

Staphylococcus aureus and Atopic Dermatitis: Unweaving a Tangled Web



Though the relationship is not fully understood, it points the way to potential treatments.

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>> There is a long history of association between atopic dermatitis (AD) and *Staphylococcus aureus*. As such, the understanding of the relationship between the two has ranged from Dr. Paul Unna's proactive push to eradicate all germs on the skin in nineteenth century Europe, to today's more reactive approach of treating infections as they occur. One idea that has persisted and is now coming to the fore is that reducing or eliminating the reservoir of bacterial pathogens will reduce the incidence of disease.¹

It has been known since at least the 1970s that AD patients have increased colonization with *S. aureus*. A recent meta-analysis placed the rate of *S. aureus* carriage by AD patients at about 70 percent on lesional skin versus 39 percent on non-lesional skin or healthy control skin, and importantly, underscored that its prevalence correlated with disease severity.² The concept of "colonization," by its very definition, suggests that the presence of the bacteria, while not necessarily normal, is not pathogenic. To wit, even current guidelines from the American Academy of Dermatology on the treatment of AD have recommended against using antimicrobials

without the signs of true secondary infection.³

Dr. Unna defined AD as "a chronic parasitic catarrh of the skin" and recommended treatment by "destruction of every single germ in the depths of the epidermis."⁴ In the intervening 120 years, this recommendation has gone largely ignored. Yet, as we learn about the microbiota imbalance in AD, the contribution of *S. aureus* is becoming increasingly clear. A number of compounds produced by *S. aureus* that contribute to the intensity of symptoms have now been characterized, including delta-toxin, which stimulates mast cells, alpha-toxin, which damages keratinocytes, phenol-soluble modulins, which stimulate cytokine release by keratinocytes, and superantigens, which trigger B-cell expansion and cytokine release, to name a few.⁵

In healthy individuals, *S. aureus* can be a commensal found on the skin's surface, often causing little harm. As an opportunistic bacterium, *S. aureus* can be dangerous to those with weakened innate immune systems, such as AD patients with compromised skin barriers. As research on the microbiome advances, it is becoming increasingly clear that *S. aureus* can exacerbate disease by increasing inflamma-

tion and allergic sensitization through various virulence factors.⁶

The tide has begun to shift, perhaps started by Huang et al's 2009 paper looking at dilute bleach baths in the treatment of AD.⁷ This seminal paper put forth the notion that dilute bleach works via decreasing *S. aureus* to improve disease severity. Though, as we will discuss, it is possible—even likely—that this was not the actual mechanism at work. Kong et al's paper in 2012 further solidified this concept by boldly putting forth a model in which "increases in the proportion of Staphylococcus and reductions in microbial diversity precede worsening of AD disease severity."⁸

Currently, there is a growing focus on ways to decrease *S. aureus* as a means to treating AD. Herein we will review some of these approaches and look to future possibilities.

STAPH AS A COLONIZER

The skin surface has protective properties that prevent dangerous colonization and infection by pathogens. *S. aureus* can exist harmlessly on the skin surface but can also produce virulence factors that exert direct effects on keratinocytes to influence the onset and persistence of AD.⁶

In AD, high carriage rates of *S. aureus* on involved skin are found, with recent analyses showing colonization in 70 percent of affected individuals.² High colonization burden of *S. aureus* has been linked to disease severity in AD, yet only modest advances have been made in understanding this relationship. Microbiome studies indicate that commensal Staphylococci may have a protective effect during infancy, as this type of bacteria is less abundant in children who develop AD by 12 months. Thus, cutaneous microbial imbalances, or dysbiosis, appear to be a contributor to the development of AD and the abundance of pathogenic *S. aureus* seen in AD.⁹

STAPH AS A DRIVER OF AD

Dysbiotic environments can be conducive to the proliferation of *S. aureus* and its virulence factors. Virulence factors enable *S. aureus* to adhere to skin cells and the extracellular matrix, evade the host's innate and adaptive immune responses, and destroy tissues to facilitate invasion.⁶ These factors are dependent on the expression of regulatory genes activated in response to signals from the environment and function to support the metabolic needs of the disseminating bacteria.¹⁰

Adhesins are one of the more well-understood virulence factors of *S. aureus*, especially in its exacerbation of AD, as bacterial adherence seems to be elevated in AD patients.¹¹ In addition to adhesins, *S. aureus* releases various cell-damaging and immune-activating exotoxins that enable invasion and dissemination to host skin. Some of these toxins share the property of superantigenicity or the stimulation of T cell proliferation through binding of the T cell receptor (TCR) and the MHC class II protein without internal processing. This binding activates multiple T cells at once, regardless of TCR specificity, and causes

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uncontrolled release of cytokines, which can be a significant contributor to the morbidity and mortality of *S. aureus*.¹²

While *S. aureus* and its virulence factors pose a considerable threat to AD patients, the use of broad-spectrum antibiotics to combat them can damage the healthy microbiome. With a growing knowledge base about the microbiome and increased concern for dysbiosis, it is becoming clear that there is a serious need for pathogen-specific therapies that do not disturb the beneficial microbiota of the human body. Precision therapy of this sort aims to neutralize key virulence factors and promote phagocytic killing of bacteria.⁶

TREATMENT APPROACHES

Therapeutic interventions in AD are focused on alleviating discomfort and severity through moisturization, reducing inflammation, and bacterial elimination. Emollients and topical corticosteroids remain the cornerstone of AD management, supplemented with a variety of topical and systemic therapies with varying efficacies.¹

Aron Regime. Popularized by the South African dermatologist Dr. Richard Aron, this topical combination of antibacterial, steroid, and

moisturizer (CASM) has anecdotally made a significant impact on the morbidity and quality of life for many patients. This compound results in a rather diluted corticosteroid along with the mupirocin (in the US; fucidic acid is typically used in Europe and South Africa), and this mixture is applied three or more times per day liberally. In a case series examining 116 AD patients suffering from refractory disease, CASM was reported to be superior to some conventional approaches in decreasing severity and body surface area (BSA) affected.¹³ However, randomized controlled trials have not yet demonstrated support of these findings, nor have microbiological studies been performed to assess the actual effect on skin bacteria. Moreover, this approach does not fully address the controversial use of antibiotics in uninfected AD individuals.

With the threat of antibacterial resistance ever looming, studies to determine CASM's long-term efficacy in improving the abnormal microbiota of AD are required, along with a proper evaluation of the safety and impact of such an approach.

Dilute Bleach Baths. Dilute bleach baths would, at first blush, appear to have fulfilled the antiseptic role without the concern for antibiotic

resistance. The initial excitement has been dampened by a sobering study: according to Hon, et al, a regimen of dilute bleach baths does not appear to be more helpful than plain water baths in reducing *S. aureus* colonization/infection and improving AD.¹⁴

This story has been further complicated by studies suggesting dilute bleach baths implemented in this context have little direct efficacy on staphylococcus. In a randomized controlled trial, Gonzalez et al found that children treated with a topical corticosteroid with or without bleach baths had “similar significant clinical improvements, associated with restoration of microbial diversity and decreased numbers of total bacteria,” suggesting that bleach baths themselves do not add antibacterial benefits.¹⁵

In an effort to provide solutions for bleach-averse patients, apple cider vinegar (ACV) has been tested against dilute bleach in a small split body trial. Results indicate that ACV has similar efficacy to topically applied bleach and that the benefit from the both does not appear to derive from any anti-microbial properties.¹⁶

It seems increasingly likely that at least some of the relief experienced from bleach baths may occur via other mechanisms, outside of antibacterial effects. For example, Perez-Nazario et al’s study of dilute bleach in AD found an improvement in the skin barrier function and a reduction in itch intensity, but not the clearance of bacteria.¹⁷ Supporting this clinical finding, in mouse models, topical hypochlorite has been shown to reversibly inhibit certain proinflammatory mediators, thereby hindering the inflammatory cascade and decreasing disease severity.¹⁸ Despite these encouraging outcomes, a recent meta-analysis concluded that bleach baths “do not appear to be more effective than water baths alone.”¹⁹

Topical Hypochlorous Acid Gels.

Antiseptic use on uninfected skin of AD patients may still be a better alternative than prophylactic antibiotics, especially when targeting *S. aureus*. Hypochlorous acid (HOCl), a major component of bleach, is a naturally occurring molecule with antimicrobial and anti-inflammatory properties, making it an integral part of topical formulations to treat various skin conditions. The antimicrobial activity of HOCl is different from conventional antibiotics in that HOCl is directly toxic to microbial cells including gram-positive and gram-negative bacteria. One study suggests HOCl also has anti-biofilm properties which, in theory, can further inhibit *S. aureus* by targeting its survival strategy.²⁰ In vitro data suggest that higher concentrations of sodium hypochlorite are superior to the 0.005% solution used in clinical bleach baths in combating biofilms,²¹ which may differentiate these products from the household bleach approach.

HOCl can attenuate inflammation by inhibiting the degranulation and release of pro-inflammatory mediators from activated mast cells. HOCl blocks the activity of phospholipase A2, a key player in the arachidonic acid cascade responsible for the exacerbation of inflammatory diseases. In addition to the anti-inflammatory and microbicidal properties of HOCl, it has also been shown to reduce AD-related pruritus.²² In a randomized control trial evaluating the utility of HOCl in 30 patients with AD-associated pruritus, 73.7 percent of subjects reported a reduction in itch between baseline and 72 hours post-application as measured by the Visual Analogue Scale (VAS) itch score.²³ As one of the most burdensome symptoms of AD, itch seems to respond to topical HOCl, which could also play a role in protecting AD skin from *S. aureus*. Overall, topical HOCl

appears to be well-tolerated and safe, without any major adverse events reported.²⁴ Unfortunately, a topical hypochlorous acid gel preparation (PR022) from Realm Therapeutics, which showed success in murine atopic dermatitis models, has recently failed its Phase 2 trial, demonstrating no significant difference in Eczema Area Severity Index (EASI) compared to vehicle.²⁵ Several formulations are still available with others in development, and these may hold promise for AD patients, no matter their mechanism of action.

Coconut oil. Patients embracing more “natural” therapies have turned to virgin coconut oil (VCO) for AD relief. While the number of high-quality clinical studies on VCO is limited, there is some evidence for its superior moisturizing properties. VCO comprises a rich combination of vitamin E and medium-chain fatty acids that is superior to mineral oil as an emollient.²⁶ Moreover, a randomized controlled trial found VCO to reduce *S. aureus* colonization by 95 percent in AD patients after four weeks of twice-daily application.²⁷ These data suggest that VCO may be a viable option in treating colonized AD. This is an encouraging outcome as we strive for safe and inexpensive agents to decolonize the skin and prevent bacterial resistance.

Topical probiotics. Multiple studies suggest Coagulase negative Staphylococcus (CoNS) could be therapeutically beneficial to AD. Skin CoNS species such as *S. epidermidis*, *S. hominis*, and *S. lugdunensis* produce potent anti-*S. aureus* molecules. Patients with chronic AD have exacerbated deficiencies in antimicrobial defense against *S. aureus*. A double-blind, placebo-controlled trial of topical CoNS species with antimicrobial activity was conducted. Results showed that topical CoNS treatment was effective in mouse models of

AD. In another study, anti-*S. aureus* CoNS species were collected from AD patients, expanded, applied to AD skin, and shown to significantly decrease *S. aureus* colonization.²⁸

Similarly, another study examining *Roseomonas mucosa* found that topical application of this bacteria led to decreased AD severity, pruritus, and use of topical steroids.²⁹ While more data are needed about commensal bacteria as a treatment for AD, current trials suggest topical probiotics may play a role in reducing disease severity and controlling *S. aureus* growth.

Antimicrobial enzymes. In the current era of increasing incidence of bacterial resistance, interest has shifted toward bacteriophage-focused interventions. In particular, research has focused on manipulating the endolysins of bacteriophages, the hydrolytic enzymes capable of cleaving peptidoglycan bacterial cell walls. The growing interest in lysins as antibacterial agents can be attributed to their effectiveness in eliminating specific pathogens in comparison to antibiotics, which are more susceptible to bacterial resistance. According to Fischetti, lysins exhibit numerous advantages over antibiotics, including specificity for pathogens without disturbing natural bacterial flora, low risk of bacterial resistance to lysins, and their ability to eliminate bacterial colonies on mucosal surfaces, a capacity previously unavailable.³⁰

A European product uses extracted natural phage endolysins specific to targeting *S. aureus*. This product has two promising features in treating AD patients: selective degradation of specific bacteria and a very limited likelihood of emerging resistance. Early feedback is promising, and it is planned for release in the US. The MAAS trial (Microbiome in atopic dermatitis during anti-staphylococcal therapy and the effect on steroid use),

a double-blind, placebo-controlled trial, followed 100 AD patients and assessed the need for corticosteroid co-therapy between a bacteriophage endolysin-treated group and placebo group. The MAAS trial also assessed the microbial composition (including *S. aureus*) between the two groups throughout the trial.³¹ While results have yet to be reported, a successful outcome of reduced need for corticosteroids and decreased *S. aureus* colonization in the endolysin-treated patients would be an exciting addition to the long history of AD and *S. aureus*. ■

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