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REVIEW ARTICLE

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Modulations of the skin microbiome in skin disorders: A narrative review from a wound care perspective

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Abstract

The cutaneous microbiome represents a highly dynamic community of bacteria, fungi and viruses. Scientific evidence, particularly from the last two decades, has revealed that these organisms are far from being inconsequential microscopic hitchhikers on the human body, nor are they all opportunistic pathogens waiting for the chance to penetrate the skin barrier and cause infection. In this review, we will describe how dermatological diseases have been found to be associated with disruptions and imbalances in the skin microbiome and how this new evidence had shaped the diagnosis and clinical practice relating to these disorders. We will identify the microbial agents which have been found to directly exacerbate skin diseases, as well as those which can ameliorate many of the symptoms associated with dermatological disorders. Furthermore, we will discuss the studies which suggest that bacteriotherapy, either by topical use of probiotics or by bacteria-derived compounds, can rectify skin microbial imbalances, thereby offering a promising alternative to antibiotic treatment and reducing the risks of antibiotic resistance.

KEYWORDS

microbiota, multiple drug resistance, probiotics, skin, wounds and injuries

Key Messages

The cutaneous microbiome is an important player in the maintenance of skin barrier integrity and wound healing, which has been historically underrated. Here, we discuss the involvement of the commensal skin microbiota in skin disorders, from atopic dermatitis to non-healing wounds. We describe the microbial signatures that are associated with disease, as well as the mechanistic insight gained from preclinical models as to how these microbes affect cutaneous health. Finally, we describe those studies that investigate the therapeutic benefits of topical probiotics and propose that clinical practice in dealing with skin disorders should take this research into consideration with regards to patient care.

1 | INTRODUCTION

The skin is the largest organ in the human body which, in an average adult, can reach 2 m^2 and 3.6 kg.[1] The skin provides vital functions for the human body, ranging from the physiological to the molecular level. At the structural level, the skin is the barrier between the human body and the outside world, designed to keep moisture in and dangerous agents out. When the integrity of this physical barrier is compromised, therefore, there are significant consequences to human health, including dehydration, local or systemic inflammation and infection.

Several cellular and molecular processes are responsible for the maintenance of skin barrier integrity. The outermost layer of the skin, the epidermis, is itself composed of multiple layers of keratinocytes at different stages of differentiation, terminating in the outermost layer, the stratum corneum, composed of terminally differentiated, tightly cross-linked, enucleated keratinocytes or squames.[2–4] Molecular processes such as the maintenance of a trans-epidermal calcium gradient, the ability of keratinocytes to uptake and respond to calcium signals and the correct production of gap junction proteins and skin lipid production all work in concert to form and maintain a strong and intact stratus corneum.[3] In addition to human genetics, several environmental factors can influence these molecular processes and either aid or compromise skin barrier integrity. One of the most important extra-genetic factors is the composition of the commensal skin microbiota, composed of bacteria, fungi, viruses and mites.[2,4] Though not as diverse as the gut microflora, the skin can collectively house 19 different bacterial phyla and over 200 bacterial genera, whose appropriate balance is critical to its proper maintenance.[2,4–6] Also like the gut microbiome, the skin microbiota is highly variable between different populations, with factors like delivery mode, geography and lifestyle being the most important factors to determine this variability.[7–10]

Historically, microbes inhabiting the skin were considered insignificant at best or potentially dangerous infectious agents at worst, and thus, protecting the balance of the skin microbiome, or exploiting it for the benefit of the patient, was not given due consideration. However, while the precise role of each cutaneous commensal microorganism is still being characterized, many crucial physiological processes have been attributed to the skin microbiota in recent years (Figure 1). Developmentally, the skin microbiota rapidly diversifies in the first year of life, an event which coincides with the maturation of the skin and reduction of transepidermal water loss, skin pH and sebaceous activity.[13] Symbiotically, skin commensals secrete sphingomyelinase and other bacterial enzymes, which in turn stimulate the production of ceramides from the host, prevent dehydration of the skin and help maintain skin barrier integrity.[14,15] Immunologically, receptors on the keratinocytes in the stratum corneum respond to the molecules coating microbial cell walls, in turn precipitating a molecular cascade which initiates an innate immune response, regulating local inflammatory processes and priming it to respond to future infection.[4,15–20] Furthermore, commensal microorganisms can compete with opportunistic pathogens, directly impeding their ability to infect the host by either producing antimicrobial peptides, changing the local environment to suppress their growth or by forcing them to shift towards a more commensal state.[2,15,21–24] With the emergence of the benefits of the commensal skin microbiome in both healthy and diseases states, as well as the ever-growing threat of antimicrobial resistance, clinicians must consider the cost–benefit trade-off of using topical antibiotics and disinfectants when combatting skin disorders.

Given the multitude of ways that skin commensals can help mitigate the effects of opportunistic pathogens, many clinical studies are emerging into the benefits of prebiotic, probiotic and postbiotic topical treatments.[25–27] For example, one randomized placebo-controlled study found that topical treatment containing cell-free extract from *Lactobacillus brevis* DSM17250 stimulated the growth of cutaneous commensal bacteria, reduced transepidermal water loss and improved symptoms associated with dry skin.[28] Similarly, another clinical trial found that collecting *S. epidermis* from participants, growing it in culture and then reapplying it to their own faces twice weekly were sufficient to increase skin lipid content and improve moisture retention.[29] Furthermore, postbiotics derived from *Epidermidibacterium keratini* EPI-7 were found to stimulate the growth of skin commensals and improve skin barrier function and skin elasticity when applied topically in a split-face clinical study.[30] Collectively, these data support the hypothesis that using either bacteria or bacteria-derived metabolites can lead to significant improvement in skin barrier function, without destroying the skin microbiome in the process.

In this review, we will discuss what is currently known about the cutaneous microbiome in the context of different skin-related diseases. We will discuss the evidence of how the skin microbiota can precipitate, aggravate or ameliorate various skin conditions. Furthermore, we will discuss how this knowledge of the skin microbiome has uncovered novel, innovative therapies in the treatment of these diseases, and we underscore the most important factors of the skin microbiota that clinicians must take into consideration when choosing the most

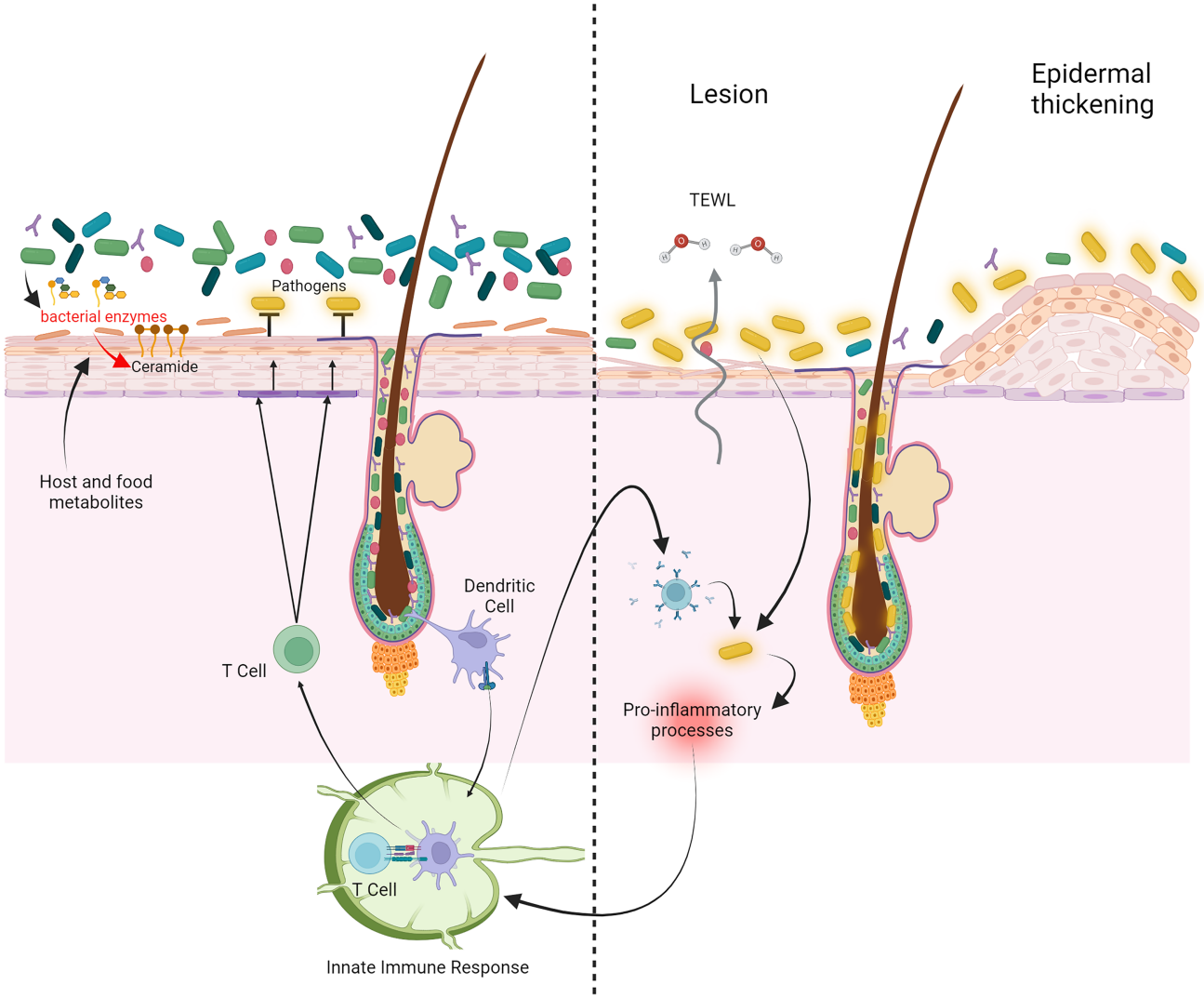

FIGURE 1 The commensal cutaneous microbiota is involved in many physiological processes in the skin. Left panel: the skin microbiota and its interactions with the host in a healthy state. Sphingolipids in the skin that protect the skin barrier are produced either entirely from metabolic processes within the host[11,12] or in response to bacterial-derived metabolic enzymes. The commensal microbiota also interacts with the host's immune system, which in turn becomes primed to fight future pathogenic invasion and precipitates molecular cascades in keratinocytes which aid in suppressing the overgrowth of opportunistic pathogens on the skin surface. Right panel: the consequences of impaired skin barrier integrity and/or a dysbiotic skin microbiome. A compromised skin barrier can result in either epidermal thickening or thinning, leading to transepidermal water loss (TEWL) which, among other alterations, can change the environment and thus favour the overgrowth of opportunistic pathogens. Furthermore, microbial species can slip through the compromised skin barrier and cause infection within the host, precipitating localized and systemic inflammatory processes.

appropriate treatment for their patients. Finally, in order to provide an overview of the role of the skin microbiota in numerous different diseases, we have restricted this review to the discussion of the skin microbiota specifically and topical treatments only. For more information on what is known of the gut-skin axis, the role of the intestinal microflora in skin conditions and the use of orally administered probiotics in the treatment of cutaneous diseases, we direct the reader towards these other, excellent reviews.[31–34]

2 | THE SKIN MICROBIOME IN ATOPIC DERMATITIS

Dermatitis is a group of skin conditions, such as eczema, characterized by dry inflamed skin and itchy eruptions, affecting around 15%–20% of children and 1%–3% of adults worldwide.[35,36] Both adults and children are at an increased risk of developing multiple fungal, bacterial and viral skin infections, possibly due to an altered skin barrier function.[37] Furthermore, children with atopic

TABLE 1 Microbial signatures associated with skin disorders.

Method	Comparison	Increased genera/species	Decreased genera/species	Ref
Atopic dermatitis				
16S	12 AD vs. 11 HS	*S. aureus*		44
16S	10 AD vs. 10 HS	*Staphylococcus* spp., *Lactobacillus* spp.	*Chryseobacterium* spp., *Kocuria* spp.	45
16S	10 affected vs. unaffected skin	*S. aureus*	*Propionibacterium* spp., *Bacteroidetes* spp., *Fusobacteria* spp.	45
16S	10 AD vs. 10 HS	*Staphylococcus* spp., *Gemella* spp.		46
qPCR/16S	35 AD vs. 29 HS	*Bacilli* spp., *Staphylococcus* spp.	*Actinobacteria* spp., *Lautropia* spp., *Cupriavidus* spp.	47
SG/WGS	7 AD vs. 7 HS	*Staphylococcus* spp., *S. aureus*		48
16S	75 AD vs. 20 HS	*Staphylococcus* spp., *Streptococcus* spp.	*Klebsiella* spp., *Pseudomonas* spp., *Paracocus* spp.	49
16S	49 before vs. 49 after emollient	*Staphylococcus* spp.	*Stenotrophomonas* spp.	51
16S	108 mild vs. severe AD	*Staphylococcus* spp.	*Dolosigranulum* spp.	39
16S	18 affected vs. unaffected skin	*S. aureus*; *Staphylococcus* spp.	*Propionibacterium acnes*; *S. epidermidis; Corynebacterium* spp.	40
16S	25 severe AD vs. 28 HS	*Staphylococcus* spp., *Finegoldia* spp. and *Aerococcus* spp.	*Veillonella* spp., *Actinomyces* spp., *Granulicatella* spp., *Porphyromonas* spp., *Haemophilus* spp., *Microbispora* spp., *Leptotrichia* spp., *Jeotgalicoccus* spp.	41
16S	63 affected vs. unaffected skin	*Staphylococcus* spp.	*Streptococcus* spp. and *Corynebacterium* spp.	42
16S	67 AD vs. 28 HS	*S. aureus*, *S. epidermidis*	*Corynebacterium* spp., *Micrococcus* spp., *Cutibacterium* spp., *Streptococcus* spp	52
qPCR/16S	38 alpine climate vs. 36 maritime climate		*S. aureus*	53
16S	51 AD vs. 31 HS	*Pseudomonas* spp., *Prevotella* spp., *Acinetobacter* spp., *Chryseobacterium* spp., *Desulfovibrio* spp.	*Streptococcus* spp., *Parabacteroides* spp., *Clostridium* XIVa, *Acinetobacter* spp., *Corynebacterium* spp.	54
SG	34 AD vs. 54 HS	*S. aureus*	*Staphylococcus hominis*, *Cutibacterium acnes*, *Malassezia globose*	55
16S	28 AD vs 14 HS	*S. aureus*		56
16S/ITS	17 AD vs. 9 HS	*Staphylococcus* spp.		57
Acute urticaria				
BC	75 AU vs. 30 HS	*Propionibacterium* spp., *S. aureus*, *S. epidermidis*		58
Diaper dermatitis				
16S	54 DD vs. 31 HS	*Enterococcus* spp., *Erwinia* spp., *Pseudomonas* spp., *S. aureus*	*Clostridium* spp., *Actinomyces* spp., *S. epidermidis*, *Bifidobacterium* spp.	59
16S/ITS	18 severe vs. mild	*Enterococcus* spp., *S. aureus*, *Candida albicans*, *Aspergillus* spp., *Lasiosphaeriaceae* spp.	*Anaerococcus* spp., *Finegoldia* spp., *S. haemolyticus*	60

TABLE 1 (Continued)

Method	Comparison	Increased genera/species	Decreased genera/species	Ref
Acne vulgaris				
16S	24 acne vs. 12 HS	*Staphylococcus* spp., *Enterococcus* spp. *Planococcaceae* spp., *Aeromicrobium* spp., *Hyphomicrobiaceae* spp., *Gemellates* spp., *Paenibacillus* spp., *Nocardiaceae* spp., *Mycobacterium* spp., *Rhodococcus* spp.	*Propionibacterium* spp., *Pilimella* spp., *Lentzea* spp., *Nodularia* spp., *Lachnospira* spp., *Citricoccus* spp., *Chitinophagaceae* spp., *Chroococcidiopsis* spp. and *Caloramator* spp.	61
BC	100 acne vs. 28 HS	*Malassezia globosa*		62
Congenital ichthyoses				
SG	12 NS vs. HS (family members)	*S. aureus*, *Corybacterium bovis*, *Prevotella bivia*, *Streptococcus agalactiae*, *Str. Dysgalactiae*, *C. striatum*	*Cutibacterium acnes*, *Dermacoccus* spp. *Ellin185*, *Gordonia paraffinivorans*, *Lactobacillus lactis*, *Gordonia paraffinivorans*, *Lactococcus lactis*, *Malassezia globosa*, *Malassezia restricta*	63
SG	22 CI vs. 16 HS	*Staphylococcus* spp., *Corynebacterium* spp., *Trichophyton* spp., *Malassezia slooffiae*	*Cutibacterium acnes* and *Malassezia globosa*, *Malassezia sympodialis and Malassezia restricta*	64
16S/ITS	3 NS vs. 9 HS	*Staphylococcus* spp., *Corynebacterium* spp.,	*Lactobacillus* spp.	57
16S/ITS	4 IV vs. 9 HS	*Staphylococcus* spp., *Corynebacterium* spp.,		57
Diabetic foot ulcers				
16S	Severe vs. mild DFUs	*S. aureus*		65
16S	8 DFUs vs. 8 HS	*Staphylococcus* spp., *Pseudomonas* spp., *Corynebacterium* spp., *Streptococcus* spp., *Finegoldia* spp.		66
16S	Skin vs. tissue swabs	*Actinobacteria* spp., *Staphylococcus* spp., *Corynebacterium* spp., *Propionibacterium* spp.		67
Decubitus ulcers				
16S	15 DUs vs. 15 HS	*S. aureus*, *S. epidermidis*, *Enterococcus* spp., *Bacteroides* spp., *Eubacterium dolichum*, *Parabacteroides distasonis*, *Sarcina* spp., *Dorea* spp., *Ruminococcus* spp., *Ruminococcus gnavus*, *Lactococcus* spp., *Blautia producta*, *Lactobacillus zeae*, *Allobaculum* spp., *Christensenella* spp.	*Ruminococcus bromii*, *Pseudoclavibacter bifida*, *Actinobaculum* spp., *Mycobacterium vaccae*	68
16S	9 DUs that worsened vs. 15 DUs that improved	*Anaerococcus* spp., *Finegoldia* spp., *Proteus* spp., *Morganella* spp., *Peptoniphilus* spp.	*Pelomonas* spp.	69
Epidermolysis bullosa				
16S	8 uninvolved skin vs. EB wounds	*S. epidermidis*		70

Abbreviations: 16S, amplicon-based metagenomic sequencing method based on amplification of the bacterial 16S rRNA gene; AD, atopic dermatitis; AU, acute urticaria; BC, bacterial culture; CI, congenital ichthyosis; DD, diaper dermatitis; DFU, diabetic foot ulcer; EB, epidermolysis bullosa; HS, healthy subjects; ITS, amplicon-based metagenomic sequencing method based on amplification of the fungal internal transcribed spacer of nuclear DNA; IV, ichthyosis vulgaris; NS, Netherton syndrome; SG, untargeted shotgun metagenomic sequencing; WGS, whole-genome sequencing.

dermatitis (AD) are also highly predisposed to develop allergic disorders later in life, though whether or not AD can be classified as a bona fide allergic skin disease is still a matter of debate.[35] What is known is that AD is a multifactorial disease, with underlying causes of genetic, epigenetic, immunological and environmental origins.[35]

Recent evidence has also implicated the microbiota of the skin as a contributing factor to the recurrence of dermatitis flares. Multiple studies from across the world have revealed that AD is characterized by an unbalanced, or dysbiotic skin microbiota, with reduced bacterial diversity and a prevalence of *Staphylococcus aureus* rather than *Staphylococcus epidermidis*, their respective ratio also correlating with AD severity[36–51] (Table 1). Furthermore, the proportion of *S. aureus* within skin lesions is significantly higher than it is in adjacent, non-lesioned skin,[38–40,42,47,50,51,71] implicating *S. aureus* in the inflammatory processes which characterize the disease. Strain-specific effects have also been described for *S. aureus*, where shotgun metagenomic sequencing identified particular *S. aureus* strains within skin lesions of patients with particularly severe forms of AD, which alone were capable of inducing epidermal thickening and skin inflammation in a cutaneous colonization mouse model.[48] Mechanistically, *S. aureus* has been found to secrete toxins and virulent peptides that cause keratinocytes to precipitate an inflammatory response,[72–74] thus demonstrating a causal link between *S. aureus* colonization and the inflammation underlying AD flares.

Interestingly, longitudinal studies have found that *S. aureus* colonization does not occur during infancy, though the reduction of other commensal *Staphylococcus* species during infancy was predictive of AD development later in life.[46] Given the likely role of *S. aureus* in the pro-inflammatory processes that both precipitate and maintain skin flares in AD, therapeutic options which target this particular species are gaining more attention in recent years. Multiple studies have found that the abundance of *S. aureus* on the skin of AD patients decreasing post AD treatment, including following emollient therapy, use of topical corticosteroids and diluted bleach baths, resulting in a microbial composition which more closely resembles that of healthy controls.[38,44,47,48,51,54,56,75,76] Furthermore, *S. aureus* abundance has been found to change even in response to those AD therapies that do not involve the application of specific compounds to the affected areas, which could in turn directly impact bacterial growth. Climatotherapy, for instance, is the practice of exposing patients to different, often high-altitude climates, and has been found to be beneficial for those affected by AD, particularly those for whom conventional treatment fails.[53,77] In addition to helping alleviate AD symptoms, exposing AD patients to an alpine climate for 6 weeks significantly altered the microbial composition of their skin, including a significant decrease in the relative abundance of *S. aureus*.[53]

While *S. aureus* is not generally found on the skin of healthy children,[36,55] its presence alone does not determine the presence of skin flares in those affected by AD, as its complete elimination is not required for AD remission.[36,44] Rather, the skin microbiome of a patient with AD in remission is characterized by a particular microbial balance, with a lower relative abundance of *S. aureus*, and a higher relative abundance of *S. epidermidis*, *Streptococcus*, *Propionibacterium*, and *Corynebacterium*, among others, compared to those in an active disease state ([13,14,23,31]; Table 1). These data suggest that, just as some skin microbes may precipitate AD, others may attenuate *S. aureus*-induced inflammation and ameliorate pathology.

For example, specific coagulase-negative, lantibiotic-producing strains of *S. epidermis* and *Staphylococcus hominis* were found to be abundant on the skin of healthy subjects and depleted on the skin of AD patients.[21] Furthermore, these strains were found to be able to selectively kill *S. aureus* both in vitro and in vivo,[21] demonstrating the ability of these commensal microbes to protect the host by keeping the populations of opportunistic pathogens in check. Similarly, *Roseomonas mucosa* isolated from healthy subjects was able to suppress the growth of *S. aureus*, both in vitro and when used to colonize the skin of a mouse model of AD.[78] In humans, an open-label clinical trial found that topical transplantation of *R. mucosa* on AD patients resulted in an improvement in skin barrier function, attenuation of disease severity, a reduction in the need for topical corticosteroid treatment and a suppression of *S. aureus* skin populations, without any serious adverse events.[79,80] Interestingly, the positive effects of *R. mucosa* on AD may be strain-specific, as *R. mucosa* isolates from the skin of AD patients had either no effect or even worsened inflammation in the AD mouse model.[78] Similarly, topical treatment with a prebiotic colloidal oatmeal ointment was found to improve skin barrier function, as well as increase the growth and lactic acid production of skin commensals in AD patients.[76,81]

Mechanistically, in vitro studies have found that *S. epidermidis*, *Klebsiella oxytoca*, *Micrococcus luteus* and *Kocuria rhizophila* can inhibit *S. aureus*–induced production of the proinflammatory cytokines interleukin (IL)-1α and IL-6.[41] Furthermore, all four species were found to inhibit *S. aureus* growth and biofilm formation.[41] In monocyte-derived dendritic cells, the *S. aureus* secretome induced the release of the pro-inflammatory IFN-γ and the expansion of CD4+ T-cells, while exposure to the *S. epidermidis* secretome induced the production of the anti-inflammatory cytokine IL-10 and promoted the activity of regulatory T-cells, which in turn suppressed the proliferation of CD4+ cells.[82] Taken together, these in vitro studies further underscore the hypothesis that AD skin lesions are not precipitated solely by the presence or absence of one particular bacterial species.

Rather, AD flares are likely, at least partially, precipitated by an unbalance of the skin microbiota, each member of which may have contrasting effects on skin barrier integrity and local inflammatory processes.

3 | URTICARIAL DERMATITIS

Urticaria is a skin condition characterized by the sudden onset of raised, inflamed, pruritic wheals, which can be precipitated by allergic or autoimmune triggers.[83] Urticaria can be either acute or chronic. Acute urticaria is by far the most common condition, usually affecting children, and can affect up to 25% of people at some point in their lives.[84] Acute urticaria is self-limiting and usually resolves in a few days or weeks. Chronic urticaria, on the other hand, is far less common, affecting only 0.1%–3% of the population, mostly adults, and is defined as recurring episodes lasting over 6 weeks.[84]

Similar to AD, acute urticaria has also been associated with *S. aureus* colonization on the skin and was found to be more abundant on affected skin compared to both unaffected skin of patients and healthy controls.[58] In addition to an overrepresentation of *S. aureus*, affected skin of children suffering from acute urticaria was also dominated by *Propionibacterium* spp., *Streptococcus pyogenes* and *Bacteroides* spp., while being depleted of *Eubacterium* spp.[42] When taking the direct role of *S. aureus* in the local inflammatory processed of AD into consideration, these studies suggest that there may be a similar role for the skin microbiota in the precipitation of urticaria as well. However, to date, no studies have been conducted in the direct modification of the skin microbiota in the treatment of urticaria. Instead, clinicians have focused on the role of the gut microbiome in urticaria, and how modifying the microbial populations of the gastrointestinal tract may impact this skin disorder. While some studies have shown promising results in oral probiotics use as an adjuvant therapy for urticaria,[85,86] information on the intricacies of the gut-skin access and its influence in dermatological disorders is plentiful and beyond the scope of this review.

4 | CONTACT DERMATITIS

Contact dermatitis is caused by physical contact with an irritant or allergen and thus is not contagious. Irritant contact dermatitis and allergic dermatitis are typically characterized by a very rapid onset for the former and a tendency to spread across the skin for the latter.[87] One very common example of irritant contact dermatitis in infants and small children is diaper rash, which manifests as red, inflamed and sometimes cracked skin on the buttocks and genital area as a result of prolonged contact with a wet and/or soiled diaper. Urine in an unchanged diaper causes softening of the stratum corneum which, combined with friction, compromises the skin barrier, allowing for the penetration of skin irritants.[88,89] Ureases found in faecal matter break down the urea found in urine and increase skin pH levels, which in turn further damages the skin barrier and activates lipases and proteases found in faecal matter, further irritating the skin and causing a painful and inflamed rash.[88] While any child can develop diaper rash if left unchanged for long enough, some children are more vulnerable than others, and this predisposition to developing diaper rash may be due to many underlying causes.

Given the prolonged contact with urine and faecal matter, it is no surprise that the buttock and genital area possesses a unique and rich microbial community, populated in part by bacteria normally found in the intestine.[90] However, some of these gut-derived microbes can also act as irritants, which can precipitate or exacerbate diaper rash. As with other forms of dermatitis, affected skin is often populated by *S. aureus*,[59,60] with a concomitant decrease in the abundance of *Staphylococcus haemolyticus*, particularly when the rash is located to the intertriginous area.[60] However, given the more diverse microbial nature of the diaper area, many different genera and species have been associated with diaper rash and have been found to be specific to particular areas. For example, *Enterococcus* spp. were found to be highly abundant on affected skin in the genital area, while expanded populations of *Bacteroides* spp., *Enterococcus* spp. and *Faecalibacterium* spp. characterized the affected perianal area.[60] On the buttock, the *Enterococcus*, *Erwinia* and *Pseudomonas* genera were found to be enriched in children with diaper rash, while the *Clostridium* and *Actinomyces* genera were depleted, when compared to healthy children.[59] Furthermore, populations of *S. epidermidis* and *S. haemolyticus* were found to recover more rapidly following treatment with emollients, further underscoring the connection between rash formation and local microbial colonization.[59]

In addition to bacteria, the presence of fungal species can also exacerbate diaper dermatitis. The most commonly associated fungal agent is *Candida albicans*, whose overgrowth on the skin is favoured by the increased pH of the diaper area, and has been found to be positively correlated with rash severity.[60,90,91] Other fungi, such as *Aspergillus cibarius*, were only detected on affected skin, while others such as *Kondoa yuccicola*, *Filobasidium* spp., *Vishniacozyma* spp. and *Mycosphaerella tassiana*, were only detected on unaffected skin in the diaper area.[60] Therefore, while the initial rash may be

precipitated by moisture, elevated pH and faecal-derived proteases and lipases, the local microbial community can affect local inflammatory responses and either attenuate or exacerbate the severity of the rash.[92] Despite these insights, studies into prophylactic probiotic therapies are still lacking. While some private market research conducted by companies that produce probiotics indicate that mothers self-report a substantial reduction in diaper rash severity upon probiotic supplementation,[92] placebo-controlled studies into this potential therapeutic alternative are still lacking.

5 | ACNE VULGARIS

Acne vulgaris (AV) is one of the most prevalent skin conditions in the world, occurring when a subcutaneous hair follicle becomes clogged with sebum and keratinous material.[93] Anaerobic bacteria within this clogged follicle take advantage of these favourable conditions and replicate, precipitating local inflammation and the formation of characteristic white pus within those clogged pores.

Historically, it was believed that AV was mainly caused by the hyperproliferation of *Cutibacterium acnes*, formally known as *Propionibacterium acnes*, within the clogged follicle.[94,95] Due to this belief, acne has been commonly treated with topical antibiotics aimed to suppress bacterial overgrowth.[52,94,96,97] While *C. acnes* hyperproliferation undoubtedly contributes to the development of this disorder, new evidence suggests that acne aetiology is far more complex than one species, one condition. Instead, recent evidence has suggested that AV is actually precipitated by the loss of bacterial diversity in general and *C. acnes* phylotype diversity in particular, coupled with dysbiosis of other microbial members of the skin microbiota,[61,94,98,99] factors which can be worsened by antibiotics treatment. In fact, while *C. acnes* is found in the follicles of both healthy subjects and people with AV in similar numbers, the skin of affected individuals is overpopulated by specific, particularly virulent *C. acnes* strains,[94,98–100] which can induce a much stronger inflammatory response than the phylotypes that are associated with healthy skin.[100]

Furthermore, some studies have implicated certain fungal species, such as *Malassezia* spp., in the development of AV.[52,101] While *Malassezia* spp., like *C. acnes*, are a normal commensal found on healthy skin, studies have found a correlation between *Malassezia* spp. load and inflammatory acne.[62,101,102] However, others point out that *Malassezia* folliculitis (MF) is a clinically distinct dermatological condition and is often misdiagnosed as AV,[103–105] which may confound some studies into the role of *Malassezia* in AV. Further complicating things is the fact that many patients can be affected by both conditions, with one study diagnosing almost a quarter of AV patients with MF as well.[103,105] However, whether or not *Malassezia* spp. contribute to AV or only exist as a separate concurrent condition, the fact that MF is often misdiagnosed as AV represents an additional complication with antibiotics use. As fungal species, *Malassezia* spp. are, of course, unaffected by the use of topical or oral antibiotics. Instead, the use of antibiotics reduces the bacterial commensal organisms on the skin that compete with their fungal counterparts for resources, which could potentially aggravate any opportunistic fungal infection. Furthermore, the use of topical antibiotics has led to an increased prevalence of antimicrobial resistant *C. acnes* strains, which in turn can transfer those resistance cassettes to other bacterial species, comporting another important risk to human health.[96,97,106]

Given this new evidence, some researchers suggest moving away from the use of topical antibiotics as a treatment for acne, especially in the absence of a diagnostic test for MF.[105] Even in the absence of a concurrent opportunistic fungal infection, many highlight the need for alternative treatment options capable of combatting the more problematic *C. acnes* strains without further sacrificing skin microbial diversity or inducing antimicrobial resistance.[96,97,99,107] One study found that two human-derived *Lactobacillus reuteri* strains could significantly inhibit the growth of acnegenic bacteria when co-cultered in vitro.[108] Similarly, in an ex-vivo skin model, serum containing *Lactiplantibacillus plantarum* showed promising results in inhibiting growth and counteracting the negative effects of a virulent phylotype of *C. acnes*.[109] In human trials, one randomized placebo-controlled study found that a lotion supplemented with secretory products purified from *Enterococcus faecalis* SL-5 was more efficient in reducing inflamed pustules in patients with mild to moderate acne than an unfortified lotion.[110] Furthermore, *S. epidermidis* has been found to inhibit *C. acnes* overgrowth and suppress *C. acnes*–induced inflammation, implicating the possibility of developing probiotic *S. epidermidis* strains for topical use.[111,112] However, more studies are needed to develop alternative therapeutic strategies for those suffering from AV.

6 | CONGENITAL ICHTHYOSIS

While the reasons for the development of disorders like AD and AV are multifactorial and still remain to be fully elucidated, other, more severe skin conditions have a well-described genetic cause. Congenital ichthyoses are a group of disorders precipitated by different genetic mutations, but which share the clinical manifestation of

hyperkeratosis (i.e. skin thickening), resulting in excessively dry skin, scaling, inflammation and impaired skin barrier function.[113] Due to this improper skin development, children suffering from congenital ichthyosis are also prone to developing other skin-related complications, such as AD and secondary skin infections.[113] Therefore, though microbial dysbiosis may not be the cause of the disorder, the skin microbiota can still have a profound effect on the precipitation of secondary symptoms and quality of life.

For example, Netherton syndrome (NS), a rare yet life-threatening congenital ichthyosis subtype caused by mutations in the *SPINK5* gene, has also been associated with a decreased microbial diversity coupled with *S. aureus* colonization,[63,64,114] a signature they share with both AD and patients suffering from other types of ichthyosis.[57,64] In addition to *S. aureus*, other microbial species have also been associated with the skin microbiota of NS patients, including *S. epidermidis*,[114] *Streptococcus agalactiae*[63] and *Corynebacterium* spp.[57,64] Shotgun metagenomic studies have revealed an increased abundance of genes encoding for the *S. aureus*–derived cysteine proteases staphopain A (ScpA) and staphopain B (SspB), whose abundance was, in turn, positively correlated with disease severity[114] and the development of secondary skin infections.[63] Furthermore, either *S. aureus* or *S. epidermidis* isolated from NS patients was sufficient to induce inflammation and skin barrier dysfunction in mice, indicating a direct role for *Staphylococcus*-derived proteases in the exacerbation of NS clinical symptoms.[114] Given these promising results, further studies into the use of topical probiotics as an adjuvant therapy for NS or other congenital ichthyoses are warranted.

7 | THE COMMENSAL SKIN MICROBIOTA IN WOUND HEALING

As stated above, the primary function of the skin is to act as a barrier between the body and the rest of the world, by both retaining water within and keeping pathogens without. However, even in the absence of underlying conditions, this barrier is not impenetrable, and thus, there are complex mechanisms in place to repair lesions and restore skin barrier integrity as quickly as possible. When a wound occurs, the body reacts to repair the damage in four main steps: (1) haemostasis, whereby platelets plug the aperture to prevent excessive blood loss; (2) inflammation, whereby immune cells flood the wound site to clear it of debris and potential pathogens; (3) proliferation, whereby the keratinocytes in the epidermis migrate and replicate to close the wound while the initial platelet clot is replaced by granulation tissue; and (4) remodelling, during which phase the skin is structurally and physiologically restored, if possible, to its former state.[6,115] These four broad stages are each composed of several intricate processes involving molecular cascades, tightly controlled cellular differentiation and communication between multiple different cell types, including the commensal skin microbiota.

The formation of a wound itself has been shown to be enough to alter the composition of the skin microbiota.[116] For example, burning the skin reduces alpha diversity, reduces the abundance of *C. acnes* and *S. epidermidis* and favours the colonization of thermophile bacteria, such as *Aeribacillus*, *Caldalkalibacillus* and *Nesterenkonia* spp.[116–118] Penetrating wounds have also been found to result in changes in microbial diversity and composition compared to uninjured skin.[119,120] On the surface, these results may seem fairly obvious, as we do not live in a sterile world, and thus microbes that live in the environment would naturally be introduced into a wound when an injury is caused by material in that environment. Similarly, burning the skin changes the environment in which these microorganisms live in terms of temperature and moisture, as well as killing any microbes that come in direct contact with the source of the burn, which would naturally have an impact on microbial colonization in the aftermath. Furthermore, burning also increases skin permeability, thereby increasing the chance of external microbes penetrating to deeper tissues and causing infection.[6] However, these perturbations in the skin microbiome have also been implicated mechanistically in wound healing, making these changes relevant to the prognosis of the injury.

In vitro and preclinical studies have implicated microorganisms in wound healing by multiple different pathways.[121] On the one hand, studies in mice suggest that wound healing is best achieved in the complete absence of skin microbiota, leading to faster healing and little to no scarring.[122,123] However, other studies in mice have found that *S. epidermidis* can recruit T-cells to the skin, enhance barrier immunity and suppress pathogen invasion of wounds, without inducing inflammation in the process.[17,19,124] Furthermore, studies on cultured keratinocytes found that lysates from the popular probiotic strains *Lactobacillus rhamnosus GG* and *Lactobacillus reuteri* were capable of promoting keratinocyte proliferation, migration and the formation of tight barrier junctions, all processes integral to the reestablishment of the skin barrier.[125] Other studies found that these same probiotic strains were able to protect keratinocytes from *S. aureus* infection by both inhibiting its growth and physically displacing it by competitive exclusion.[126,127] Similarly, the fermentation products of *C. acnes* have been found to inhibit the growth of a highly prevalent

strain of methicillin-resistant *S. aureus* (MRSA).[128] In a porcine wound healing model, *Pseudomonas aeruginosa* was shown to aid wound healing by suppressing the virulence factors expressed by another MRSA strain.[129] Furthermore, gels made from naturally probiotic-rich kefir outperformed conventional silver sulphadiazine treatment in promoting wound healing in rats with burn injuries.[130]

In human patients, specific members of the skin microbiome have been found to correlate either positively or negatively with infection. For example, in patients with burn injuries severe enough to necessitate skin grafting, an increased abundance of *Corynebacterium* spp. correlated positively with wound infection but negatively with sepsis, while an abundance of *Staphylococcus* spp. and *Cutibacterium* spp. correlated negatively with infection.[117] In patients with open fractures, *Acinetobacter* spp. were negatively correlated with injury severity and subsequent complications, while *Cutibacterium* spp. were positively correlated.[120] In one randomized clinical trial, topical application of *Lactobacillus plantarum* was found to perform just as well as standard silver sulphadiazine treatment in the prevention of infection and wound healing of burn victims, though without the side effects typically associated with silver sulphadiazine.[131] Taken together, these studies imply that the skin microbiota can aid in wound healing by either direct or indirect interaction with the host and with opportunistic pathogens and thus represent a resource that can be exploited for future therapeutic intervention.

8 | CHRONIC WOUNDS AND THE COMMENSAL MICROBIOTA

In most cases, wounds heal within a few weeks of their formation, especially in response to a penetrating injury. However, wounds can also be caused by underlying causes regarding the host, such as immobility, neuropathy, venous insufficiency, genetic mutations, obesity or a combination of more than one of these, which can lead to wounds that fail to heal. Chronic wounds are clinically defined as wounds which fail to heal after more than 3 months, and these represent a persistent threat to patient health, as the skin barrier is not meant to be compromised for that long. Furthermore, given the commensal microbiota on the skin and their colonization of all open wounds, it can be very difficult to clinically assess whether the microbial presence inside a chronic wound actually qualifies as an infection.[65,132] Clinically, a wound is considered infected only if the bacteria which have colonized it are actively impairing healing and/or causing tissue damage.[133] In the case of acute wounds, infection will cause pain, swelling, localized inflammation and delayed healing, symptoms which can be rapidly assessed and prompt appropriate clinical intervention.[133] However, chronic wounds are, by definition, slow to heal, making it difficult to assess whether the bacterial population in the wound is contributing to this delay. Furthermore, patients with chronic wounds often suffer from peripheral neuropathy and other comorbidities, which can mask the telltale signs of wound infection.[133] All of these factors combined lead to an increased risk of severe infection in these patients, both due to the presence of a compromised skin barrier for an extended period of time and due to the difficulty of diagnosing the infection in its early stages. However, constant prophylactic use of antibiotics is not a viable option for these patients as it comes with serious side effects, such as increasing their chance of developing fungal infections, destruction of the commensal microbiome and causing the emergence of antimicrobial resistant infections. Indeed, the frequent use of antibiotics has contributed to an increase in multidrug resistant microbial populations within chronic wounds,[133–138] which in turn increase the likelihood of amputation and death in these patients.[139] Therefore, understanding the mechanisms behind the formation and persistence of chronic wounds is of the utmost importance in the shaping of the best clinical strategies to combat them.

9 | COMMENSAL MICROBIOTA VERSUS BIOFILMS

Further complicating treatment of chronic wounds is the formation of microbial biofilms. Biofilms are formed by the secretion of extracellular polymers, forming a dense water-logged structure in which microorganisms can live and thrive.[140] Studies have shown that microbial biofilms are not only exceedingly common in chronic wounds, but their presence can also impair proper tight junctions from forming in repaired skin, predisposing the patient to wound recidivism and/or future infection.[141,142] Unfortunately, the presence of biofilms in chronic wounds also lead to additional challenges in their treatment with antibiotics.[140,143–145] First of all, any non-bacterial component of the microbial community will remain completely unaffected, thus allowing a fungal or viral infection to persist uninterrupted. Secondly, even the bacteria who would normally be susceptible to antibiotics treatment find themselves somewhat protected from antimicrobial therapies, thanks to the incomplete penetrance of antibiotics into the biofilm, as well as the presence of "persister cells" within the biofilm microbial

community.[146–148] These bacteria enter into a dormant, non-dividing state, allowing them to avoid death by antibiotics, and thus will quickly repopulate the wound and reform the protective biofilm once the threat has passed.[146,149] Furthermore, since antimicrobial susceptibility is generally tested on free-living bacteria, even the precise diagnosis of the infectious species present in the wound may not be sufficient to predict whether or not antimicrobial treatment will be successful.[146] Indeed, one study found that chronic wound debridement was more efficient at promoting healing than was antibiotic treatment.[150] Given all of these difficulties, either alternative or adjuvant therapy specifically targeting biofilm formation is being developed to combat persistent chronic-wound infection while mitigating the overuse of antibiotics.[151]

Bacteria rarely live in monoclonal communities, and as such have developed several mechanisms which they can use to outcompete one another for habitat and resources. Clinical research has thus aimed to uncover which bacterial species may interfere with pathogen biofilm formation, while not having a detrimental impact on the host.[145,152] For example, in vitro studies have found that two probiotic *Bacillus* strains secrete compounds which can directly inhibit biofilm formation in both methicillin-resistant and methicillin-sensitive *S. aureus* strains isolated from chronic wounds.[153] Other in vitro studies found that several members of the *Lactobacillus* genus, such as *L. rhamnosus* and *L. paracasei*,[154] *L. casei*,[155,156] *L. plantarum*,[157–162] *L. acidophilus*,[155,159,163,164] and *L. fermentum*[165] produce compounds that could inhibit the growth of and biofilm formation in infectious *S. aureus* and/or *Pseudomonas aeruginosa* strains. Furthermore, in vivo experiments found that topical application of *L. plantarum* could prevent wound infection in mice[159] and led to the complete healing of wounds in over 40% of patients with chronic leg ulcers.[166] While further clinical trials are needed, these studies provide evidence for a bacteria-derived alternative to antibiotics in the treatment of infected wounds, especially in those cases where antibiotic treatment is likely to be ineffective.

10 | THE SKIN MICROBIOTA IN DIABETIC FOOT ULCERS

Chronic foot ulcers affect 25% of patients with type-II diabetes (T2D), predisposing them to skin, soft tissue and bone infections and, often, precipitating the need for amputation and significantly decreasing patient life expectancy.[147,167] As such, diabetic foot ulcers (DFUs) represent one of the many comorbidities that can substantially impact the quality of life of T2D patients, necessitating the development of treatment options which can prevent, or at the very least delay, the need for drastic measures such as amputation.

Historically, the diagnosis of DFU infection has relied on traditional culture methods. However, while multiple studies of this nature have been conducted, they are often highly variable and contradictory, especially when comparing results from different parts of the world.[134,137,168–171] Furthermore, it has been shown that traditional culture methods are not always adequate at identifying pathogenic species within DFUs[65,132,172–174] and are quite poor at characterizing the commensal microbiota on the skin of the diabetic foot.[167] Metagenomic sequencing has allowed researchers to move past some of these limitations, allowing them to produce more accurate and diverse microbial profiles of DFUs, in order to identify and distinguish between (1) which microorganisms may influence the formation and healing time of a DFU and (2) which microbes cause an active infection within that DFU.

As is the case with most skin conditions, DFUs are characterized by a reduced microbial diversity compared to both the skin of healthy subjects and to unaffected skin from the same patient.[66,67] The DFU microbiota has been shown to be populated primarily by *Staphylococcus* spp., particularly *S. aureus* and *S. pettenkoferi*, the later having been independently associated with osteomyelitis in patients with chronic DFU.[65,175] While some studies did not find a significant correlation between wound duration and any particular bacterial genus,[66] other studies found an increased abundance of *Prevotella*, *Peptoniphilus*, *Porphyromonas* and *Dialister*, coupled with a decrease in Firmicutes, in severe DFUs compared to mild ones.[67] Furthermore, shotgun metagenomic sequencing has identified certain *S. aureus* strains to be significantly correlated to healing outcomes, while others were not, suggesting that studies which provide a lower taxonomic resolution in metagenomic sequencing could fail to uncover important bacterial associations with wound prognosis ([122]; Table 1). Moreover, one study found that the DFU microbiome forms highly dynamic communities which often shift dominance from one genus to another.[65] Interestingly, DFUs with the most dynamic microbial communities were more likely to heal than those populated with more stable microbial communities, suggesting that the fluidity of the microbial ecosystem, where no one species dominated and overpopulated the wound for long, was more important for a positive prognosis than the presence or absence of any one particular species.[65] Another study found that *Corynebacterium striatum* was able to strongly influence the transcriptome and the subsequent phenotype of *S. aureus*, suppressing

its virulence and causing it to "behave" more like a commensal microbe than an infectious one.[22] Taken together, these studies suggest that the microbial balance between different species is an important, often overlooked factor in DFU studies. Rather than associating one particular species to these chronic wounds or to wound healing, these studies suggest that a particular microbial network composition may actually be the driver of wound healing or progression.

Moreover, other studies have found that the length of time needed for healing, wound necrosis and poor prognosis were all significantly correlated with the presence of specific fungal taxa, many of which were not diagnosable by traditional culture-based methods.[176] Specifically, higher relative abundances of *Ascomycota* in DFUs were correlated with longer wound healing times, and opportunistic fungal pathogens were strongly correlated with wound necrosis.[176] Furthermore, fungal and bacterial species isolated from DFUs were shown to form mixed biofilms and coexist non-competitively in culture, suggesting that bacteria and fungi form a trans-kingdom network that influences healing times and DFU outcome.[176]

Given the poor prognosis of patients with hard-to-heal DFUs, multiple therapeutic options are currently being explored. Some of these alternative therapies include drugs that specifically inhibit biofilm formation,[135] extracellular matrix inhibitors and other anti-inflammatory agents,[177,178] surgery to improve lower limb circulation,[179] silver-based topical treatments,[180] bioengineered skin substitutes,[181] stem cells,[182,183] and maggot debridement therapy,[184–186] all of which have had some success in improving DFU outcome. In addition to these treatment options, some preliminary studies have been conducted to see whether or not bacteriotherapy, in the form of topical probiotics, could be used to aid chronic wound healing. One retrospective study found that topical probiotics could help wound closure in patients with non-infected DFUs which were resistant to standard treatment, though the lack of an appropriate control group makes it difficult to draw any conclusions on the effectiveness of this treatment.[187] However, another placebo-controlled study found that, when used as an adjuvant to surgical debridement, topical application of *Lactiplantibacillus plantarum* ATCC 10241 cultures significantly accelerated wound healing and significantly decreased bacterial counts within complicated DFUs.[188] Another placebo-controlled study found that even oral probiotic supplementation was sufficient to reduce wound size in patients with grade 3 DFUs.[189] Taken together, these preliminary studies paint a promising picture of the use of probiotics to accelerate wound healing and increase the quality of life for patients with DFUs.[190,191]

11 | DECUBITUS ULCERS

Pressure ulcers, also known as decubitus ulcers (DUs), are a frequent complication in people with limited mobility, occurring on the parts of the body that are most compressed and subjected to shearing forces in those that are bed- or wheelchair-bound. Preventative DU care consists of moving potentially affected body parts regularly, to relieve some of the pressure and improve blood flow to the area. However, it seems that some patients are more prone to DUs than others, and this susceptibility to DU development could, in part, be due to the composition of the cutaneous microbiome.[192]

Unlike other chronic wounds, the microbial diversity of the DU microbiome is not consistently decreased. One study found that the microbial diversity of DU skin was unchanged compared to unaffected controls.[68] Other studies found that severe DUs had an increased microbial diversity compared to both superficial DUs and unaffected skin from the same patient,[69,193] while yet another found a decrease in diversity on healed DU skin in patients with recurring DUs compared to patients with non-recurring DUs.[194] However, the composition of the cutaneous microbiome was found to be significantly altered in DU patients. Compared to controls, DUs were characterized by an increased abundance of *S. aureus*, *Eubacterium dolichum*, *Dorea* spp., *Lactobacillus zeae* and *Enterococcus* spp. and a decreased abundance of *Ruminococcus bromii*, *Pseudoclavibacter bifida* and *Actinobaculum* spp.[68] Compared to unaffected skin from the same patient, DUs were characterized by a decrease in *Corynebacterium* spp., *Acinetobacter* spp., *Cutibacterium* spp., *Brevibacterium* spp. and *Staphylococcus* spp., though whether this decrease was due to *S. epidermidis*, *S. aureus* or another *Staphylococcus* species was not addressed.[193] Similarly, a decrease in *Corynebacterium* spp. was found in DUs that had worsened after a 28-day follow-up compared with those that had improved, along with and an increase in *Proteus* spp. and *Morganella* spp.,[69] while another study identified *Ezakiella* spp. as a possible biomarker for DU complications.[193] Yet another study found that, rather than correlating with any one bacterial species, hard-to-heal DUs where characterized by a greater taxonomic dissimilarity with the peri-wound skin, when compared to healing DUs.[195] Taken together, these studies suggest that, similar to DFUs, DU susceptibility and prognosis is likely due to multiple different microbial agents, rather than a single opportunistic pathogen. Furthermore, and perhaps most importantly, one of the aforementioned studies made a direct comparison between 16S next generation sequencing (NGS) and the traditional culture-based microbiological methods that have been used profile chronic wounds and diagnose

infection for decades. This study found that, while both methods adequately identified the high abundance of *Staphylococcus* spp. in DUs, NGS protocols revealed that two anaerobes, namely *Finegoldia* spp. and *Anaerococcus* spp., were almost if not just as abundant as *Staphylococcus* spp. were.[193] On the other hand, despite their abundance, microbiological cultures did not detect these two species at all and significantly underestimated the abundance of several others.[193] This study illustrates how information gathered from microbiological cultures may be severely biased by the optimal growing conditions of each microbial species and thus provide a skewed picture of the problem at hand.

12 | VENOUS LEG ULCERS

Venous leg ulcers (VLUs) are wounds that develop between the knee and the ankle in patients with poor peripheral circulation, causing blood to build up in the veins and capillaries.[196] This build-up creates increased pressure, localized hypoxia and increased inflammation, which can in turn precipitate the formation of an open sore.[196] There exists a great heterogeneity between patients suffering from VLUs in terms of recurrence and healing times, though, as a whole, VLUs are the most difficult to treat and have the worst prognosis compared to both DUs and DFUs.[196,197] However, while the initial cause of wound formation is precipitated by venous insufficiency, they can persist or recur even when the underlying causes are addressed by pharmacological or surgical means, suggesting that other factors, such as microbial composition, may contribute to the persistence of VLUs.[197] For example, one study found that VLUs which persisted after 6 months were characterized by an increased microbial diversity and a particular bacterial signature compared to those that had healed, including an increased abundance of Actinomycetales and a decrease of Pseudomondaceae.[198] Another study found that *S. epidermidis* strains isolated from VLUs often possessed antimicrobial resistance and virulence cassettes, as well as biofilm-forming capabilities, not found in commensal *S. epidermidis* strains found on healthy skin.[199] Though metagenomic investigations into the VLU microbiome are still in their infancy, these first studies suggest that, once VLUs are formed, the microbiota of the skin can influence their healing times and recurrence. However, further studies are needed, not only to fully comprehend the structure and dynamics of the VLU microbiome but also to understand when and how particularly virulent/antimicrobial resistant strains are acquired by patients suffering from VLUs.

13 | EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) is a group of rare but debilitating skin diseases, characterized by very fragile skin that blisters and tears easily, thickened or absent nails and toenails and often blisters inside the mouth and/or gastrointestinal tract, causing chronic, suppurating wounds. EB is usually caused by mutations in genes encoding for key skin structural proteins, such as keratins 5 and 14 (as in the case of EB simplex) or in the *COL7A1* gene (as in the case of dystrophic EB).[200,201]

However, despite the known genetic origin, EB blisters and wounds have also been found to be associated with shifts in the skin microbiota. When comparing untreated wounds, perilesional skin and normal-appearing skin from EB patients compared to healthy controls, studies have shown that bacterial diversity is inversely correlated with skin integrity, with wounds being the least diversely populated and skin from healthy volunteers the most.[70,202,203] EB wounds were found to be populated by *S. aureus*, *Pseudomonas* spp. and *Candida* spp., suggesting that microbial colonization and infection may participate in the delayed wound-healing from which EB patients suffer.[202–204] Indeed, in vitro studies have found that *S. aureus* infects EB-derived keratinocytes more readily than keratinocytes derived from healthy donors, provoking the proliferation of CD4+ and CD8+ peripheral memory T-cells, which in turn secrete IFN-γ.[203] Interestingly, CD8+ cytotoxic T lymphocytes are capable of identifying and destroying these infected cells in vitro, but this is clearance of infected cells is not reliably performed in EB patients, suggesting other immune-suppressive mechanisms at play which exacerbate EB symptoms.[203] Furthermore, skin lesions from people suffering from squamous cell carcinoma (SCC), a skin cancer to which EB patients are highly susceptible, have also been found to be strongly associated with *S. aureus* colonization.[205–207] Moreover, studies have shown that *S. aureus* is capable of inducing SCC cell proliferation in vitro,[206] suggesting a causative role for this pathobiont in the development of SCC. Given the likely role of bacterial pathobionts in the exacerbation of EB symptoms, it would be interesting to see whether bacteriotherapy in the form of topical and/or oral probiotics could help to improve the quality of life of these patients.

14 | CONCLUDING REMARKS

Though the gut microbiome remains the most diverse and the most studied of the microbiological ecosystems that exist in the human body, there is an ever-growing

appreciation for those than exist in other human ecological niches as well. The skin microbial community, while not as diverse as that of the gastrointestinal tract, has still co-evolved with humans and can still influence human health in many ways outside an infectious context. The cutaneous microbiota contribute to skin maturation, innate immunity and skin barrier integrity.[1,13,14,133,208] Given their symbiotic role, it is perhaps unsurprising that, in a pathological context, the community structure of the skin microbiota has been found to be altered, whether it be in relatively mild dermatological conditions, such as urticaria, or more severe ones, such as congenital ichthyoses or chronic wounds (Table 1). Not only have they been found to be altered by underlying skin conditions, but many bacterial species, such as *S. aureus*, have been found to directly exacerbate many dermatological disorders. These studies are suggestive of the existence of a negative feedback loop, whereby an underlying condition provokes changes to the commensal microbial community, favouring the growth of opportunistic pathogens, which in turn further aggravate patient symptoms. Conversely, other microorganisms, in turn, can enter into direct competition with these opportunistic pathogens, by either reducing their numbers or causing them to change their behaviour, which in turn can ameliorate the symptoms associated with skin disorders.

With increasing appreciation for the crucial role of the commensal microbiota in human health, as well as the complexity and rapid evolution of microbial communities causing an increase in multidrug resistance, clinical practice has largely phased out the indiscriminate use of antibiotics, especially topically.[133,208] Instead, a new chapter of clinical research has taken on the challenge of discovering how to selectively target opportunistic pathogens without harming the commensal microbiota. Strategies to achieve this goal can include the use of prebiotics, which favour the growth of those commensals which in turn inhibit the overgrowth of pathogenic phylotypes,[76,81] probiotics, which involves introducing live bacteria to affected skin in order to aid healing,[79,80,188] or postbiotics, in the form of cell supernatants or heat-killed bacteria, which can act on targeted pathogens without the need for live bacteria to colonize the skin.[110,208]

In an ideal future, any skin condition, from acne to diabetic foot ulcers, would undergo rigorous, strain-level metagenomic and metabolomic profiling for thorough diagnosis. The presence of fungi, antimicrobial resistance cassettes, virulence factors, extracellular compounds and trans-kingdom networks would all be assessed in order to determine which microbes were causing the most problems, which microbes should be targeted, which should be protected and what strategy would best attack the most problematic microbial species. Unfortunately, at this point in time, such in-depth analyses are both costly and time-consuming and thus are usually impractical in a clinical setting. When a patient is diagnosed with an infection, for instance, they cannot wait for days or weeks for tests to be conducted without seriously endangering their health and even their lives.[174] Although treatment with the wrong antibiotic can potentially make the infection worse, in many cases clinicians have little choice but to prescribe a treatment and monitor the outcome closely, rather than conduct the extensive testing required to predetermine the presence of antimicrobial resistance cassettes, or fungal or viral coinfections. Furthermore, while microbiological technologies are consistently being developed, substantially bringing down the cost and time requirements for such tests, many alternative therapies are still insufficiently validated, or even experimental. Due to these clinical challenges, alternative therapeutic strategies need to be further developed alongside the perfection of diagnostic technologies. Given their highly dynamic nature and their ability to evolve rapidly in response to adverse conditions, perhaps one of the best ways to combat harmful microorganisms is with the use of equally dynamic and rapidly evolving beneficial ones. Perhaps, the answer to the question of how to combat multidrug resistance is actually more bacteria or at least different ones.

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