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REVIEW ARTICLES

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The infantile cutaneous microbiome: A review

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Abstract

Recent focus on the neonatal intestinal microbiome has advanced our knowledge of the complex interplay between the intestinal barrier, the developing immune system, and commensal and pathogenic organisms. Despite the parallel role of the infant skin in serving as both a barrier and an interface for priming the immune system, large gaps exist in our understanding of the infantile cutaneous microbiome. The skin microbiome changes and matures throughout infancy, becoming more diverse and developing the site specificity known to exist in adults. Delivery method initially determines the composition of the cutaneous microbiome, though this impact appears transient. Cutaneous microbes play a critical role in immune system development, particularly during the neonatal period, and microbes and immune cells have closely intertwined, reciprocal effects. The unique structure of newborn skin influences cutaneous microbial colonization and the development of dermatologic pathology. The development of the infantile skin barrier and cutaneous microbiome contributes to future skin pathology. Atopic dermatitis flares and seborrheic dermatitis have been linked to dysbiosis, while erythema toxicum neonatorum is an immune response to the establishment of normal bacterial skin flora. Physicians who care for infants should be aware of the impact of the infantile skin microbiome and its role in the development of pathology. A better understanding of the origin and evolution of the skin microbiome will lead to more effective prevention and treatment of pediatric skin disease.

KEYWORDS
atopic dermatitis, erythema toxicum neonatorum, infant, microbiome, neonatal cutaneous microbiome, seborrheic dermatitis, skin

1 | INTRODUCTION

While the infantile intestinal microbiome has been linked to obesity, diabetes, inflammatory bowel disease, cancer, necrotizing enterocolitis, neurodevelopment, and asthma, the ontogeny of the skin microbiome has been relatively neglected.[1-4] The neonatal gut and skin evolve in parallel, developing a barrier to the outside world and shaping the immune system. A possible link between the skin and gut is elucidated by the literature exploring the role of probiotics in the prevention of atopic dermatitis (AD). Elazab et al[5] found that pre- and/or early-life antibiotic administration reduced atopic sensitization (as measured by skin prick test). A later systematic review and meta-analysis demonstrated that probiotic supplementation in both the pre- and postnatal period reduced the incidence of pediatric AD.[6] In contrast, probiotics do not appear to be beneficial in treatment of pediatric AD.[7] This gut-skin link in the prevention, but not treatment, of AD highlights the importance of host-microbe interactions in the perinatal period.

The cutaneous microbiome encompasses the microbes that live in and on the skin, including bacteria, archaea, fungi, viruses, and mites.[7] The colonizing microbes influence both infectious and inflammatory skin conditions as well as immune system development.[7-10] The composition of the cutaneous microbiome changes over the first year of life, beginning with the rapid colonization that occurs at birth.[8,11] While the neonatal period (the first month of life) is of particular interest as a time of rapid change, the evolution of the microbiome continues throughout the infantile period. The dynamic state of the infantile microbiome allows for pathology if development goes awry, but also for opportunities to intervene, thereby preventing disease.[7,11]

There are scarce data on the composition of the neonatal microbiome, as well as its relationship to common neonatal skin conditions. Existing studies are limited by small sample size and lack of controls.[12,13] Herein, we summarize the existing literature on the infantile cutaneous microbiome, its relation to normal skin barrier development, and its contribution to three common skin conditions: AD, seborrheic dermatitis (SD), and erythema toxicum neonatorum (ETN). Knowledge gaps in our understanding of the infantile cutaneous microbiome are identified, as well as the potential impact on the treatment and prevention of disease.

2 | DISCUSSION

2.1 | Factors influencing the neonatal cutaneous microbiome

2.1.1 | Neonatal skin structure in the development of the cutaneous microbiome

Neonatal skin is dynamic in both structure and function. Skin barrier function begins between 20 and 24 weeks gestation.[14] The stratum corneum (the outermost layer of skin) is formed by the third trimester of pregnancy, providing both immune and structural protection from the microbes and dry environment encountered at birth.[15,16] In premature infants, an immature stratum corneum results in increased permeability, temperature fluctuations, water loss, electrolyte imbalances, and risk of infection.[15] Premature infants also have increased skin cytokines compared to term infants, possibly due to stress.[15] In contrast, the stratum corneum of term infants has nearly adult-like properties at birth, and preterm infants reach this level of maturation by 2-9 weeks of life.[15,17]

At birth, the pH of the skin is uniformly neutral, but development of skin acidity (ie, the acid mantle) starts within the first 16 hours of life. This leads to site-specific differences in skin pH, resulting from external influences, as manifested by differing pHs in diapered and non-diapered skin.[18] Skin acidity is of particular importance, as it functions to inhibit the growth of pathogenic bacteria and possibly facilitate colonization by commensal organisms.

Vernix caseosa is a white, greasy, lipid-rich biofilm present in variable amounts on the skin of infants at birth.[19-21] Produced during the last trimester of pregnancy, it plays a role in prevention of water loss, temperature regulation, and innate immunity after birth.[19,20,22] The role of vernix seems particularly important, given the sudden exposure at birth to microbes, toxins, oxidative stress, variable temperatures, and humidity.[22] Vernix is also a key player in the development of early cutaneous innate immunity. It contains LL-37 and lysozyme, two antimicrobial substances that work synergistically, as well as lactoferrin, alpha-defensins, and other antimicrobial peptides.[20,21,23-25] Vernix appears to selectively inhibit some bacteria (*Klebsiella*, *Bacillus megaterium*, *Listeria monocytogenes*, *Group B Streptococcus*, and *Candida albicans*[20,23-26]), but not *Pseudomonas aeruginosa*, coagulase-negative *Staphylococcus*, or *Serratia marcescens*.[24,25] This selective inhibition may be mediated, in part, by the role of vernix in the development of the acid mantle.[22] Further research is needed to examine the role of the vernix in the development of cutaneous immunity and the microbiome (Figure 1).

2.1.2 | From womb to the outside world

Historically, the womb has been presumed to be a sterile environment.[27] Recently, researchers have explored the possibility of an intentionally non-sterile womb.[28,29] Maternal intestinal and oral microbes may be selectively transported to the placenta and amniotic fluid in order to colonize the fetus.[28,29] Studies have focused on the relationship between the non-sterile womb and infant gut development; however, there is a connection to the skin as well, as these two systems are continuous in utero.[29] Critics of the non-sterile womb

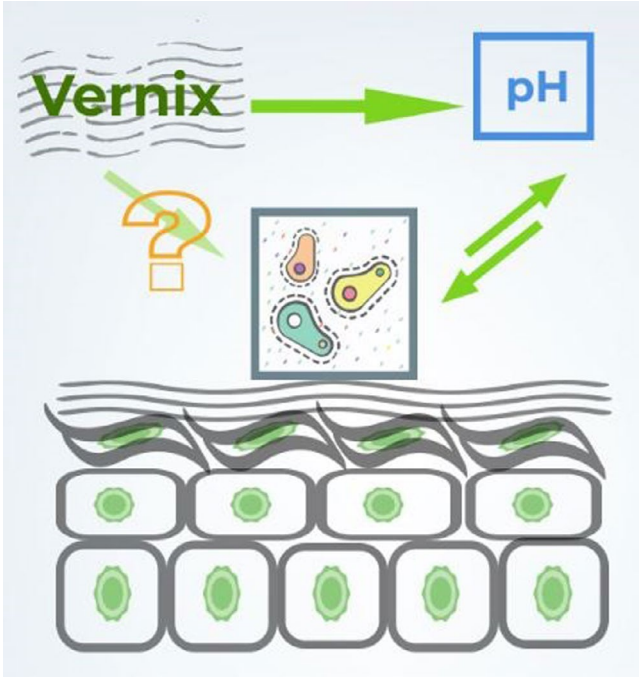

FIGURE 1 Factors influencing the early establishment of the cutaneous microbiome. Vernix influences pH, facilitating early development of the acid mantle. pH in turn has reciprocal effects on commensal organisms. The direct influence of vernix on the skin microbiome is unknown but may be mediated by antimicrobial peptides

hypothesis question the detection of bacterial DNA, which may represent contamination rather than viable bacteria.[27]

Colonization of the neonatal intestinal tract begins shortly after birth.[30] Reduced inflammatory cytokine production and a predominance of regulatory immune responses allow the neonate to adapt to colonization.[31,32] Breast milk, containing microbes, microbial metabolites, IgA antibodies, and cytokines, influences microbiome development and the neonate′s response. This interaction between the microbes and host sets the stage for future function of the mucosal and systemic immune systems.[31] For example, in murine models, *Clostridium* species and *Bacteroides fragilis* induce production of T regulatory cells, which play a key role in immune tolerance.[33,34]

At delivery, neonatal skin is exposed to the microbe-rich world outside of the womb. Shortly after birth, mode of delivery is the major determinant of the newborn′s cutaneous microbiome composition.[27,35,36] The skin of newborns delivered via cesarean section is colonized by bacteria most similar to those on their mothers′ skin, particularly *Staphylococcus*, *Streptococcus*, *Corynebacterium*, and *Propionibacterium*.[35,36] Bacteria on the skin of newborns delivered vaginally are similar to their mothers′ vaginal flora, containing predominantly *Lactobacillus*.[35,36] In contrast, at sites such as the nares and oral cavity, neonates born vaginally have bacterial communities equally similar to both maternal skin and vaginal flora.[36] Neonates born via labored cesarean display communities similar to both maternal skin and vaginal flora at all sites (skin, nares, and oral cavity).[36] In a recent study, infants born via cesarean section and artificially exposed to maternal vaginal flora had cutaneous microbiome compositions partially resembling vaginal flora, demonstrating the easily influenced and dynamic nature of the neonatal cutaneous microbiome.[37] In contrast to that of adults, the early skin microbiome does not differ significantly in composition based on anatomic location.[35,36]

Like many aspects of infant physiology, the cutaneous microbiome is dynamic, continuously evolving and diversifying with age.[11,37,38] Gestational age, bacterial richness, and bacterial diversity are positively correlated, while significant antibiotic use (defined as use for > 48 hours) and bacterial diversity are negatively correlated.[12,39] A recent study of 12 very low birthweight infants in the neonatal intensive care unit showed that, despite initially high cutaneous microbial diversity in 11 of 12 infants, cutaneous bacterial diversity was markedly decreased in all infants by 3 weeks of life after treatment with prophylactic antibiotics.[39] In this small study, treatment of sepsis with additional antibiotics did not impact cutaneous microbial diversity, and no association was found between changes in the cutaneous microbiome and sepsis. In a larger study,[40] a significant portion of the infant skin microbiome was acquired from the hospital environment.

2.1.3 | The composition of the infantile cutaneous microbiome

The influence of delivery mode appears to dissipate by 1 month of life, with similar bacterial colonization patterns emerging for all infants regardless of mode of delivery.[11,36] This change is driven primarily by body site. Between 3 weeks and 3 months of life, infants begin to develop the site-specific bacterial profiles known to exist in adults.[11,36,41-43] For example, at 6 weeks of life, infant skin and nares were colonized by *Staphylococcus* and *Corynebacterium*, similar to those same sites in adults.[36] The skin appears to have the most "adult-like" microbial composition at 6 weeks of life compared to other body sites[36,43] but still differs significantly from the adult skin microbiome until late adolescence.[44]

In infants, *Firmicutes* (specifically genera *Staphylococcus* and *Streptococcus*) are the predominant bacteria on the skin, followed by bacteria from the phyla *Actinobacteria*, *Proteobacteria*, and *Bacteroidetes*.[11,12,39,43] Preterm infants have an increased abundance of *Staphylococcus*, *Corynebacterium* (phylum *Actinobacteria*), and *Prevotella* (phylum *Bacteroidetes*) relative to the *Brevundimonas*, *Flavobacterium*, and *Sphingobacterium* in term infants.[12] In adults, *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* are the predominant phyla, and *Corynebacterium*, *Propionibacterium*, and *Streptococous* and *Staphylococcus* are the predominant genera (Table 1).[9,45,46] Additional bacteria found frequently on adult skin include *Micrococcus*, *Veillonella*, and *Acinetobacter*.[9] Many of the bacteria that commonly reside on the skin may become pathogenic. Little is known about the contribution of the cutaneous microbiome to morbidity and mortality in preterm infants.[9]

There are also scarce data on the fungal components of the infantile cutaneous microbiome (the mycobiome). In adults, *Malassezia* (specifically *Malassezia globosa* and *Malassezia restricta*), as well as lipophilic yeasts, are the major components of the cutaneous mycobiome.[46-48] As with bacteria, fungal colonization is site-specific.[49] Nagata et al.[50] found *Malassezia* on the skin of 24 of 27 infants on the day of birth and all infants at 1 day of life. *Malassezia* colonization and diversity increased with age, becoming adult-like by 1 month of life. The strain sequence identity of *Malassezia* colonizing neonates and their mothers was very similar, suggesting transmission from mother to infant.

TABLE 1 Common bacterial components of the cutaneous microbiome, demonstrating differences between full-term infants (months 1-3 after birth) and adults[11,85]

Predominant bacterial composition of the cutaneous microbiome		
	Phylum	**Genus**
Term infant	*Actinobacteria*	***Propionibacterium***
		Corynebacterium
	Firmicutes	***Staphylococcus***
		Streptococcus
		Clostridium
Adult	*Actinobacteria*	***Propionibacterium***
		Corynebacterium
		Micrococcus
	Firmicutes	***Staphylococcus***
		Streptococcus
		Veillonella

Note: Dominant genera are in bold.

As with bacteria and fungi, there are diverse viruses present on human skin.[51] Researchers are beginning to investigate the viral cutaneous microbiome, including bacteriophages, human papillomaviruses, human polyomaviruses, and human herpesviruses.[46,52] As with bacteria and fungi, research in adults has shown that viral components of the cutaneous microbiome are site-specific, with large interpersonal variation.[46,49,53] Further studies are needed to characterize the viral component of the neonatal cutaneous microbiome, its relationship to skin pathology, and its importance in cutaneous immunity.[51]

2.1.4 | Microbes and the immune system

In the gut, bacteria have a critical role in regulation of immune function,[54] and the cutaneous microbiome likely plays a parallel role in cutaneous homeostasis and inflammatory response modulation.[8,11] Lipoteichoic acid, a product of *Staphylococcus*, suppresses skin inflammation during wound repair by acting on a keratinocyte receptor (Toll-like receptor 2), indicating that bacteria may protect against aberrant inflammatory response.[55] *Staphylococcus epidermidis* has also been shown to modulate host innate immune response.[56] The immune system also modulates the organisms able to colonize the skin, particularly innate immunity via host-defense proteins. Lysozyme, lactoferrin, and other host-defense proteins are found on newborn skin, and active lysozyme is found at concentrations five times that of adult skin.[16]

In a mouse model, Scharschmidt et al.[10] found that the presence of cutaneous microbes during the neonatal period was obligatory in order to establish tolerance to these microbes. An immune response composed mainly of regulatory T cells (which prevent inflammation and promote immune tolerance) resulted from the presence of cutaneous bacteria during the neonatal period, but not later in life. An influx of activated regulatory T cells occurred during week 2 of life, but when this influx was blocked prior to bacterial colonization, tolerance did not develop.[57] Scharschmidt also found that regulatory T cells were decreased if either hair follicle morphogenesis or colonization by commensal microbes was disrupted; thus, both hair follicles and commensal microbes have independent, critical roles in the development of cutaneous immunity.[58] The cutaneous microbiome is critical to immune system development and thus a potential source of pathology and opportunity for intervention.

An increasing body of evidence supports an association between microbial imbalance of the gut and the development of allergic diseases.[59-61] Reduced gut microbial diversity is associated with an increased risk of AD later in life.[62,63] Cytokine production elicited by intestinal microbes varies between atopic infants and healthy infants, favoring pro-inflammatory responses in the atopic infant.[64] A recent study shows an overgrowth of gut bacteria in infants with respiratory allergies with and without coexisting AD. In a subsequent mouse model, this increase of bacteria-induced cytokine production from colonic tissue stimulated T-helper 2 cell (Th2) inflammation. Th2-predominant inflammation is central to the pathogenesis of many allergic diseases.[65] Additional research focused on the immune interaction between the gastrointestinal and cutaneous microbiome is needed to further elucidate this link.

2.2 | Clinical presentation: The role of the cutaneous microbiome in pediatric skin disease

2.2.1 | Atopic dermatitis

Atopic dermatitis is a common, chronic skin condition with typical onset during early childhood. It is characterized by dry skin, intense itching, and a defective skin barrier, leaving patients vulnerable to superinfection.[66] AD contributes to significant psychosocial morbidity for patients and families, and it places a large financial burden on society.[67] AD is termed the first step of the "atopic march," as patients with AD have an increased risk for the subsequent development of both allergic rhinitis and asthma.[68]

Barrier dysfunction, inflammation, and microbes contribute to the pathogenesis of AD, and the relationship between AD and microbes is well established.[69] While few healthy individuals are colonized with *Staphylococcus aureus*, 70% of patients with AD are colonized at lesional sites.[70] During AD flares, cutaneous microbial diversity has been shown to decrease remarkably, with predominance of *S epidermidis*, *S aureus*, and *Malassezia*.[69,71] These changes normalize after successful treatment.[71] In a mouse model,[72] both *S aureus* and *Corynebacterium bovis* played important roles in the pathogenesis of AD-like disease, with *S aureus* driving dermatitis development and *C bovis* contributing to the pathogenic immune response. Treatment of dermatitis flares normalizes the skin's bacterial components, supporting the critical role microbes play in AD pathogenesis.

Alterations in the cutaneous microbiome caused by external factors, such as antibiotics, may contribute to the increasing incidence and complex pathogenesis of AD. Studies examining the relationship between perinatal antibiotic exposure and AD have produced conflicting results.[73,74] In one study, prenatal exposure to antibiotics was positively correlated with the subsequent development of AD, but postnatal exposure and AD were negatively correlated.[73] Early *Staphylococcal* colonization may be critical in the prevention of AD through modulation of the cutaneous immune system. Kennedy et al[38] found that infants who had AD at 1 year of age had significantly less commensal *Staphylococci* in the antecubital fossa at age 2 months compared with unaffected infants. However, there were no significant differences in the cutaneous microbiome compositions between the groups at 1 year of age. Thus, early exposure to *Staphylococcus* may reduce the development of AD.

2.2.2 | Seborrheic dermatitis

Seborrheic dermatitis is a common chronic inflammatory skin disease present in 1%-3% of the population[75] and is characterized by erythema with overlying greasy scale. Infantile SD typically affects the scalp, but it can also affect the face, ears, neck, and diaper area.[76,77]

Adult SD typically affects sebum-rich sites such as the scalp, ears, forehead, nasolabial folds, chest, and upper back.[75,77,78]

The exact etiology of SD is unknown, but many studies have implicated a relationship with the lipophilic yeast *Malassezia*.[75-79] *Malassezia* are part of the resident cutaneous microbiota in healthy skin, but they can become pathogenic.[75,78] The most common species found on both healthy and diseased skin are *M restricta* and *M globosa*.[50,78,79] The proportion of *Malassezia* yeasts on the scalp is higher for patients with SD than for control subjects, but data in lesional vs non-lesional skin is inconclusive.[75] *Malassezia* degrade sebum and use lipase to split triglycerides into fatty acids. They consume specific saturated fatty acids and leave behind unsaturated fatty acids, which are thought to contribute to the irritation seen in SD.[79] Changes in the *Malassezia* community likely alter the resident bacterial microbiota as well. *Staphylococcus*, *Streptococcus*, and *Acinetobacter* are more abundant at lesional than at non-lesional sites, as is *M restricta*.[77] These bacteria are not thought to be causative, but they may help supply nutrients that promote the growth of *Malassezia* species.[77] This may partially explain the commonly observed overlap between infantile seborrheic and atopic dermatitis.

It is unclear why *Malassezia* organisms promote inflammation in SD, since they are also present in healthy skin. Both the yeast and the host play a role in the development of SD, particularly regarding the immune system response.[78] This is highlighted by the increased incidence of severe SD in immunocompromised patients, especially those with acquired immunodeficiency syndrome.[75,78] The interplay among the early cutaneous microbiome, the evolving immune system, and the development of SD deserves further study.

2.2.3 | Erythema toxicum neonatorum

Erythema toxicum neonatorum is a common, benign neonatal skin condition consisting of papules and pustules on an irregular erythematous base.[8,80] The condition usually develops between days 2 and 4 of life and regresses spontaneously within a week. The lesions occur most commonly on the trunk, thighs, and buttocks and notably spare the palms, soles, and penis—all areas without hair follicles.[8,80] Estimates of prevalence range from 3.7% to 72%, with the condition being more common in vaginally delivered neonates and those of greater gestational age and birthweight.[80,81] ETN is rare in premature infants. Skin biopsies of affected areas reveal a predominately eosinophilic dense dermal infiltrate with edema.[8,80,82]

Erythema toxicum neonatorum likely represents an immune response to the establishment of commensal bacteria in the skin, via the hair canal. Marchini et al[8] found that lesions of ETN had bacteria, primarily *Staphylococcus*, present in hair follicular epithelium and in immune cells surrounding the hair follicle. Notably, hair follicles play an important role as an "effector arm" of the early developing immune system.[83] The presence of numerous pro-inflammatory markers (including Interleukin-1, Interleukin-8, E-selectin, and psoriasin, among others) in lesions of ETN supports the hypothesis that ETN represents an immune response to bacteria in hair follicles rather than a failure of the hair follicle to control bacteria.[8,84,85] Further studies are needed to explore whether this response offers an adaptive benefit.

3 | CONCLUSIONS

There are significant knowledge gaps in our understanding of the infantile cutaneous microbiome. The dynamic nature of infantile skin in its barrier and immunologic function, and its unique relationship to the cutaneous microbiome, deserves further exploration. A better understanding of this early microenvironment will have far-reaching implications in the treatment of pediatric skin disease. Early preventative strategies including oral and topical probiotics, or even specific microbial metabolites, may prevent dermatologic pathology.

AUTHORS' CONTRIBUTIONS

JS, RM, KS, and JH contributed to article selection/review and manuscript writing. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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