FEATURE ARTICLE

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Atopic Dermatitis and *Staphylococcus aureus*

A Complex Relationship With Therapeutic Implications

Andrea M. Rustad, Melissa A. Nickles, and Peter A. Lio

ABSTRACT: A strong association has been established between *Staphylococcus aureus* and atopic dermatitis (AD). Although the exact mechanism of this relationship remains unclear, many studies have characterized differences in *S. aureus* between individuals with AD and unaffected controls. Patients with AD have higher cutaneous colonization with *S. aureus*, with increased bacterial density correlating with AD severity. *S. aureus* virulence factors can exacerbate the immune dysregulation seen in AD. Consequently, AD treatments have shifted to focus on *S. aureus* as a therapeutic target, including skin bacterial transplant and probiotics. In addition, traditional mainstays of AD treatment, such as corticosteroids, have been found to induce changes in the cutaneous microbiota and *S. aureus* levels, underscoring its importance in the pathogenesis of AD. Nonpharmacological treatments have been investigated as well, without definitive results. Both bacteriotherapy and nonpharmacological treatments merit continued study on their effects on *S. aureus* colonization and role in the treatment of AD.

Key words: Atopic Dermatitis, Bacterial Infection, Colonization, Microbiome, *Staphylococcus aureus*

Atopic dermatitis (AD) is a common inflammatory skin condition that arises due to a complex interaction of genetic and environmental factors. Skin barrier dysfunction is invariably present in AD, and the microbiome is an integral part of the skin barrier (Strugar et al., 2019). While *Staphylococcus aureus* can be part of the normal, commensal skin microbiota in a healthy skin barrier, it is well established that patients with AD have higher cutaneous colonization with *S. aureus* than those without AD (Kim et al., 2019). *S. aureus* colonizes skin in 60%–100% of patients with AD as compared to 5%–30% of healthy controls (Kim et al., 2019). *S. aureus* density directly correlates with disease severity on the Scoring Atopic Dermatitis index (Tauber et al., 2016). In addition, the bacteria is more commonly found on lesional compared to nonlesional skin on patients with AD (Totté et al., 2016) Whether *S. aureus* is pathogenic in the initiation of AD or proliferates secondary to AD remains unclear, though increasing evidence suggests it is a primary driver of disease in at least some scenarios (Byrd et al., 2017).

The impaired skin barrier in AD allows virulence factors from *S. aureus* to exacerbate AD symptoms of inflammation and allergic sensitization. In addition to triggering skin symptoms, the increased density of *S. aureus* can predispose patients with AD to extracutaneous conditions, from the atopic march and food allergies (Kim et al., 2019; Tsilochristou et al., 2019) to severe bloodstream infections via intravascular catheter infection (Mathé et al., 2020). Although such infections must be treated, antibiotics can further harm the already compromised AD skin

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barrier. To prevent disruption to the skin microbiome, antibiotic-sparing therapies have been developed to treat *S. aureus* and other pathogens in AD.

TOXINS/VIRULENCE

The main virulence factors of *S. aureus* implicated in AD are adhesins and exotoxins, many of which are superantigens that mediate bacterial invasion and spread (Table 1). Recently, second immunoglobulin-binding protein has been shown to be a predominant virulence factor, promoting Type 2 inflammation via IL-33 release in a mouse model (Al Kindi et al., 2020). *S. aureus* superantigen pathways have been extensively characterized for their role in AD pathogenesis (Seiti Yamada Yoshikawa et al., 2019). These toxins are capable of disrupting the skin barrier and microbiome and altering immune pathways (Blicharz et al., 2019). Classically, an imbalance of the human T helper (Th) cell subsets Th1 and Th2 have been implicated in AD pathogenesis; however, Th17 and Th17 subsets may also be involved (Orfali et al., 2019). Staphylococcal enterotoxins can further disrupt the profile of Th cells and their gene products.

Variations in surface proteins and virulence factors exist between different strains of *S. aureus*, affecting adhesion to skin, immune responses, and patient symptoms (Aziz et al., 2020; Iwamoto et al., 2019). Strains of *S. aureus* in patients with AD may differ from strains carried on unaffected subjects (Simpson et al., 2018) and can vary across geographic regions (Byrd et al., 2017). *S. aureus* in patients with AD has been found to internalize and accumulate in the lysosomes of keratinocytes using such cell wall proteins, where it induces the expression of inflammatory IL-1α via toll-like receptor 9 (Moriwaki et al., 2019). Cell wall proteins and virulence factors acquired from AD strains of *S. aureus* could be potential therapeutic targets for managing colonization and infection.

MICROBIOME

The bacterial microbiome has been shown to have clinical implications in understanding and treating dermatological diseases such as AD (Reiger et al., 2020). Microbiota bacterial diversity is inversely correlated with AD symptoms, whereas the proportion of *S. aureus* is directly related to flares. Increases in S. aureus and decreased diversity could be captured as harbingers of AD flares before clinical signs are evident. Commonalities of the microbiota in AD flares are shared outside *S. aureus* prevalence (Kong et al., 2012). Skin microbiota predominantly exist in biofilms, making microbes especially persistent and adherent to keratinocytes. For the commensal microbiome, this is advantageous for adhesion against frequent friction forces on skin that occur during daily life. For pathogens like *S. aureus*, the density of the biofilm can prevent the penetration of topical treatments (Reiger et al., 2020).

Factors that make the skin of patients with AD more conducive to *S. aureus* colonization include higher pH levels, decreased levels of filaggrin and filaggrin degradation products, and lower levels of antimicrobial peptides, such as dermicidin and β-defensins (Hata et al., 2010; Hülpüsch et al., 2020; B. Shi et al., 2018). External factors such as harsh soaps, antibiotics, and topical corticosteroids further dampen the immune response to pathogens and tissue damage and increase susceptibility to colonization (Kim et al., 2019).

In addition, the microbiome is dynamic, varying both topographically and temporally. The skin microbiome displays substantial heterogeneity across areas of the body. For example, the antecubital and popliteal creases, which

TABLE 1. Factors in *Staphylococcus aureus* Involved in Atopic Dermatitis (AD) Pathogenesis

Protein or Virulence Factor	Implication in AD
Enterotoxins A, B, C[a]	Mediate bacterial invasion and spread[a], stimulate T-cell cytokine production and toxicity
Toxic Shock Syndrome Toxin 1	Upregulate anergy-related genes EGR2 and IL13, impairing T-cell response to antigens (Enterotoxin A)[b]
	Induces T-cell receptor Vα-specific expansion of T cells[c]
Surface proteins	Adhere to skin and affect immune response[d]
Alpha toxin	Keratinocyte membrane damage and lysis[e]
Delta toxin	Activates mast cell degranulation[f]
Second immunoglobulin-binding protein	Stimulates IL-33 release driving inflammation[g]

[a]Blicharz et al. (2019).
[b]Orfali et al. (2019).
[c]Aziz et al. (2020).
[d]Iwamoto et al. (2019).
[e]Geoghegan et al. (2018).
[f]Nakamura et al. (2013).
[g]Al Kindi et al. (2020).

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are frequently affected in AD, have significantly elevated proportions of *Staphylococcus* species. Furthermore, the microbiome can collectively shift in a group of people when in close contact for an extended time (Gibbons et al., 2019). The immensity of the microbiome presents a challenge for effective culture; however, recent genome sequencing advancements are improving the study of human microbiomes.

Of note, commensal *S. aureus* may play a protective role against AD in infancy, indicating that the presence of this bacterium may not be harmful in and of itself, but rather its imbalance in the microbiome may be. With significantly increased regulatory T-cell levels, neonatal immune systems are skewed to promote increased immune tolerance to both endogenous and exogenous antigens (Yang et al., 2015). At birth, infant microbiomes differ from that of adults. External factors, including the type of delivery and maternal commensals (Capone et al., 2011), can impact the infant microbiome, whereas adult microbiome composition is affected by elements such as age, climate, and UV exposure (Lunjani et al., 2019; van Mierlo et al., 2019). Proper immune system function and development appears to depend on signals and interaction with commensal microbes, such as *Staphylococcus epidermidis* (Belkaid & Naik, 2013; Lai et al., 2010; Naik et al., 2012). In general, findings demonstrate that increased cutaneous *S. aureus* abundance contributes to decreased microbiome diversity (including changes in *S. epidermidis*), both of which are integral to AD pathogenesis (Kennedy et al., 2017).

TREATMENTS

Antimicrobial or anti-inflammatory treatments can prevent or even reverse changes in the low microbiota diversity of AD flares; these changes can manifest prior to measurable clinical improvement. Treatment is related to greater bacterial diversity and, thus, less symptom burden. Continuous treatment more significantly decreases inflammation, but even occasional treatment was associated with an increase in bacterial diversity (Kong et al., 2012). Treatments focusing on the microbiome could reduce the necessity of corticosteroids, a mainstay of AD treatment. Bacteriotherapy is an emerging, broad therapeutic category aimed to restore the cutaneous microflora to its healthy, diverse state while decreasing *S. aureus* levels and its ability to cause AD flares. Types of bacteriotherapy include skin bacterial transplant and topical probiotics or microorganisms, which have shown potential as treatments for AD in both animal and human studies (Hendricks et al., 2019; Perin et al., 2019). Skin bacterial transplants involve the transplantation of the skin microbiome from healthy individuals to those with AD. Recent studies indicate that commensal microorganisms could be applied topically to decrease *S. aureus* colonization and improve AD symptoms; however, these studies are still in early stages, and the long-term efficacy and safety are still unknown (Paller et al., 2019).

Both oral and topical probiotics have been studied in patients with AD, and although there are conflicting data, overall, they appear to be safe and promising therapies to alleviate AD symptoms such as erythema, pruritus, and scaling in children and adults (Butler et al., 2020; Knackstedt et al., 2020; Navarro-López et al., 2018; Yu et al., 2020). The reduction in *S. aureus* observed from probiotic therapy is presumably due to species antagonism, but the exact mechanism is unknown (Knackstedt et al., 2020).

Risk of AD development in infants can be decreased with prenatal and postnatal treatment with probiotics, such as particular strains of *Lactobacillus* and *Bifidobacterium* (Li et al., 2019). Bacterial metabolites have also produced encouraging results for inhibiting *S. aureus* proliferation in animal models but may not be clinically applicable due to vehicular and dosage incompatibilities (Traisaeng et al., 2019).

Given the diversity of microbiota between and within individuals, bacteriotherapy must be personalized in determining individualized microbial complementation and augmentation. More research on many aspects of bacteriotherapy is necessary (Hendricks et al., 2019). For example, maintaining the additive bacteria on the recipient skin long enough for therapeutic effect could prove difficult; therefore, bacterial keratinocyte adhesion may need optimization (Hendricks et al., 2019). Even beyond selecting the correct strain or strains, optimal dosing and vehicles, risks, and resistance would need to be characterized for each of the many potentially therapeutic bacterial strains, which is challenging (Di Domenico et al., 2019). Understanding the mechanism of action and safety profiles of various treatments should be explored further.

Other established AD treatments, such as topical corticosteroids, calcineurin inhibitors, and cyclosporine, may also exert their effects in part through alteration of the microbiome (Hung et al., 2007). Dupilumab, the interleukin-4 receptor α antibody, approved as a second line treatment for moderate-to-severe AD, has been found to increase microbial diversity and decrease *S. aureus* abundance in both lesional and nonlesional skin (Callewaert et al., 2020). In addition, narrow-band UVB and 308-nm excimer light are efficient treatments for moderate-to-severe AD that have been found to shift the bacterial makeup of AD skin, including decreasing *S. aureus* (Kurosaki et al., 2020; Silva et al., 2006). These microbial changes have been correlated with beneficial clinical results (Kurosaki et al., 2020).

Many nonpharmaceutical treatments can impact the AD microbiome without significant side effects. Topical coal tar is a safe and effective treatment that has been used to treat a variety of dermatological conditions and has been shown to affect microbiota, including decreasing levels of Staphylococci, although notably not *S. aureus* (Smits et al., 2020). Coal tar was recently discovered to exert its effects through transcription regulation via activation of the aryl hydrocarbon receptor, inducing antimicrobial peptides from keratinocytes (Smits et al., 2020). Vitamin D3 supplementation can also significantly decrease *S. aureus* colonization in

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children with AD (Zulkarnain, 2019). Climate can affect the development and maintenance of a personal microbiome and may serve as a potential therapy for AD (Brandwein et al., 2019). Dead Sea climatotherapy can be used to improve AD symptoms by affecting the balance of commensal bacteria, although it has not been shown to significantly decrease *S. aureus* colonization (Brandwein et al., 2019).

The use of emollients is a central pillar to AD management, and incorporating antiseptics into emollients may prove more beneficial than emollients alone by decreasing *S. aureus* levels (Spada et al., 2019). One study found that ozone hydrotherapy and ozonated oil decreased *S. aureus* prevalence in AD lesions in just 3 days, suggesting the efficacy of topical ozone therapy for AD through restoring microbiome diversity (Zeng et al., 2020). Topical fatty acids such as virgin coconut oil and derivatives exhibit anti-inflammatory and antibacterial properties, as well as aiding to moisturize the skin barrier in AD (Chew, 2019; Hwang et al., 2020). Conversely, olive oil can further aggravate AD symptoms, such as xerosis (Karagounis et al., 2018). Other naturally derived oils, such as sea buckthorn fruit oil, can improve AD symptoms when taken orally (Moore et al., 2020). Bacteriophage endolysins are being explored as additives to topical moisturizers, with greater specificity for pathogens and less susceptibility to bacterial resistance than antibiotics (Bilimoria & Lio, 2019).

Topical antiseptics such as hypochlorous acid, which is found in bleach, may provide benefit over antibiotics for *S. aureus* treatment in patients with AD (Kuraitis & Williams, 2018). Bleach baths are likely anti-inflammatory but are not antibacterial, at least at the concentrations routinely recommended in clinical practice (Leung et al., 2013; Sawada et al., 2019). Although bleach baths are often used in conjunction with standard AD treatment and may provide some therapeutic benefit, the mechanism does not appear to involve the cutaneous microbiome (Lim et al., 2019; Perez-Nazario et al., 2015). Furthermore, some evidence suggests that bleach baths may not provide further improvement than topical corticosteroids alone (Gonzalez et al., 2016) and may have equal magnitude of effect on skin barrier function to water baths (V. Y. Shi et al., 2016). Alternative modalities such as passive and active vaccination for *S. aureus* are under active investigation (Clowry et al., 2019). Because of the role of *S. aureus* as both a commensal and pathogenic organism and its evolutionary resistance, antibody-based vaccination used for other opportunistic bacteria have been ineffective (Fowler & Proctor, 2014).

The treatments previously discussed can improve AD symptoms by decreasing *S. aureus* colonization but do not constitute a primary therapy for active infection with *S. aureus*. Although *S. aureus* skin and soft tissue infections can partly be prevented by decolonization methods such as topical antimicrobials and antiseptics, antibiotics are still required for acute infections, with the accompanying problem of bacterial resistance (McNeil & Fritz, 2019).

CONCLUSION

Although much remains unknown about the intricacies connecting *S. aureus* and AD, there is a clear difference in *S. aureus* colonization in those with AD compared to unaffected individuals. Increased colonization levels of *S. aureus* in AD affects patients' cutaneous microbiome, immune regulation, and skin barrier, contributing to disease flares and susceptibility to irritation and infection. Bacteriotherapies and nonpharmacological therapies targeting *S. aureus* and the microbiome imbalance are active and promising areas of research that may be beneficial as adjunctive treatments for AD. ■

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DISCLOSURE STATEMENT

Dr. Lio reports research grants/funding from the National Eczema Association, Regeneron/SanofiGenzyme, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, Galderma, and L'Oreal; reports consulting/advisory boards for Dermavant, Regeneron/Sanofi Genzyme, Dermira, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos (stock options), La Roche Posay/L'Oreal, Pierre-Fabre, Johnson & Johnson, Unilever, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Franklin Bioscience/Altus Labs (stock options), Galderma, Arbonne, Amyris, Bodewell, YobeeCare (stock options), and Burt's Bees. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member of the National Eczema Association. The remaining authors have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

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