Clinical Relevance of the Microbiome in Pediatric Skin Disease: A Review

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KEYWORDS

• Microbiome • Pediatric • Acne • Alopecia areata • Atopic dermatitis • Eczema • Psoriasis • Seborrheic dermatitis

KEY POINTS

- The human microbiome encompasses the microorganisms that live in and on the body, including bacteria, viruses, fungi, archaea, and mites.
- During the prenatal and infantile periods, foundations for the cutaneous and gut microbiomes are being established and refined concurrently with the development of immune function.
- Microbes and the immune system play critical roles in the pathogenesis of commonly encountered disorders in pediatric dermatology, including acne, alopecia areata, atopic dermatitis, psoriasis, and seborrheic dermatitis.
- Alterations in the microbiome are also noted during the treatment of the aforementioned disorders, suggesting a possible target for future therapeutic interventions.

INTRODUCTION

The human microbiome encompasses the microorganisms that live in and on the body. While much research focuses on bacteria, also included in this domain are viruses, fungi, archaea, and mites.[1] The microbiome is pertinent to diverse aspects of human health, from psoriasis to neonatal sepsis to cystic fibrosis.[2–4]

During the prenatal and infantile periods, all aspects of physiology are adapting and maturing in response to innate genetic predispositions and the external environment. Foundations for the cutaneous and gut microbiomes are likely established prenatally,[5] with further refinement occurring during and after birth. External factors, such as mode of delivery and method of feeding, transiently or longitudinally impact the trajectory of the microbiome.[6,7] This impressionable phase is transient, and a more stable, adult-like microbiome develops with time. The cutaneous microbiome of infants, for example, has different dominant bacteria and limited diversity that then increases and matures with time.[8] Concurrently, immune function is emerging. Microbes are crucial to the development of the immune system during the neonatal period, "teaching" it to tolerate normal flora and preventing future maladaptive inflammatory responses.[9] Both immune function and cutaneous microbes are closely involved in the development of dermatologic conditions.

Herein, we review the relevance of the microbiome to five commonly encountered pediatric skin conditions: acne, alopecia areata (AA), atopic dermatitis (AD), psoriasis, and seborrheic dermatitis. Understanding the role microbes play in these conditions will allow innovation in future therapeutic interventions.

DISCUSSION

Overview of the Microbiome

The composition of the cutaneous microbiome is determined by a number of variables, including

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anatomic location, genetics, and environmental factors.[10] A sebaceous site such as the forehead, for example, creates an environment that is hospitable to different organisms than is the dry environment of the forearm. A recent review highlighted Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes as the dominant phyla overall in both adults and children.[11] In the gut, Firmicutes and Bacteroidetes dominate.[12] The presence of diverse microbial species is generally considered to be favorable.

Acne

Acne vulgaris is common in adults and children, and less common in infants. Clinical presentation consists of comedones, papules, pustules, and/or cysts mainly on the face, upper chest, and upper back. The condition is associated with significant morbidity, including depression, anxiety, and the potential for permanent scarring.[13] Follicular hyperkeratosis, androgenic stimulation of sebum production, inflammation, and proliferation of *Propionibacterium acnes* (now *Cutibacterium acnes*) contribute to the condition.[14]

The microbiome is central both to the pathogenesis of acne and to its treatment. *C. acnes* is the major bacterial species present in the pilosebaceous unit, accounting for nearly 90% of the bacteria in the pilosebaceous units of the nose in one study.[15] Relative abundance is similar between those with and without acne, but the presence of specific strains differs.[15] *C acnes* plays several roles in the development of acne, including increasing sebum production,[16] stimulating comedone formation,[17] and promoting inflammation.[18,19] *Malassezia* may also contribute to the disease. In a study[20] of skin surface swabs and follicular contents from inflammatory acne lesions, *Propionibacterium*, *Staphylococcus*, and *Malassezia* were noted. The amount of *Malassezia*, but not *Propionibacterium* or *Staphylococcus*, was correlated with the number of inflammatory acne lesions. In a study of preadolescent acne,[21] increasing age and increasing number of acne lesions were associated with increased *C acnes* and decreased *Streptococcus mitis*. In another smaller study of preadolescent acne,[22] all preadolescents had a predominance of *Streptococcus*, but those with acne had more *Staphylococcus* and *Propionibacterium* at all examined sites. Compared with controls, patients with acne had greater cutaneous bacterial diversity at all examined sites aside from the postauricular region. In another study, however, general loss of bacterial diversity was noted in patients with acne and correlated with disease severity.[23]

Gut dysbiosis is also seen in those with acne. In a study[24] of fecal samples, the phylum Actinobacteria was decreased in patients compared with controls, while Proteobacteria was increased. The genera *Bifidobacterium*, *Butyricicoccus*, *Coprobacillus*, *Lactobacillus*, and *Allobaculum* were decreased in those with acne relative to controls. These microbial alterations may alter the intestinal epithelial barrier and promote inflammation. The "gut–brain–skin axis" theory proposes that emotions like worry or depression alter gastrointestinal function. This, in turn, may lead to microbial dysbiosis that then contributes to inflammation locally and systemically.[25]

Microbiome alterations are also central to the treatment of acne. Treatment with isotretinoin modulates TLR2 expression to decrease the inflammatory response to *C. acnes*.[26] The effect of benzoyl peroxide, an antiinflammatory, bactericidal, and comedolytic agent, on microbial diversity is unclear. In a study of preadolescent acne,[21] treatment with benzoyl peroxide did not alter microbial diversity. In another study of preadolescent acne,[22] a decrease in microbial diversity was seen in patients with acne after treatment with both benzoyl peroxide and topical 0.025% tretinoin cream, resulting in diversity similar to what was seen in control patients. A nonsignificant decrease in the relative abundance of both *Propionibacterium* (at all examined facial sites) and *Staphylococcus* (at all sites except for the nose) was noted in preadolescents treated with benzoyl peroxide. Treatment with doxycycline was associated with an overall increase in bacterial diversity, a decrease in the relative abundance of *C. acnes,* and an increase in *Propionibacterium granulosum*.[27] The impact of doxycycline on the gut microbiome depends on the dose and duration of therapy.[28] Low doses seem to have little effect on the composition of the microbiome. Changes noted at higher doses seem to normalize after the cessation of treatment, though follow-up periods are limited. Probiotics have also shown promise in the treatment of acne.[29,30] Further studies are needed for a more complete understanding of the role the microbiome plays in acne.

Alopecia Areata

AA is a nonscarring form of hair loss most commonly involving the scalp, though potentially affecting any hair-bearing body site. Patients present with the rapid onset of single or multiple well-demarcated patches of alopecia. Disease course can be unpredictable: resolving in some, following a relapsing and remitting course in others, and becoming progressive in a small subset of

patients. The most severe end of the disease spectrum includes alopecia totalis (loss of all scalp hair) and alopecia universalis (loss of all body hair).[31] Consistently effective treatments are lacking, and morbidity in pediatric patients is considerable. Children experience bullying, embarrassment, school absences, and psychiatric comorbidities, including both anxiety and depression.[32,33] The etiology of this condition is not fully understood but is thought to involve both genetic and environmental factors, including T-cell-mediated autoimmunity and loss of immune privilege in hair follicles.[34,35] Recently, the skin and gut microbiomes have been implicated in its pathogenesis.

Aberrations in the cutaneous microbiome are noted in AA. In a study[36] of the scalp microbiome, those with AA had an increased incidence of *C acnes* and a decrease in *Staphylococcus*, particularly *Staphylococcus epidermidis*, compared with the scalps of controls. Additionally, those with AA had a predominance of *Staphylococcus aureus* relative to *S. epidermidis* compared with the opposite seen in controls.

Changes in the gut microbiome are also noted in those with AA. In a study[37] of the gut microbiome in 15 patients with and 15 without alopecia universalis, bacterial species richness (known as alpha diversity) was similar between cases and controls, though the specific microbial taxa making up the microbiome differed. Those with AA had more *Parabacteroides distasonis* and *Bacteroides eggerthii*, among others. Some of the bacterial species with increased prevalence in AA have been similarly noted in gut microbiome studies of other inflammatory diseases, such as ankylosing spondylitis.[38] These bacterial shifts potentially contribute to the inflammatory environment, resulting in AA. Another possible explanation is the role of bacterial metabolic products, which can influence the development of inflammatory cells. For example, short-chain fatty acids induce the development of immune-suppressing regulatory T cells.[39] A recent review[40] on the role of micronutrients in AA noted that serum folate, vitamin D, and zinc levels tended to be lower in those with AA compared with those without AA. However, the clinical significance of these findings, including if they develop before or after the onset of alopecia, merits further research.

Striking clinical examples of the gut–skin connection in AA have been reported. In a case report of two patients with AA receiving fecal microbiota transplants for recurrent *Clostridium difficile* infections, both experienced hair regrowth following transplant.[41] One patient, after having alopecia universalis for 10 years, experienced patchy hair growth on the head and arms eight weeks following the transplant. A second patient with Crohn's disease and a 2-year history of alopecia universalis refractory to several treatments experienced hair regrowth after fecal transplant. Further research is needed to better understand the role of the microbiome in AA, particularly in the pediatric population.

Atopic Dermatitis

AD is a common childhood skin condition, with 85% of patients diagnosed before the age of five years.[42] Distribution of the pruritic, pink, scaly patches, and plaques varies with age. Infants and young children classically have involvement of face, scalp, and extensor extremities, while older children and adults have more notable involvement of the flexures. Negative consequences of the condition include chronic school absenteeism,[43] behavioral challenges,[44] and sleep disturbances,[24,25,45] among others. This condition is of particular importance given its position as the first step in the "atopic march." Skin barrier defects, inflammation, and microbial alterations seen in AD may result in subsequent food allergies, asthma, and allergic rhinitis through percutaneous sensitization to allergens.[46]

The cutaneous microbiome is of paramount importance to the pathogenesis of AD. *S. aureus* is a key player in flares, but its role in disease development remains unclear. In a study by Kennedy and colleagues[47] examining the infantile skin microbiome during the first six months of life, those who developed AD by 12 months old had significantly less colonization by commensal staphylococci, lending support to the concept of early immune tolerance preventing AD. Infants with AD were not colonized with *S. aureus* and did not have cutaneous microbial dysbiosis as is seen in older children and adults with AD. In contrast, another study[48] of infants during the first two years of life found an increased prevalence of *S. aureus* at age three months in infants who went on to develop AD. This increase was noted at the time of disease development as well as during the preceding two months. Further studies are needed to discern the role the early cutaneous microbiome plays in the development of AD.

Microbial alterations are seen at baseline and during flares in those with AD, specifically an overall decrease in bacterial diversity and overabundance of *S aureus,* that affects the inflammatory response.[49–53] A recent systematic review and meta-analysis of 95 studies found that those with AD were more likely to be colonized with *S. aureus* than were controls.[54] Disease severity and

prevalence of *S. aureus* colonization were positively correlated for lesional skin sites. Patients with AD colonized by *S. aureus* not only have greater disease severity but also have increased barrier dysfunction and allergen sensitization compared with those with AD lacking *S. aureus* colonization.[55] Similar findings were noted in a study specifically examining pediatric patients.[56] Those with more severe disease had increased *S. aureus* during flares compared with those with less severe disease, in whom *S. epidermidis* predominated. Fungal and viral elements of the cutaneous microbiome were similar between groups during the study period.

Shifts in the cutaneous microbiome are noted with the treatment of AD. In a study of pediatric patients,[57] treatment of AD was associated with an increase in cutaneous bacterial diversity. Increased *S. aureus* and *S. epidermidis* were noted during flares. With treatment, increased *Corynebacterium, Propionibacterium,* and *Streptococcus* were noted. In a study of pediatric patients aged three months to five years examining the effect of topical corticosteroids alone versus topical corticosteroids and bleach baths, treatment with either regimen reestablished cutaneous microbial diversity to resemble that of controls.[52] In a study of adults,[58] treatment with topical steroids and oral antihistamines eliminated *S. aureus* from lesional and nonlesional skin in 70% of patients. Possible explanations for this change include immune alterations, skin barrier repair, or less trauma from scratching. Treatment with emollients alone similarly showed the diversification of the cutaneous microbiome, with decreased *S. aureus* following treatment.[53] Probiotics may be beneficial in the treatment and prevention of AD, but studies are still limited and conflicting.[59–61] Novel therapeutic prospects may rely on manipulating microbial alterations.

Psoriasis

Psoriasis is an inflammatory skin condition characterized by the presence of well-demarcated pink plaques with a silvery scale. Disease pathogenesis involves both genetic and environmental factors that impact innate and adaptive immunity.[62] Guttate psoriasis, presenting with many small pink scaly papules, is a variant of the classic plaque-type psoriasis which is more commonly seen in kids than in adults.[63] Pediatric psoriasis, particularly childhood guttate psoriasis, can be triggered by a preceding infection, often an oropharyngeal or perianal streptococcal infection.[63–65] A possible explanation for this association is the activation of T cells by streptococcal superantigens[66] and cross-reactivity to skin components.[67] Beyond this long-known association between microbes and psoriasis, research is now identifying a link between psoriasis and both the gut and skin microbiomes.

Gut dysbiosis is noted in patients with psoriasis. In a review of eight studies evaluating the gut microbiome in psoriasis,[68] five studies found imbalances in Firmicutes and Bacteroidetes, the two most abundant phyla in the gut microbiome. In a 100-patient study by Waldman and colleagues,[69] those with psoriasis had significantly higher levels of *Candida* in both saliva and fecal samples than did controls. The increased prevalence of psoriasis seen in those with Crohn's disease as well as the association between psoriasis and periodontal disease further suggests a gut–psoriasis connection.[70,71] As hypothesized with AA, microbial alterations may lead to disease via altered metabolism and metabolic products.[68] Alternatively, gut microbiome changes may alter immune function and the inflammatory response, as shown in murine models.[72] Treatment with secukinumab is associated with significant alterations in the gut microbiome, specifically decreased Bacteroidetes and Firmicutes and increased relative abundance of Proteobacteria.[73] Interestingly, the baseline gut microbiomes differed significantly between treatment responders and nonresponders, suggesting that the gut microbiome plays a role in treatment efficacy. Treatment with ustekinumab was not associated with any significant changes in the gut microbiome.

The cutaneous microbiome in psoriasis also differs from that of controls. In a study examining skin biopsies,[74] both those with and without psoriasis had skin predominated by Firmicutes (mainly *Staphylococci* and *Streptococci*), followed by Proteobacteria and Actinobacteria. Relative to controls, patients with psoriasis had a greater abundance of Proteobacteria and a lower abundance of Actinobacteria, with increased *Streptococci* and decreased *Staphylococci*. In a study[4] evaluating the cutaneous microbiome using skin swabs, Firmicutes were the most abundant phylum in lesions of psoriasis compared with Actinobacteria for nonlesional and control skin. Lesions of psoriasis had less *Propionibacterium* relative to nonlesional skin, which had less than control skin. *Streptococcus* was increased in lesional compared with nonlesional skin. In another study using skin swabs,[75] those with psoriasis had more diverse and heterogenous skin microbiomes than did those without psoriasis. Contrary to the aforementioned study using skin biopsies,[74] relative enrichment of *Staphylococcus*

aureus was noted in both lesional and nonlesional skin of those with psoriasis, while *Staphylococcus epidermidis* and *Cutibacterium acnes* were decreased in lesional compared with healthy skin. Several other studies report increased *Staphylococcus aureus* in lesional skin along with more toxigenic strains.[76,77] Detection of these toxigenic strains correlates with disease activity, similar to what is seen in AD.[78] In susceptible individuals, breakdown of immune tolerance to cutaneous microbes may lead to the development of psoriasis via the activation of the immune system.[79] Alternatively, the differences in the cutaneous microbiome between cases and controls may relate to increased antimicrobial peptides in psoriasis.

Specifically in the pediatric population, Chen and colleagues[80] examined the impact of infection and antibiotic exposure on the future development of psoriasis in 1527 patients. Skin bacterial and viral infections, as well as fungal infections during the first two years of life, were associated with psoriasis, but exposure to systemic antibiotics was not. Another study[81] had similar findings, with infections associated with pediatric psoriasis. In a murine study,[82] neonates treated with antibiotics targeting gram-negative and gram-positive bacteria showed dysbiosis in gut and skin flora as adults, and were more susceptible to experimental psoriasis. Interestingly, adult mice treated with these same antibiotics showed decreased susceptibility to experimental psoriasis. Both findings were mediated by altered immune reactivity, including T cells and inflammatory cytokines. In another study, newborn mice with skin colonized by *S. aureus* showed a strong Th17 response that was not seen in mice colonized with *S. epidermidis*.[75] Additional research is needed to better understand the role of alterations in cutaneous flora play in psoriasis.

Seborrheic Dermatitis

Seborrheic dermatitis presents with erythema and greasy white–yellow scale or crust in areas of high sebaceous gland concentration, including the face, scalp, postauricular region, and intertriginous areas. The condition is common both in infancy and from adolescence through adulthood. In infants, the condition is commonly limited to the scalp (hence the colloquial term “cradle cap”)

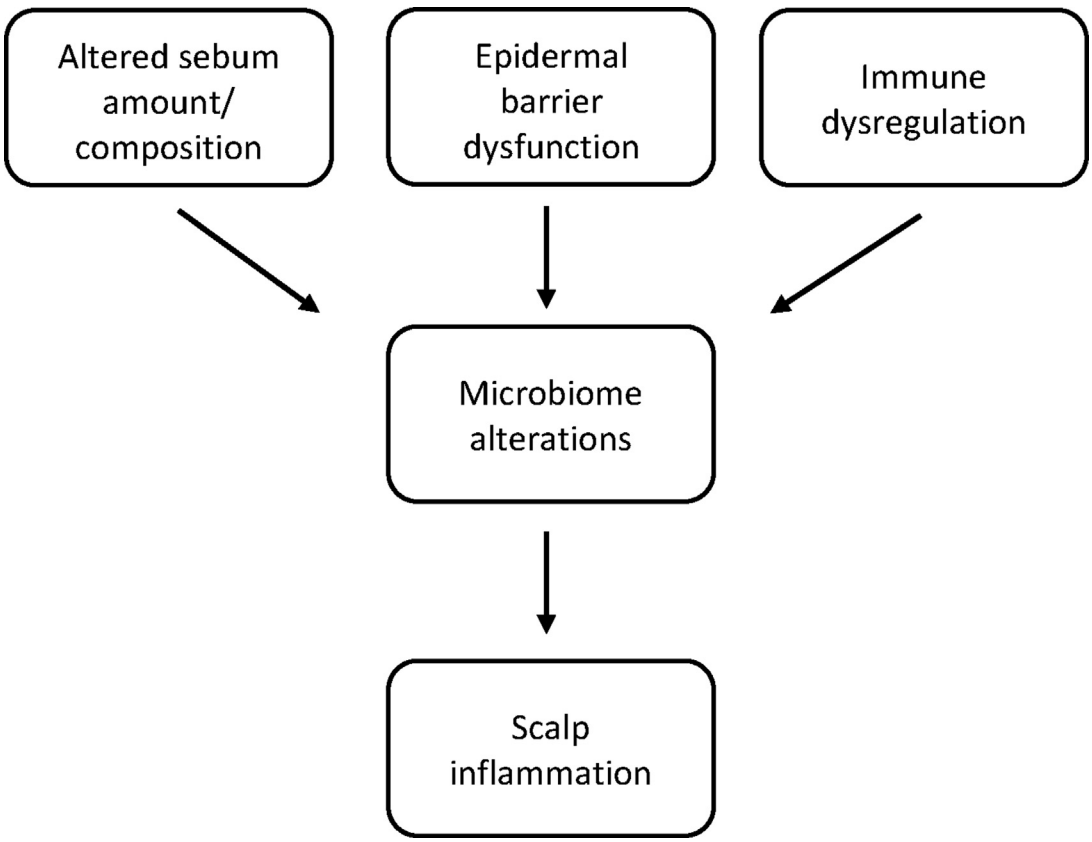

Fig. 1. Proposed model for the pathogenesis of seborrheic dermatitis.

though can be more widespread and overlap with AD.[83] Altered sebum production, host immune factors, and microbes contribute to disease development.

Bacterial and fungal dysbiosis is noted in those with seborrheic dermatitis. Studies show an increased incidence of *Malassezia* (specifically *Malassezia restricta* in some studies) and *Staphylococcal* species on the scalps of those with seborrheic dermatitis, both in adults and in infants.[84–88] Some studies also show decreased *C. acnes* in affected individuals.[85,86] The precise role these microbiome changes play, however, remains unknown. Previously, an abundance of *Malassezia* was thought to directly cause the condition because antifungals are an effective therapy, and the amount of *Malassezia* on the scalp decreases with treatment.[89–91] However, a recent review[92] of disease pathogenesis suggests that predisposing host factors, including altered sebum amount or composition, epidermal barrier dysfunction, or immune dysregulation, are the initial triggers. These alterations may then lead to microbiome changes, which in turn cause scalp inflammation and the clinical presentation of seborrheic dermatitis (**Fig. 1**). *Malassezia*, a lipophilic yeast that thrives in a sebum-rich environment, may be overrepresented in those with seborrheic dermatitis due to aberrant sebum production.[93] In infants, maternal androgens are thought to promote disease by increasing sebaceous gland activity.[94] Sebum excretion rates are highly correlated between mother and baby during the perinatal period, with rates in infants then decreasing postnatally until puberty.[95]

Notable clinical differences between pediatric patients and adults with seborrheic dermatitis suggest that etiologic differences may exist as well. In contrast to the chronic, relapsing-remitting nature of adult seborrheic dermatitis, infantile seborrheic dermatitis is usually self-limited, resolving by eight to twelve months of age in most patients.[31] Infants may also respond to more conservative treatments than are needed in adults. In addition to topical ketoconazole or topical corticosteroids, those with mild disease may respond to more frequent bathing and shampooing.[14] Future studies are required to better understand the role of the cutaneous microbiome in seborrheic dermatitis.

SUMMARY

The microbiome is pertinent to the most commonly treated pediatric dermatologic conditions, from acne to seborrheic dermatitis. Therapeutic strategies related to the microbiome are slowly being uncovered. Current research on the skin microbiome largely consists of adult subjects. Given the evolution of both the microbiome and the immune system in infants and children, this population may be a promising focus for future studies.

CLINICS CARE POINTS

- *C. acnes* contributes to the development of acne by increasing sebum production, stimulating comedone formation, and promoting inflammation, with relative abundance being similar in those with and without acne but the presence of specific strains differing.
- Gut microbiome alterations are associated with AA, which may contribute to the inflammatory environment or impact bacterial metabolic products that then influence the development of inflammatory cells.
- Flares of AD are associated with a decrease in bacterial diversity and an overabundance of *S. aureus*, but treatment restores balance to the microbiome.
- Pediatric psoriasis, particularly childhood guttate psoriasis, can be triggered by a preceding infection, possibly via immune activation and cross-reactivity to skin components.
- Altered sebum amount or composition, epidermal barrier dysfunction, or immune dysregulation are likely the initial triggers of seborrheic dermatitis which then lead to microbiome changes that cause scalp inflammation.

DISCLOSURE

The authors have no relevant conflicts of interest to disclose.

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