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Review article

Skin bacterial transplant in atopic dermatitis: Knowns, unknowns and emerging trends

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ABSTRACT

Dysbiosis is a key pathogenic factor in the cycle of skin barrier impairment and inflammation in atopic dermatitis (AD). Skin microbial composition in AD is characterized by increased presence of *Staphylococcus aureus* (*S. aureus*) and decrease in microbial diversity and commensal bacterial species. Attenuation of *S. aureus*-driven inflammation aids in breaking the itch-scratch cycle via modulation of the cutaneous immune response. Skin bacterial transplant (SBT), a form of bacteriotherapy, is an intriguing treatment modality for restoration of a healthy skin microbiome in AD patients. Studies on the effects of topically-applied bacterial products, probiotics and SBT have yielded promising results in animal models and human studies of AD. This review discusses the rationale and evidence for SBT in AD and outlines future investigative directions for the clinical application of microbiome restoration in dermatology.

1. Introduction

Skin dysbiosis in atopic dermatitis (AD) manifests as alteration of microbial composition with decrease in commensal species, increase in *Staphylococcus aureus* (*S. aureus*), and overall decreased microbial diversity. Bacterial composition varies with disease severity, with predominance of *S. aureus* in severe pediatric AD skin samples compared to prominent *Staphylococcus epidermidis* in milder AD cases [1]. Clonal *S. aureus* is also associated with severe AD flares [1], suggesting that a loss of bacterial diversity plays a role in pathogenesis. Kong et al. identified a temporal association between AD flares and low bacterial diversity in the absence of recent antibiotic treatment compared to intermittent or active treatment [2]. Increased *S. aureus* load and decreased microbial diversity precede AD flares, with decline in *S. aureus* and recovery of microbial diversity following treatment [2]. Therefore, control and eradication of *S. aureus* colonization are mainstays of AD management, aiming to decrease the cutaneous inflammatory response and prevent secondary impetiginization.

As described in the leaky skin model of AD presented by Zhu et al. [3], skin barrier dysfunction allows entry of environmental and cutaneous pathogens and immunogens through the epidermis. With altered skin microbial composition in AD, fewer commensal bacteria are present to compete against pathogenic strains such as *S. aureus*. Decreased expression of antimicrobial peptides including β-defensins and cathelicidins also creates favorable conditions for *S. aureus* colonization [4]. Entry of *S. aureus* through the impaired skin barrier leads to enhanced expression of inflammatory cytokines interleukin (IL)-4, IL-13, IL-17, IL-22 and thymic stromal lymphopoietin [5]. The subsequent increase in barrier permeability drives a vicious cycle of inflammation, itch and skin barrier breakdown [3].

Current methods for combating *S. aureus* colonization include topical and oral antibiotics and bleach baths, but these non-targeted therapies affect beneficial as well as pathogenic bacterial species. The goal of bacteriotherapy in AD is to decrease colonization by pathogenic bacteria via restoration of a diverse microbiome comprising commensal species that intrinsically inhibit *S. aureus* growth, thereby controlling a major exacerbating factor in the itch-scratch cycle. Furthermore, commensal bacteria appear to play a modulatory role in the cutaneous immune response, although the exact mechanism has yet to be elucidated. The term "bacteriotherapy" encompasses a variety of bacterial products and application modalities involving isolated or diverse bacterial species, and can be used broadly to describe any use of bacteria or bacterial components for therapeutic benefits. Bacteria-derived enzymes, probiotics and bacterial transplant as treatment strategies in AD have gained attention in recent years and show promise for restoration of a healthy skin microbiome with further investigation and application

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in human trials. According to a consensus statement put forth by the International Scientific Association for Probiotics and Prebiotics, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host", and contain select, specified bacterial species (commonly *Lactobacillus* and *Bifidobacterium*) [6]. In contrast, skin bacterial transplant (SBT) involves transplantation of diverse cutaneous flora from one individual to another. SBT has recently been coined the "future of eczema therapy" [7]. This review aims to characterize the rationale for bacteriotherapy in treatment of AD, to summarize existing and ongoing studies of probiotics and bacterial transplant in AD, and to discuss future investigative directions for bacteriotherapy in AD management.

2. Methods

In November 2018, two research personnel conducted a literature review using PubMed, Google Scholar, EMBASE, and ClinicalTrials.gov databases. Search terms included combinations of the following key words: atopic dermatitis, eczema, microbiome, transplant, bacteriotherapy, skin microbiome restoration, probiotics, and commensal bacteria. Inclusion criteria are *in vitro*, animal model, and human studies as well as clinical trials and case series. Review articles, case reports and non-English articles were excluded. A total of 9 publications were selected for evaluation in this review.

3. Results

3.1. Topical bacterial lysate

Topical application of commensal bacterial lysates has shown efficacy in treating AD in human and mouse models. In a double-blind, randomized, placebo-controlled trial involving 75 patients with mild AD published in 2008, Gueniche et al. compared the effects of a topical 5% *Vitreoscilla filiformis* (Vf) lysate cream vs. placebo applied to lesional areas twice daily [8]. Study endpoints were change in SCORing Atopic Dermatitis (SCORAD) index, pruritus, sleep loss, transepidermal water loss (TEWL), and skin microflora assessed on days 0, 15, and 29. By day 15, early and significant improvement in mean SCORAD index ($p < 0.0001$) and pruritus ($p < 0.0002$) compared to baseline was evident in the Vf-treated group. At day 29, the Vf group demonstrated significant improvement in mean SCORAD index (15.1 vs. 24.9, $p < 0.004$) and decreased pruritus (1.8 vs. 3.4 visual analog scale (VAS), $p = 0.017$) compared to placebo [8]. TEWL decreased significantly in both treatment and placebo groups without a significant intergroup difference at the end of the 30-day treatment period, indicating that vehicle alone was sufficient for skin barrier restoration. Furthermore, no significant difference in *S. aureus*,*Streptococci*, or *Escherichia coli* colonization was found between the experimental and control groups [8]. These findings demonstrated that Vf lysate significantly improves AD symptoms, independent of restoring skin barrier integrity or decreasing bacterial colonization. The authors hypothesized that Vf plays an immunomodulatory role leading to improvement in AD clinical manifestations, although further investigation is needed to define the precise mechanisms of immune regulation.

Additional studies evaluating the effects of Vf lysate were conducted in mouse models by Volz et al. in 2014 [9]. Application of Vf lysate to the ears of allergen-sensitized AD-like mice attenuated skin swelling after allergen challenge by nearly 50% compared to mice not exposed to Vf [9]. To elucidate the mechanisms by which Vf attenuated the inflammatory response, the authors exposed murine bone marrow-derived dendritic cells to Vf *in vitro*, and found that Vf exposure induced dendritic cell maturation and production of the anti-inflammatory cytokine IL-10. Co-culture of Vf-exposed dendritic cells with T-helper cells induced T-regulatory cell differentiation with high IL-10 expression. In mice previously exposed to Vf, *in vivo* assessment of draining lymph nodes showed decreased T cell proliferation and higher IL-10 production by T cells after allergen re-challenge compared to mice not exposed to Vf, indicating a role of Vf in induction of immune tolerance [9].

3.2. Topical bacteriophage-derived enzymes

Staphefekt SA.100 is a topical recombinant phage endolysin that kills *S. aureus* via cleavage of peptidoglycan bonds in the bacterial cell wall [10]. Staphefekt effectively kills both methicillin-resistant and methicillin-sensitive *S. aureus* without affecting commensal skin bacteria. Furthermore, endolysins have not been found to induce bacterial resistance, making Staphefekt an intriguing alternative to traditional antibiotics in reducing *S. aureus* load [11]. In a recent randomized double-blind placebo-controlled superiority trial involving 100 subjects with moderate to severe AD, subjects were randomized into two groups to apply either triamcinolone 0.1% and Staphefekt cream or triamcinolone 0.1% and placebo cream twice daily on lesional skin for 12 weeks. Primary endpoints are decrease in topical corticosteroid use, and secondary endpoints are Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), number of flares, and quality of life [10]. The study was completed in February 2018, and no results have been published to date [12].

3.3. Topical probiotics

3.3.1. Epidermis construct

Topical application of heat-treated *Lactobacillus johnsonii* NCC 533, a non-replicating probiotic, to a reconstructed human epidermis model resulted in a dose-dependent reduction of *S. aureus* adhesion by up to 74% and enhanced expression of cutaneous antimicrobial peptides (β-defensin 2 and psoriasin) by nearly three-fold [13]. Topical application of commensal bacteria demonstrates potential as AD therapy by stimulating innate immunity and controlling *S. aureus* colonization.

3.3.2. Animal models

After discovering that culturable gram-negative bacteria (CGN) from healthy humans can activate cutaneous innate immunity, enhance skin barrier function, and control *S. aureus*, Myles et al. set out to evaluate the effect of transplanting CGN bacteria from healthy volunteers onto a mouse model of AD [14]. Mice were treated with a vitamin D analog for 14 days to induce AD-like dermatitis. Healthy human volunteer-sourced *Roseomonas mucosa* (HV-RM), AD-sourced *R. mucosa* (AD-RM), and healthy volunteer-sourced *Pseudomonas aeruginosa* (HV-PA) were isolated and applied on the ears of AD mice once daily for 3 days, beginning on day 13. Compared to mice treated with AD-RM and HV-PA, anti-inflammatory effects were evident in HV-RM treated mice, with significant improvement in skin thickness and reduction in visible erythema at day 21 [14]. Mice treated with AD-RM had significantly higher serum IgE compared to mice treated with HV-RM or HV-PA. Notably, application of lethally irradiated HV-RM failed to improve ear skin thickness or redness [14], suggesting that live cultures are needed to attenuate the inflammatory response. In addition to limiting inflammation, CGN inhibited *S. aureus* growth *in vivo*. *S. aureus* growth on the ears of healthy mice was reduced by approximately 66% and 75% when co-inoculated with HV-RM and HV-PA, respectively, compared to a 25% reduction when co-inoculated with AD-RM [14]. Mice treated with HV-RM also demonstrated enhanced filaggrin gene transcription compared to those treated with AD-RM. TEWL was not affected in the subset of healthy mice treated with HV-RM, but was increased in AD-RM treated healthy mice, confirming a causal role of AD skin microbes in epidermal barrier dysfunction [14]. These findings indicate a role of *R. mucosa* in decreasing inflammation, inhibiting growth of pathogenic bacteria, and stimulating filaggrin transcription, all of which help to combat the symptoms of AD.

Nakatsuji et al. found that antimicrobial peptide-producing coagulase-negative *Staphylococcus* (CoNS) strains were common on the skin of healthy volunteers but rare in AD patients despite similar overall bacterial load [15]. The group then set out to determine if CoNS strains with antimicrobial activity could confer resistance to *S. aureus* in a mouse model. In mice with *S. aureus* skin colonization, application of *Staphylococcus hominis* A9 twice daily for one week led to complete eradication of *S. aureus* colonization [15]. Similar to the findings reported by Myles et al. [14], application of UV-killed *S. hominis* A9 or non-antimicrobial peptide-producing *S. hominis* strains showed no inhibition of *S. aureus* [15], suggesting that live CoNS strains are necessary to exert an anti-pathogenic effect.

3.3.3. Human trials

With success in animal and *in vitro* studies demonstrating anti-inflammatory effects of *R. mucosa*, Myles et al. aimed to evaluate the effect of *R. mucosa* on the cutaneous innate immune response in humans through quantification of blister fluid cytokine levels [14]. Blisters were induced on the forearms of healthy volunteers using suction, and following removal of the epidermal blister roof, the dermal blister base was exposed to lethally irradiated isolates of *R. mucosa* from either healthy volunteers or AD patients. After 18–20 hours of *R. mucosa* exposure, blister fluid was collected to evaluate cytokine levels. Compared to exposure to AD-RM or saline control, blister fluid from HV-RM-exposed skin had elevated IL-6 levels. However, no differences in levels of IL-17, IFN-γ, IL-4 or antimicrobial peptides were observed [14]. These findings suggest that healthy-sourced *R. mucosa* has greater potential to stimulate specific mediators of innate immunity compared to AD-sourced *R. mucosa*, although the significance of this observation remains to be established.

3.4. Autologous bacterial transplant

Nakatsuji et al. demonstrated that autologous microbial transplant of CoNS decreases *S. aureus* colonization in AD human subjects [15]. CoNS strains with antimicrobial activity isolated from the non-lesional skin of *S. aureus* culture-positive AD subjects were formulated in a vehicle cream base and applied to the forearm of the same subjects. After 24 h, significantly decreased *S. aureus* colonization was observed at the autologous microbiome transplant site compared to the vehicle-treated contralateral forearm [15], suggesting that a single application was sufficient to exert antimicrobial action.

Table 1
Summary: bacterial applications in atopic dermatitis.

Reference	Experimental model	Bacteriotherapy modality	Results	Comments
Gueniche et al. [8]	Human	Bacterial lysate (*V. filiformis*)	Improvement in mean SCORAD index (15.1 vs. 24.9, p < 0.004) and decreased pruritus VAS (1.8 vs. 3.4, p = 0.017) in *V. filiformis*-treated group compared to placebo	Randomized placebo-controlled study of 75 subjects with mild AD
Volz et al. [9]	Murine	Bacterial lysate (*V. filiformis*)	Nearly 50% reduction in skin swelling upon allergen challenge in *V. filiformis*-treated group. *V. filiformis* induces dendritic cell and T-regulatory cell maturation, IL-10 release	
Totte et al. [10] NCT02840955 [12]	Human	Bacteriophage-derived endolysin (Staphefekt SA.100)	***None published to date*** Primary endpoint: decrease in TCS use Secondary endpoints: EASI, IGA, number of flares, QoL	Randomized placebo-controlled study of 100 subjects with moderate-to severe AD
Rosignoli et al. [13]	*In vitro*	Topical probiotic (heat-treated *Lactobacillus johnsonii)*	Dose-dependent reduction of *S. aureus* adhesion by up to 74% 3-fold enhanced expression of cutaneous antimicrobial peptides β-defensin-2 and psoriasin	*In vitro* study in reconstructed human epidermis
Myles et al. [14]	Murine	Topical probiotic (*R. mucosa*)	Improvement in skin thickness and erythema in mice treated with *R. mucosa* from healthy volunteers Increased serum IgE, decreased filaggrin transcript level in mice treated with AD-sourced *R. mucosa* vs. healthy-sourced	
Nakatsuji et al. [15]	Murine	Topical probiotic (*S. hominis* A9)	Complete eradication of *S. aureus* colonization following twice daily application for 1 week	
Myles et al. [14]	Human	Lethally irradiated *R. mucosa*	Elevated IL-6 levels in blister fluid after exposure to *R. mucosa* from healthy volunteers Lower IL-6 levels in blister fluid after exposure to AD-sourced *R. mucosa* vs. healthy volunteer-derived *R. mucosa* or saline control	Small sample size (n = 6)
Nakatsuji et al. [15]	Human	Autologous bacterial transplant (multiple CoNS strains with anti-microbial activity)	24 hours after a single application, significant decrease in *S. aureus* colonization at autologous bacterial transplant site vs.vehicle-treated site (p = 0.04)	Small sample size (n = 5)
Myles et al. [16]	Human	Allogeneic bacterial transplant (*R. mucosa*)	Significant reduction in SCORAD index, pruritus, TCS use, and *S. aureus* colonization	Small sample size (n = 15, 10 adult and 5 pediatric)
Gallo et al. NCT03151148 [17]	Human	Allogeneic bacterial transplant (targeted microbiome transplant lotion)	***None published to date*** Primary endpoints: adverse events Secondary endpoints: EASI, SCORAD, pruritus VAS, Rajka-Langeland, abundance of live CoNS	Randomized placebo-controlled study of 54 subjects with AD

AD – atopic dermatitis; CoNS – coagulase-negative *Staphylococcus*; EASI – Eczema Area and Severity Index; IGA – Investigator Global Assessment; QoL – quality of life; *R. mucosa* – *Roseomonas mucosa*; *S. aureus* – *Staphylococcus aureus*; *S. hominis* – *Staphylococcus hominis*; SCORAD – SCORing Atopic Dermatitis; TCS – topical corticosteroid; *V. filiformis* – *Vitreoscilla filiformis*; VAS – Visual Analogue Scale.

3.5. Allogeneic bacterial transplant

The first-in-human SBT in AD was an open-label phase I/II trial involving 10 adult and 5 pediatric patients with moderate-to-severe AD. *R. mucosa* was isolated from healthy volunteers, then cultured and formulated in a topical preparation. In adults, the solution was applied twice weekly to the bilateral antecubital fossae and one additional lesional site for 6 weeks, and in children, twice weekly to all lesional body surface area for 16 weeks [16]. *R. mucosa* application was associated with significant reduction in SCORAD index (mean 63.9% improvement), pruritus, topical corticosteroid use, and *S. aureus* colonization, with no reported adverse events [16]. Decline in *S. aureus* load was observed after 8 weeks of treatment in the pediatric cohort, suggesting that microbiome restoration may require up to 2 months. Interestingly, 3 of the 4 non-responders (defined as less than 50% improvement in SCORAD) had strong family histories of AD persisting into adulthood [16]. Although it is unclear why this subset did not respond, perhaps genetic predisposition to AD makes restoration of microbial balance more difficult.

While the aforementioned studies investigated transplantation of isolated bacterial species, the only study evaluating whole skin microbiome transplant as a potential treatment for AD is currently ongoing. Subjects will be randomized into two groups to apply either an investigational Targeted Microbiome Transplant Lotion consisting of allogeneic CoNS or Cetaphil-vegetable glycerin vehicle to both lesional and non-lesional sites on the bilateral upper extremities for 7 days. Primary endpoints are EASI, SCORAD, Rajka-Langeland Score, Pruritus VAS, resilience of CoNS, *S. aureus* load, and microbial diversity [17]. Trial completion is projected for June 2020, and no preliminary results have been published to date [17].

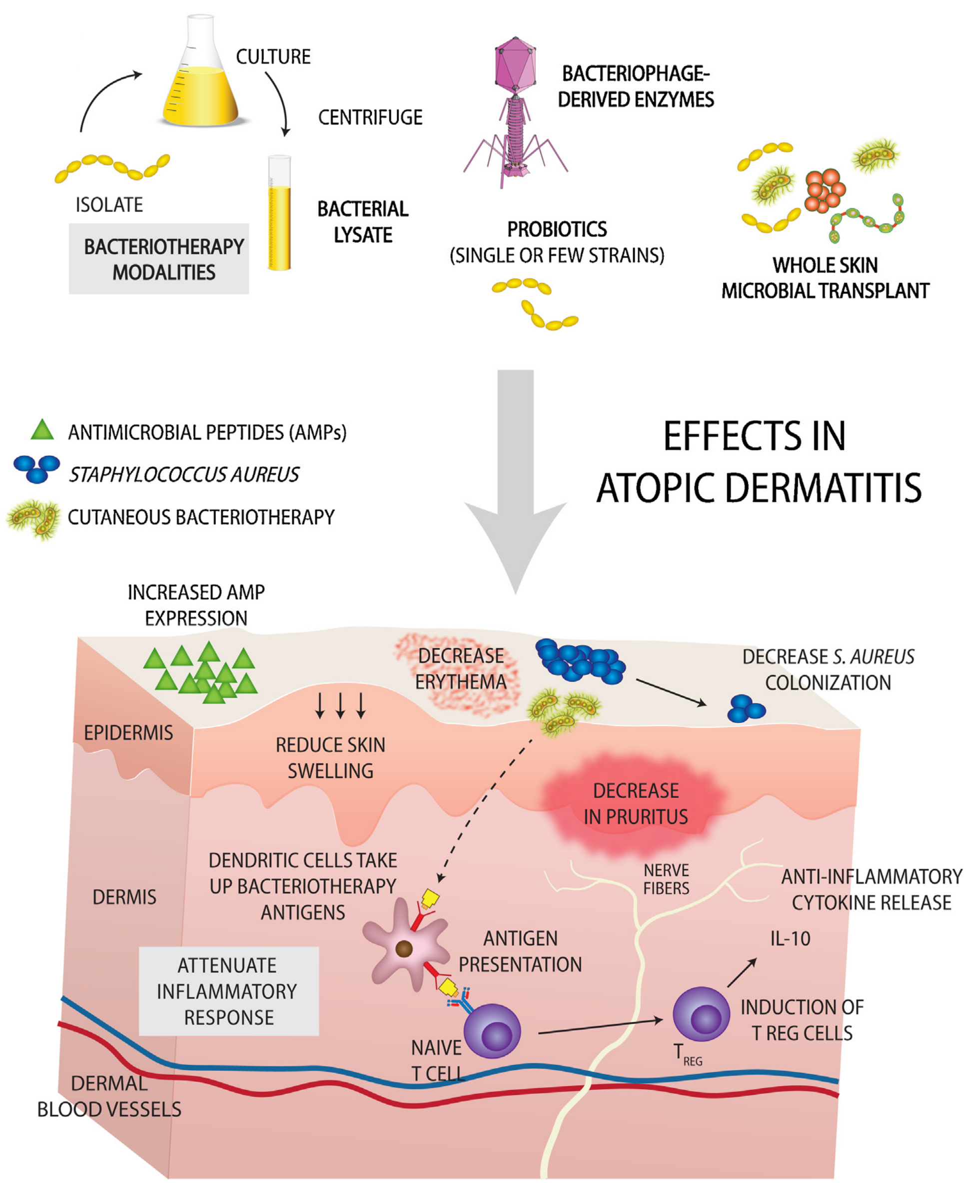

Fig. 1. Effects of bacteriotherapy in atopic dermatitis.
Cutaneous bacteriotherapy modalities include bacterial lysates, bacteriophage-derived enzymes, probiotics (single or few bacterial strains), and skin bacterial transplant of diverse microbiota. In atopic dermatitis, bacteriophage-derived enzymes, probiotics and skin bacterial transplant decrease *S. aureus* colonization, probiotics increase antimicrobial peptides, and bacterial lysates attenuate the inflammatory response by activating T-regulatory cells and increasing anti-inflammatory cytokine (IL-10) production, ultimately improving skin swelling, erythema and pruritus.

A summary of completed and ongoing investigations is presented in Table 1, and the proposed effects of bacteriotherapy in AD are illustrated in Fig. 1.

4. Conclusion

4.1. Unknowns

Bacteriotherapy as a treatment modality in AD aims to restore skin microbial diversity and limit *S. aureus*-driven exacerbation of inflammation, itch and barrier destruction. Several studies have investigated the effects of bacteria-derived enzymes, lysates and probiotics in mouse models and AD patients, yet additional work remains to be done in evaluating the methods and efficacy of SBT in humans. As this form of bacteriotherapy utilizing diverse microbiota is theoretically most restorative in treating AD-associated dysbiosis, more robust trials should be initiated to evaluate clinical response and specific effects on the cutaneous and systemic inflammatory response. Current evidence is limited by findings based on animal models and small sample size of human trials. Furthermore, as demonstrated by the recent work of Simpson et al., not all AD patients are *S. aureus*-colonized [18], and improving dysbiosis in non-*S. aureus*-dominant patients may require therapeutic approaches targeting non-pathogenic bacteria, fungi and commensal bacterial metabolites.

4.2. Future directions

Larger-scale randomized controlled trials will be pivotal in advancing our understanding of bacteriotherapy as a potential treatment for AD. Further investigation is needed to determine the optimal combination of bacterial species to be included in topical formulations and the ideal conditions for microbial transplantation and survival. As microbiome diversity is highly variable between individuals and anatomical sites, individualized microbial transplant may be necessary to complement or augment a patient's baseline microbial composition. Future work should also aim to assess the efficacy of various vehicles and growth factors that accompany donor bacterial transplant to maximize transplant survival and maintenance on recipient skin. Additional considerations include optimizing bacterial keratinocyte adhesion to ensure that newly-applied bacteria remain viable on the skin long enough to exert a beneficial effect via immune mediation, and evaluating the role of quorum sensing in growth and survival of transplanted bacteria. More thorough understanding of factors affecting bacterial survival time on the skin will guide practical considerations for frequency of topical application and expected timeline for clinical response.

Currently, the U.S. Food and Drug Administration (FDA) has not approved any oral or topical microbial-based formula as a live biotherapeutic product for the treatment of dermatologic conditions. As therapeutic applications of bacteria become more widely studied, questions arise regarding whether topical bacterial formulations should be tested and marketed as drugs or cosmetics. If intended for specific use in AD treatment, FDA testing and approval of probiotic and microbial preparations may be needed. The FDA has recently released statements on this topic, with discussion of improved techniques for testing the purity of probiotic formulations and considerations for their safe use in clinical research [19,20]. While the potential of bacteriotherapy for treatment of AD appears bright, additional studies will be critical in guiding safe and effective combination of bacteriotherapy with existing AD treatment modalities.

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AJH and BWM have no conflicts of interest to declare.

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