73,74} and their use has become a mainstay of maintenance therapy to simply and cost-effectively maintain disease control. Dilute bleach baths can be used daily for more severely affected individuals, can be tailored to soaking hands or feet for more recalcitrant localized lesions, and can be simulated by topically applied leave-on or in-shower hypochlorite solutions.⁷⁵ For recurrent infections, additional decolonization procedures may be necessary. MRSA colonization reservoirs commonly include the nostrils, throat, groin, axillae, subungual areas, and wounds. Intranasal mupirocin ointment is typically applied twice daily for 5 consecutive days monthly, and can be used by all family members. Mupirocin resistance has been increasing in AD,⁷⁶ reiterating the importance of avoiding a topical

antibiotic as well unless necessary. Of note, the same strain of *S. aureus* has been found in 65% of parents of an affected AD child. Especially with MRSA, which is notoriously difficult to eradicate, decolonization of family members may be necessary. Use of dilute bleach baths or showers for the entire family may be necessary. Pets may also harbor *S. aureus*, including MRSA, and referral to a knowledgeable veterinarian is recommended for pet assessment and management. In addition, emollients and even tubes of medication may harbor bacteria, including *S. aureus*.

Techniques to decrease the growth and repeated transfer from contaminated products include wiping the tip of the medication tube with an alcohol wipe after use, keeping emollients in the refrigerator between applications (and floating them in the bathtub to warm), and using a clean spoon to decant for each application to avoid transfer from the skin to the container. Finally, the results of vitamin D₃ supplementation are conflicting, and the impact of vitamin D₃ deficiency is unclear.^{77,78} Vitamin D₃ topically applied to skin increases cathelicidin production, but leads to irritation. In some reports, oral cholecalciferol supplementation can similarly increase stratum corneum levels of cathelicidin and even lead to improvement in inflammation.⁷⁹

Conclusions

AD skin has an increased susceptibility to infections attributed to abnormalities in the innate immune system and a muted response in generating antimicrobial peptides. Additionally, the epidermal barrier is impaired due to a deficiency of proteins, especially filaggrin, poor function of junctional regions, and abnormalities in lipids, making AD skin more susceptible to microbial colonization and penetration. In all cases of AD infection, careful genotyping and characterization of the etiologic agent (especially in cases of MRSA) is important to initiate proper treatment early and to alleviate the exacerbation of AD symptoms and continued infection. MRSA strains are associated with a heightened production of superantigens that can lead to worsening skin conditions and heightened inflammation.

There is growing evidence that suggests the treatment of the skin with commensal bacterial species could reduce *S. aureus* growth and increase skin microbiome diversity, which helps to normalize the Th1:Th2 ratio and promote commensal bacteria production of anti-*S. aureus* factors. Best practices for management of staphylococcal infections include systemic antimicrobial initiation of antiseptics (particularly dilute sodium hypochlorite baths), and periodic intranasal mupirocin to reduce the risk of recurrent infections.

References

1. Fu T, Keiser E, Linos E, et al. Eczema and sensitization to common allergens in the United States: A multiethnic, population-based study. *Pediatr Dermatol*. 2014;31:21-26.
2. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol*. 2013;133:1752-1759.
3. Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: Data from the 2003 national survey of children's health. *J Invest Dermatol*. 2011;131:67-73.
4. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population-based study. *J Allergy Clin Immunol*. 2013;132:1132-1138.
5. Hanifin JM, Reed ML. A population-based survey of eczema prevalence in the United States. *Dermatitis*. 2007;18:82-91.
6. Silverberg JI, Simpson EL. Associations of childhood eczema severity: A US population-based study. *Dermatitis*. 2014;25:107-114.
7. Breuer K, Häussler S, Kapp A, et al. *Staphylococcus aureus*: Colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol*. 2002;147:55-61.
8. Travers JB, Kozman A, Mousdicas N, et al. Infected atopic dermatitis lesions contain pharmacologic amounts of lipoteichoic acid. *J Allergy Clin Immunol*. 2010;125:146-152.e141-142.
9. Kedzierska A, Kapinska-Mrowiecka M, Czubak-Macugowska M, et al. Susceptibility testing and resistance phenotype detection in *Staphylococcus aureus* strains isolated from patients with atopic dermatitis, with apparent and recurrent skin colonization. *Br J Dermatol*. 2008;159:1290-1299.
10. Tomi NS, Kranke B, Aberer E. Staphylococcal toxins in patients with psoriasis, atopic dermatitis, and erythroderma, and in healthy control subjects. *J Am Acad Dermatol*. 2005;53:67-72.
11. Hon KL, Tsang YC, Pong NH, et al. Clinical features and *Staphylococcus aureus* colonization/infection in childhood atopic dermatitis. *J Dermatolog Treat*. 2016;27:235-240.
12. Patel D, Jahnke MN. Serious complications from *Staphylococcal aureus* in atopic dermatitis. *Pediatr Dermatol*. 2015;32:792-796.
13. Fukunaga N, Okada Y, Konishi Y, et al. Pay attention to valvular disease in the presence of atopic dermatitis. *Circ J*. 2013;77:1862-1866.
14. Petry V, Bessa GR, Poziomczyk CS, et al. Bacterial skin colonization and infections in patients with atopic dermatitis. *An Bras Dermatol*. 2012;87:729-734.
15. Beck LA, Boguniewicz M, Hata T, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol*. 2009;124:260-269.e7.
16. Leung DY. Why is eczema herpeticum unexpectedly rare? *Antivir Res*. 2013;98:153-157.
17. Harel A, Kutz AM, Hady-Rabia S, et al. To treat molluscum contagiosum or not—curettage: An effective, well-accepted treatment modality. *Pediatr Dermatol*. 2016;33:640-645.
18. Mathes EF, Oza V, Frieden IJ, et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. *Pediatrics*. 2013;132:e149-e157.
19. Lynch MD, Sears A, Cookson H, et al. Disseminated coxsackievirus affecting children with atopic dermatitis. *Clin Exp Dermatol*. 2015;40:525-528.
20. Park HY, Kim CR, Huh IS, et al. *Staphylococcus aureus* colonization in acute and chronic skin lesions of patients with atopic dermatitis. *Ann Dermatol*. 2013;25:410-416.
21. Totte JE, van der Feltz WT, Hennekam M, et al. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: A systematic review and meta-analysis. *Br J Dermatol*. 2016;175:687-695.
22. Tauber M, Balica S, Hsu CY, et al. *Staphylococcus aureus* density on lesional and nonlesional skin is strongly associated with disease severity in atopic dermatitis. *J Allergy Clin Immunol*. 2016;137:1272-1274.e3.
23. Ong PY. Association between egg and staphylococcal superantigen IgE sensitizations in atopic dermatitis. *Allergy Asthma Proc*. 2014;35:346-348.
24. Czarnowicki T, Esaki H, Gonzalez J, et al. Alterations in B-cell subsets in early pediatric atopic dermatitis. *J Allergy Clin Immunol*. 2016;134:144.e9.
25. Jones AL, Curran-Everett D, Leung DY. Food allergy is associated with *Staphylococcus aureus* colonization in children with atopic dermatitis. *J Allergy Clin Immunol*. 2016;137:1247-1248.e1241-1243.

26. Nakatsuji T, Chen TH, Two AM, et al. *Staphylococcus aureus* exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. *J Invest Dermatol.* 2016;136:2192-2200.
27. Chaptini C, Quinn S, Marshman G. Methicillin-resistant *Staphylococcus aureus* in children with atopic dermatitis from 1999 to 2014: A longitudinal study. *Australas J Dermatol.* 2016;57:122-127.
28. Park JM, Jo JH, Jin H, et al. Change in antimicrobial susceptibility of skin-colonizing *Staphylococcus aureus* in Korean patients with atopic dermatitis during ten-year period. *Ann Dermatol.* 2016;28:470-478.
29. Vaudaux PE, Monzillo V, Francois P, et al. Introduction of the mec element (methicillin resistance) into *Staphylococcus aureus* alters *in vitro* functional activities of fibrinogen and fibronectin adhesins. *Antimicrob Agents Chemother.* 1998;42:564-570.
30. Matiz C, Tom WL, Eichenfield LF, et al. Children with atopic dermatitis appear less likely to be infected with community acquired methicillin-resistant *Staphylococcus aureus*: The San Diego experience. *Pediatr Dermatol.* 2011;28:6-11.
31. De Benedetto A, Agnihothri R, McGirt LY, et al. Atopic dermatitis: A disease caused by innate immune defects? *J Invest Dermatol.* 2009;129:14-30.
32. Brunner PM, Israel A, Zhang N, et al. Early-onset pediatric atopic dermatitis is characterized by TH2/TH17/TH22-centered inflammation and lipid alterations. *J Allergy Clin Immunol.* 2018;141:2094-2106.
33. Jinnestal CL, Belfrage E, Back O, et al. Skin barrier impairment correlates with cutaneous *Staphylococcus aureus* colonization and sensitization to skin-associated microbial antigens in adult patients with atopic dermatitis. *Int J Dermatol.* 2014;53:27-33.
34. Lopes C, Rocha L, Sokhatska O, et al. Filaggrin polymorphism Pro478Ser is associated with the severity of atopic dermatitis and colonization by *Staphylococcus aureus*. *J Investig Allergol Clin Immunol.* 2016;26:70-72.
35. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol.* 2007;120:150-155.
36. van Drongelen V, Haisma EM, Out-Luiting JJ, et al. Reduced filaggrin expression is accompanied by increased *Staphylococcus aureus* colonization of epidermal skin models. *Clin Exp Allergy.* 2014;44:1515-1524.
37. Kelleher M, Dunn-Galvin A, Hourihane JO, et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol.* 2015;135:930-935.e931.
38. Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is Th2 but also Th17 polarized in skin. *J Allergy Clin Immunol.* 2016;138:1639-1651.
39. Biedermann T. Dissecting the role of infections in atopic dermatitis. *Acta Derm Venereol.* 2006;86:99-109.
40. Weidinger S, Klopp N, Rummeler L, et al. Association of NOD1 polymorphisms with atopic eczema and related phenotypes. *J Allergy Clin Immunol.* 2005;116:177-184.
41. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, et al. The toll-like receptor 2 R753 Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol.* 2004;113:565-567.
42. Zdolsek HA, Jenmalm MC. Reduced levels of soluble CD14 in atopic children. *Clin Exp Allergy.* 2004;34:532-539.
43. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med.* 2002;347:1151-1160.
44. Krishna S, Miller LS. Innate and adaptive immune responses against *Staphylococcus aureus* skin infections. *Semin Immunopathol.* 2012;34:261-280.
45. Czarnowicki T, Esaki H, Gonzalez J, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) Th2/Th1 cell imbalance, whereas adults acquire CLA(+) Th22/Tc22 cell subsets. *J Allergy Clin Immunol.* 2015;136:941-951.e943.
46. Williams MR, Gallo RL. The role of the skin microbiome in atopic dermatitis. *Curr Allergy Asthma Rep.* 2015;15:65.
47. Williams MR, Nakatsuji T, Sanford JA, et al. *Staphylococcus aureus* induces increased serine protease activity in keratinocytes. *J Invest Dermatol.* 2017;137:377-384.
48. 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;22:850-859.
49. Oh J, Conlan S, Polley EC, et al. Shifts in human skin and nares microbiota of healthy children and adults. *Genome Med.* 2012;4:77.
50. Kobayashi T, Glatz M, Horiuchi K, et al. Dysbiosis and *Staphylococcus aureus* colonization drives inflammation in atopic dermatitis. *Immunity.* 2015;42:756-766.
51. 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;75:481-493.e488.
52. Seite S, Flores GE, Henley JB, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol.* 2014;13:1365-1372.
53. Glatz, Jo JH, Kennedy EA, et al. Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. *PLoS One.* 2018;13:e0192443.
54. Nylund L, Nermes M, Isolauri E, et al. Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria. *Allergy.* 2015;70:241-244.
55. Song H, Yoo Y, Hwang J, et al. *Faecalibacterium prausnitzii* subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis. *J Allergy Clin Immunol.* 2016;137:852-860.
56. Lee SY, Yu J, Ahn KM, et al. Additive effect between IL-13 polymorphism and cesarean section delivery/prenatal antibiotics use on atopic dermatitis: A birth cohort study (COCO). *PLoS One.* 2014;9:e96603.
57. Penders J, Gerhold K, Stobberingh EE, et al. Establishment of the intestinal microbiota and its role for atopic dermatitis in early childhood. *J Allergy Clin Immunol.* 2013;132:601-607.e608.
58. Nowrouzian FL, Lina G, Hodille E, et al. Superantigens and adhesins of infant gut commensal *Staphylococcus aureus* strains and association with subsequent development of atopic eczema. *Br J Dermatol.* 2017;176:439-445.
59. Hon KL, Tsang YC, Pong NH, et al. Exploring *Staphylococcus epidermidis* in atopic eczema: Friend or foe? *Clin Exp Dermatol.* 2016;41:659-663.
60. Laborel-Preneron E, Bianchi P, Boralevi F, et al. Effects of the *Staphylococcus aureus* and *Staphylococcus epidermidis* secretomes isolated from the skin microbiota of atopic children on CD4+ T cell activation. *PLoS One.* 2015;10:e0141067.
61. Lai Y, Cogen AL, Radek KA, et al. Activation of TLR2 by a small molecule produced by *Staphylococcus epidermidis* increases antimicrobial defense against bacterial skin infections. *J Invest Dermatol.* 2010;130:2211-2221.
62. Lai Y, Di Nardo A, Nakatsuji T, et al. Commensal bacteria regulate toll-like receptor 3-dependent inflammation after skin injury. *Nat Med.* 2009;15:1377-1382.
63. Wanke I, Steffen H, Christ C, et al. Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways. *J Invest Dermatol.* 2011;131:382-390.
64. Cogen AL, Yamasaki K, Sanchez KM, et al. Selective antimicrobial action is provided by phenol-soluble modulins derived from *Staphylococcus epidermidis*, a normal resident of the skin. *J Invest Dermatol.* 2010;130:192-200.
65. Kennedy EA, Connolly J, Hourihane JO, et al. Skin microbiome before development of atopic dermatitis: Early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *J Allergy Clin Immunol.* 2017;139:166-172.
66. Meylan P, Lang C, Mermoud S, et al. Skin colonization by staphylococcus aureus precedes the clinical diagnosis of atopic dermatitis in infancy. *J Invest Dermatol.* 2017;137:2497-2504.
67. Volz T, Skabytska Y, Guenova E, et al. Nonpathogenic bacteria alleviating atopic dermatitis inflammation induce IL-10-producing dendritic cells and regulatory Tr1 cells. *J Invest Dermatol.* 2014;134:96-104.
68. 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.

69. Myles IA, Earland NJ, Anderson ED, et al. First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis. *JCI Insight*. 2018;3:120608.
70. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, et al. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: An updated Cochrane review. *Br J Dermatol*. 2010;163:12-26.
71. Huang JT, Abrams M, Tloutan B, et al. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics*. 2009;123:e808-e814.
72. Huang JT, Rademaker A, Paller AS. Dilute bleach baths for *Staphylococcus aureus* colonization in atopic dermatitis to decrease disease severity. *Arch Dermatol*. 2011;147:246-247.
73. Wong SM, Ng TG, Baba R. Efficacy and safety of sodium hypochlorite (bleach) baths in patients with moderate to severe atopic dermatitis in Malaysia. *J Dermatol*. 2013;40:874-880.
74. Barnes TM, Greive KA. Use of bleach baths for the treatment of infected atopic eczema. *Australas J Dermatol*. 2013;54:251-258.
75. Ryan C, Shaw RE, Cockerell CJ, et al. Novel sodium hypochlorite cleanser shows clinical response and excellent acceptability in the treatment of atopic dermatitis. *Pediatr Dermatol*. 2013;30:308-315.
76. Antonov NK, Garzon MC, Morel KD, et al. High prevalence of mupirocin resistance in *Staphylococcus aureus* isolates from a pediatric population. *Antimicrob Agents Chemother*. 2015;59:3350-3356.
77. Robl R, Uber M, Abagge KT, et al. Serum vitamin D levels not associated with atopic dermatitis severity. *Pediatr Dermatol*. 2016;33:283-288.
78. Chiu YE, Havens PL, Siegel DH, et al. Serum 25-hydroxyvitamin D concentration does not correlate with atopic dermatitis severity. *J Am Acad Dermatol*. 2013;69:40-46.
79. Albenali LH, Danby S, Moustafa M, et al. Vitamin D and antimicrobial peptide levels in patients with atopic dermatitis and atopic dermatitis complicated by eczema herpeticum: A pilot study. *J Allergy Clin Immunol*. 2016;138:1715-1719.E4.