

The Skin Microbiome in Atopic Dermatitis and Its Relationship to Emollients

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Abstract

Background: Human-associated bacterial communities on the skin, skin microbiome, likely play a central role in development of immunity and protection from pathogens. In atopic patients, the skin bacterial diversity is smaller than in healthy subjects.

Objective: To review treatment strategies for atopic dermatitis in Canada, taking the skin microbiome concept into account.

Methods: An expert panel of 8 Canadian dermatologists explored the role of skin microbiome in clinical dermatology, specifically looking at atopic dermatitis.

Results: The panel reached consensus on the following: (1) In atopic patients, the skin microbiome of lesional atopic skin is different from nonlesional skin in adjacent areas. (2) Worsening atopic dermatitis and smaller bacterial diversity are strongly associated. (3) Application of emollients containing antioxidant and antibacterial components may increase microbiome diversity in atopic skin.

Conclusion: The skin microbiome may be the next frontier in preventive health and may impact the approach to atopic dermatitis treatment.

Keywords

skin microbiome, atopic dermatitis, dermatology, dermatitis

Introduction

The human microbiome is the habitat of microorganisms coexisting at the surface of and inside humans. In adult individuals, almost 1 trillion bacteria (1.5 kg, >500 species) are present, accounting for 10 times the person's own cells.¹ The Human Microbiome Project, established in 2007 by the National Institutes of Health, USA, aimed to identify and characterize the microbiome and establish a database. The project further aims to explore a link between diseases and evolution of the microbiome and develop new technology and analytical tools for chronic diseases.¹ Studies on the microbiome of the gut have been the first focus of attention, followed by the skin microbiome, which is a relatively new area but increasingly exciting and of importance to dermatologists.² The microbiome is also called our second genome, where complex communities of bacteria, fungi, and viruses thrive. The composition depends on skin characteristics, such as sebaceous gland concentration, moisture, temperature, host genetics, and exogenous environmental factors. Commensal organisms comprising the skin microbiome may play a much larger role in immune modulation and epithelial health than previously expected, impacting treatment of inflammatory skin diseases. There are indications that some commonly found skin microbes can help keep away pathogens.

Our objective was to review possible treatment strategies for atopic dermatitis (AD) in Canada, taking this new concept of the skin microbiome into account.

Literature Search

A literature review was conducted using the Medline, Embase, and Cochrane databases. The search focused on recent developments in skin microbiome and inflammatory skin diseases, specifically AD. The search dates were June

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15-16, 2014. Exclusion criteria were published literature prior to 2000 and a publication language other than English, German, or French. The literature search findings were evaluated with the modified Scottish Intercollegiate Guidelines Network (SIGN): A: randomized, double-blind clinical trial of high quality (eg, sample size calculation, flow chart of patient inclusion, intention-to-treat analysis, sufficient sample size); B: randomized clinical trial of lesser quality (eg, only single-blind, limited sample size: at least 15 patients per study arm); and C: comparative trial with severe methodological limitations (eg, not blinded, very small sample size, no randomization).

Expert Panel

An expert panel of 8 Canadian dermatologists and a clinical adviser explored the role of the skin microbiome in Canadian clinical dermatology, specifically looking at inflammatory skin disorders, such as atopic dermatitis. The panel received the results of the literature searches and key articles prior to a consensus meeting. The panel convened on September 27, 2014, in Toronto, Canada, for a 1-day meeting to deliberate on the skin microbiome; participants voted blindly on statements that resulted from the literature searches that were carried out prior to the meeting.

Messages Defined by the Panel

1. The human microbiome is the habitat of microorganisms that coexist at the surface and inside the body.
2. In AD patients, the skin microbiome of lesional atopic skin is different from adjacent nonlesional skin.
3. Worsening AD and dysbiosis of the skin (microbial imbalance) are strongly associated.
4. Application of certain emollients can increase microbiome diversity in atopic skin, for instance, in using a moisturizer containing biomass lysate of *Vitreoscilla filiformis*.

Skin Microbiome

The skin may be the newest frontier in preventive health, although it is still early days to make bold claims.³ For the study of the skin microbiome, a sampling protocol was established using metagenomics, a culture-free method to assess skin microbiota.^{1,2} For this purpose during the first step, DNA is purified directly from a skin swab or biopsy specimen. This DNA contains a mixture of genomic DNA from the skin and microbial cells. Polymerase chain reaction (PCR) with primers that anneal to the conserved region of the 16S ribosomal RNA (rRNA) gene is used to amplify bacterial DNA. These PCR amplicons are then sequenced. Finally, sequences can be classified taxonomically to give species identities within the

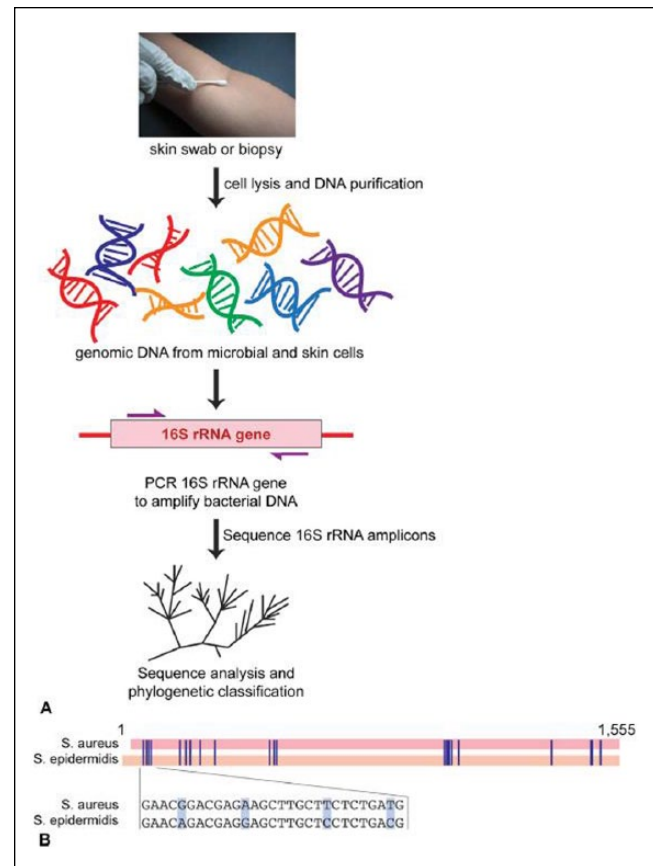


Figure 1. Sampling protocol.³

(A) Blue lines show nucleotides that differ between 2 species. Inset shows example of specific sequence differences. In analysing bacterial microbiomes, this method most often involves amplifying the prokaryotic small subunit ribosomal RNA (16S rRNA) gene by polymerase chain reaction (PCR) directly from skin samples. (B) The 16S rRNA gene exists in all bacteria and archaea but not in eukaryotes. It contains both conserved regions that serve as binding sites PCR primers and variable regions for taxonomic classification after high-throughput sequencing of the PCR products. Phylogenetic tree of example metagenome downloaded from MG-RAST. Reprinted with permission from Chen & Tsao.³

microbiome, and sequences can be counted to give relative abundances of each species. During the second step, alignment of 16S rRNA gene sequences between *Staphylococcus aureus* and *Staphylococcus epidermidis* are downloaded from the National Center for Biotechnology Information and aligned via Geneious (<http://www.geneious.com/>) (Figure 1).¹⁻³ Emerging high-throughput technologies that characterize microbial communities have enabled efficient data processing.

The microbiome composition on normal-appearing human skin consist of at least 19 phyla, of which Actinobacteria, Firmicutes, Proteobacteria, and Bacteroides are the predominant bacterial phyla in the human body, regardless of body site.^{4,5} Within these phyla, the 3 most abundant genera are: *Propionibacterium*, *Corynebacterium*, and *Staphylococcus*. An example of the phylogenetic tree is shown in Figure 2.

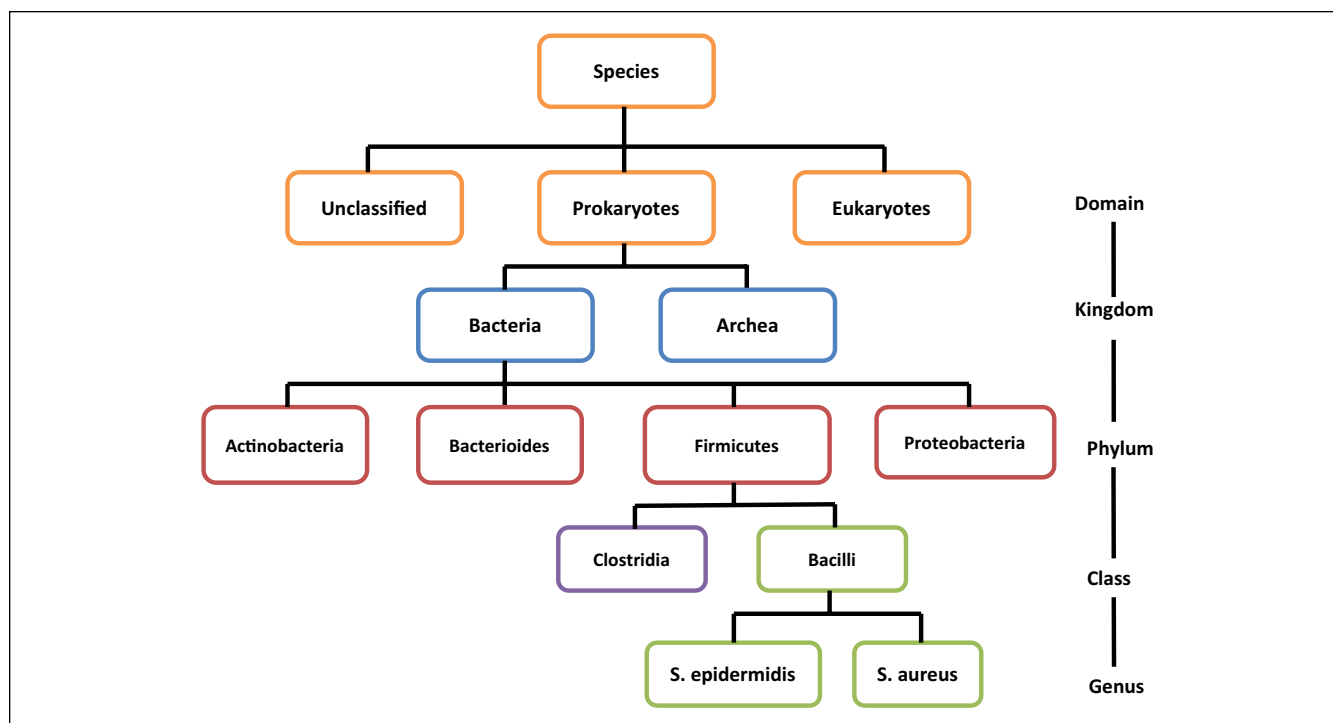


Figure 2. Phylogenetic tree.³

The microbial composition differs among habitats. *Propionibacterium* species dominate sebaceous areas, and *Staphylococcus* and *Corynebacterium* species dominate moist areas.⁴ Human-associated bacterial communities likely play a central role in host nutrition, development of immunity, and protection from diverse pathogens.⁶ A distinction can be made between commensal species (in contact with the skin and mucous membranes of a host without leading to disease), pathogenic species (able to cause a disease in a subject with a healthy defence system), and opportunistic species (may become pathogenic when the host's defences are weakened).⁶ Costello et al⁶ proposed dynamics of microbial interactions at the skin surface.⁶ Microorganisms form complex interaction networks, with beneficial situations including mutualistic and commensal relationships (Figure 3). By contrast, detrimental relationships describe correlations in which at least 1 interaction partner is harmed.^{3,6} The host immune system acts to manage microbial communities and orchestrate beneficial microbe-host relationships.^{3,6} There are indications that some commonly found skin microbes can help keep away pathogens, such as *S. epidermidis*, which has been shown to produce compounds that inhibit the related but pathogenic *S. aureus*.⁶ The ecology of the skin surface is influenced by many variables, including lifestyle, age, emotion, community, genetics, diet, hygiene products, and drugs, such as antibiotics.^{3,7} Under unfavorable conditions, an altered community of microbes can arise on the skin, leading to conditions of dysbiosis.^{7,8} Both interactions between microbes and between a microbe and the host can promote disease. Dysfunction of the capacity to

reestablish a normal microbial community may perpetuate chronic disease.^{7,8}

The Role of the Skin Microbiome in Atopic Dermatitis

Atopic dermatitis is a chronic, multifactorial, inflammatory skin disease (Figure 4).⁹⁻¹¹ Its prevalence has more than doubled in industrialized countries with no clear cause¹⁰ and at high cost.¹¹ Atopic dermatitis signs include dryness, lichenification, scaling, and occasionally nummular lesions.⁹⁻¹¹ It has been hypothesized that alteration in surface microbial composition in AD is due to dysfunction of the skin barrier. This disrupted barrier may be due to mutations in the gene that encodes for filaggrin, a protein involved in cornification.¹² Greater susceptibility to AD may also be attributable to decreased expression of antimicrobial proteins in the skin.¹² Increased levels of irritants and allergens trigger cytokine release, leading to dermal inflammation and expression of AD.^{12,13} It has been shown that water content of the stratum corneum and skin surface lipids were reduced in patients with atopic dermatitis compared with healthy subjects. Findings that skin lipids were reduced in AD gave awareness to the role of lipids in maintaining skin hydration.¹⁴ In AD-affected skin, there is an alteration in^{14,15}:

- the number of Langerhans' cells,
- blood flow and thermoregulation (blood capillaries and eccrine sweat glands),

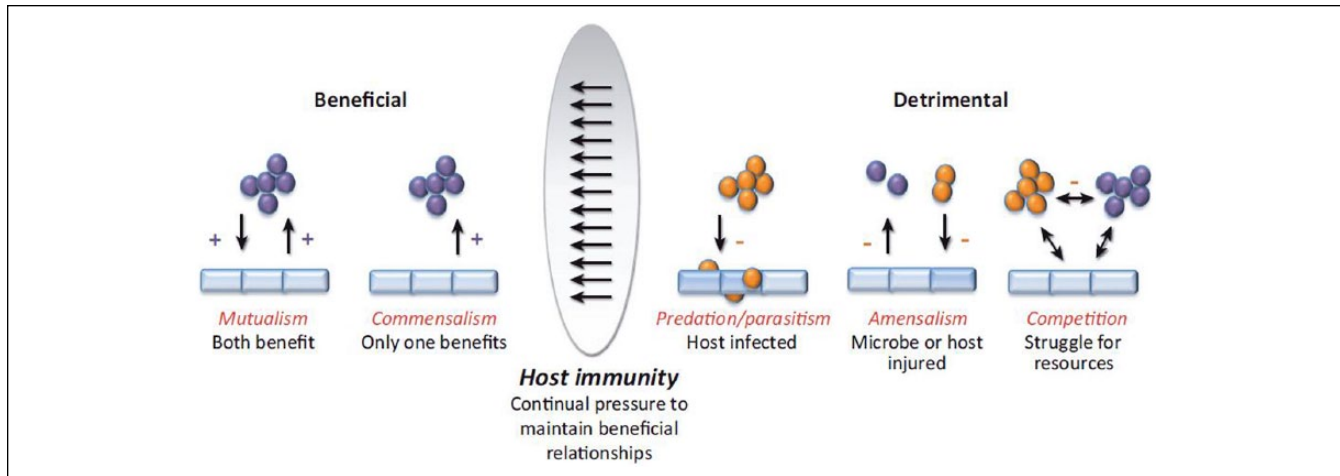


Figure 3. Dynamics of microbial interactions at the skin surface.⁶

- ability to absorb and clear substances (eg, medicated creams).

Furthermore, several functions may be altered, such as heightened inflammatory response and increased susceptibility to pathogens.¹⁴⁻¹⁸ Dysfunction of the skin barrier in AD may be seen in a different light taking into account the fact that in AD-affected skin, the microbiome may be decreased.¹⁹ High-throughput DNA sequencing of the bacterial 16S rRNA gene has revealed a vastly greater bacterial diversity on healthy human skin than demonstrated by culture-based methods.^{4,6,19} Atopic dermatitis preferentially involves the antecubital and popliteal regions, sites that harbor similar groups of organisms and share distinct compositions of microbial communities.^{4,6} These findings suggest that microbial communities might underlie or contribute to observed predilections of AD for stereotypical sites.^{4,6} Together with already established notions on the expression of AD, such as mutations in filaggrin,¹⁶ the frequent cutaneous infections with *S aureus* cultured from lesional and non-lesional skin may be contributing to flare-ups.^{4,6,12,13} It is proposed that reduced antimicrobial peptide expression in the skin of AD patients may contribute to *S aureus* susceptibility.¹⁷ While individual microbes causative of common AD skin infections have been studied, it is increasingly clear that individual microbes function within larger bacterial communities.¹⁸ Kong and Segre² suggested that when the skin barrier is impaired, homeostasis between the host and microbe is shifted. In a skin microbiome study of AD disease states (baseline disease state, disease flare, and post-treatment for disease flare) conducted in 23 children aged 2 to 15 years ($n = 12$ moderate-to-severe AD, $n = 11$ healthy controls), the role of bacterial communities in AD was investigated.² Skin samples were obtained from 36 AD patient visits and 24 control visits for a total of 151 924 near full-length 16S ribosomal RNA (rRNA) genes that were assessed.² The study showed a relationship between

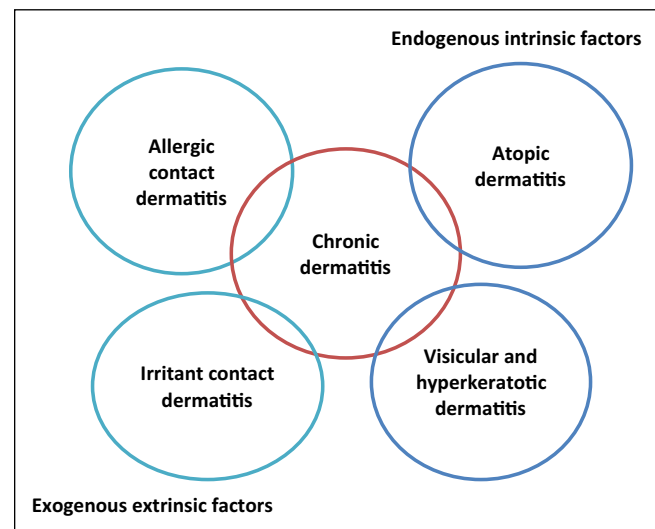


Figure 4. Atopic dermatitis is multifactorial.

Adapted from Halioua et al. *Ann Dermatol Venerol*. 2010;137(4):315-327.¹²

objective SCORAD and Shannon diversity (biological diversity index measuring 6 factors), which was significantly inversely correlated, indicating that severe AD was associated with lower skin bacterial diversity.² The AD patients using no treatments during flares exhibited markedly reduced Shannon diversity in the antecubital creases as compared with the intermittent treatment group ($P < .025$).² Seite et al²⁰ suggested that microbial diversity richness is a marker of a nonlesional (or non-flare-up) clinical condition in AD (Figures 5a and 5b). A further study evaluated differences between healthy and atopic skin microbiome and compared the number of different bacterial genera obtained on the arms of healthy patients to those of atopic patients.²⁰ On the arm of healthy subjects ($N = 92$), an average of 250 different genera were detected versus 150 on nonlesional areas ($N = 49$) on the arms of AD ($N = 10$) patients. This

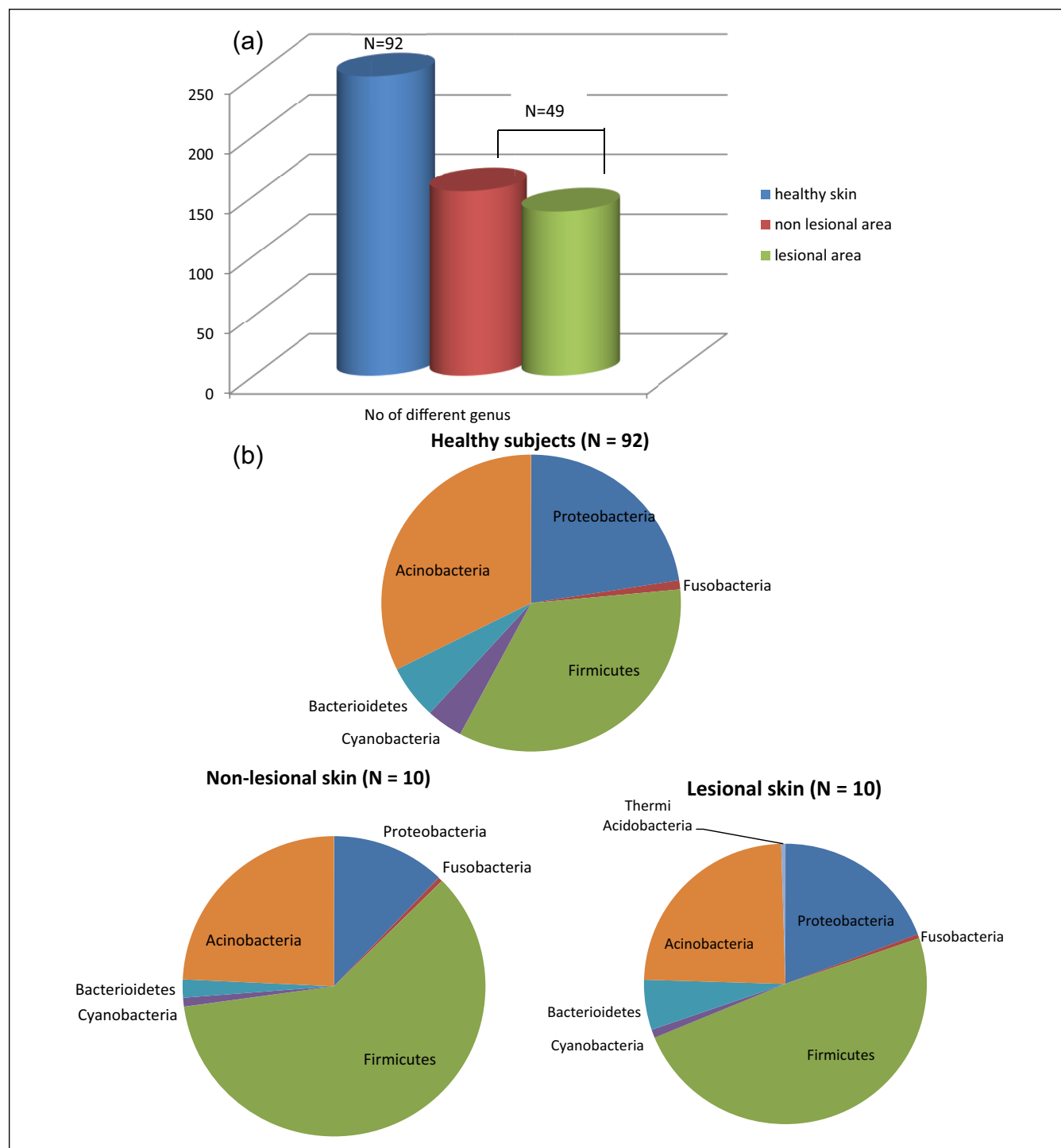


Figure 5. (a) Microbial diversity in atopic dermatitis (AD)-affected skin is lower.

Adapted from Kong and Segre. *Genome Res.* 2012;22:850-859.²

(b-1) Healthy subjects (n = 92). (b-2) Nonlesional skin in AD subjects (N = 10). (b-3) Lesional skin in AD subjects (N = 10).

In AD affected skin there is overrepresentation of Firmicutes (including *Staphylococci*) and underrepresentation of Actinobacteria, Proteobacteria, and Cyanobacteria (in nonlesional and even more in lesional areas).

number was even lower on lesional areas, reaching as low as 137 different genus (Figure 5).¹⁹

Specific AD disease states are characterized by concurrent and inversely related shifts in microbial diversity and

proportion of *Staphylococcus*. Since untreated flares have reduced diversity and high *Staphylococcus* proportions as compared with baseline, postflares, and notably, intermittent-treatment flares, the authors proposed that increases in

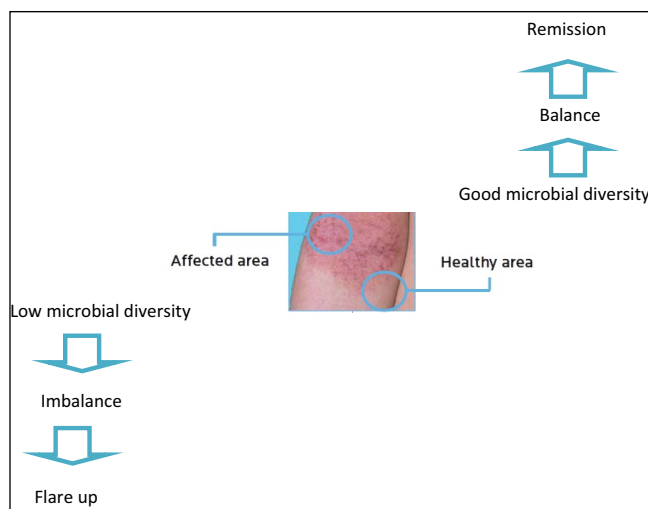


Figure 6. Greater bacteria diversity can protect against flares.⁴

the proportion of *Staphylococcus* and reductions in microbial diversity precede worsening of AD disease severity as observed in no-treatment flares.² The decrease in microbial diversity on the skin could precede atopy flares. Therefore, increasing bacterial diversity could help prevent flares (Figure 6).^{4,19-26} The authors concluded that the richness of the skin microbiome is a marker of healthy skin and that in AD, bacterial diversity on the skin is smaller than in healthy subjects.² Dysbiosis on the skin is a marker of atopy and is linked with state or severity of AD.²

Dysbiosis on the Skin in AD Impact Treatment Approaches in the Canadian Setting

Currently, guidelines for AD treatment have been implemented in Canada and are widely used in clinical practice.²⁷ The guidelines include history taking, physical examination, assessment of severity (mild, moderate, or severe), and diagnostic procedures (if clinically indicated and available, exclusion of bacterial and/or fungal infection and identification of allergens using patch testing).²⁷ Prevention, avoidance strategies, and education are key in the approach to treatment, as are emollient and moisturizer therapy.²⁷ These products may contain lipids, cholesterol, and fatty acids, which aim to mimic natural lipids.²⁷⁻²⁹ They may reduce the need for anti-inflammatory medications²⁹ and are often used in combination with topical steroids and other treatments if monotherapy with these products is unsuccessful.²⁷⁻²⁹ Topical steroids are the mainstay of treatment for mild to moderate inflammatory dermatoses and are also used in severe conditions to reduce the dose of oral treatments and the need for ultraviolet light therapy.²⁷⁻²⁹ However, they should be used for as short a period as possible, followed by tapering and discontinuation. Phototherapy may also be

considered, and for severe cases, topical corticosteroids may be combined with methotrexate or cyclosporine.^{27,28}

Moisturizers Help to Restore the Skin Microbiome

The principle of increasing diversity of the microbiome and thus restoring microbial balance has already been applied in other areas.²⁵ The effectiveness of fecal and earwax transplant suggests that the microbiome plays a clinically meaningful role in the maintenance of health.²⁴⁻²⁶

In AD-affected skin, there is overrepresentation in nonlesional and even more in lesional areas of Firmicutes, including *Staphylococci*, and underrepresentation of Actinobacteria, Proteobacteria, and Cyanobacteria.² Restoring microbial balance on the skin may be clinically meaningful in inflammatory skin diseases, such as atopic dermatitis.²²⁻²⁶ Moisturizers and emollients are considered to be the cornerstone of AD treatment.²⁷⁻²⁹ They help restore and preserve skin barrier integrity, combat xerosis, and enhance treatment efficacy and are reported to have a corticosteroid-sparing effect.²⁸ If one takes into account the dysbiosis on the skin in atopic patients, the focus of AD treatment may shift to a moisturizer that also contains the ingredients to help restore the skin microbiome and thus skin barrier function (Figure 7).²²⁻²⁶ *Vitreoscilla filiformis* biomass (VFB) has been widely used in skin care emollients and was shown to modulate the major inducible free-radical scavenger mitochondrial superoxide dismutase in skin cells.²² In reconstructed epidermis, the biomass stimulated mRNA expression and antimicrobial peptides.²² A moisturizer was developed that contains a biomass lysate of *V. filiformis* cultivated on a thermal spring water medium.³⁰ A predictive computer model, which was used to analyze transducing events within the reconstructed skin epidermal cells, suggested that the protective activity of the moisturizer may involve the Toll-like receptor 2/protein kinase C, zeta transduction pathway.²² Protein kinase C, zeta inhibition was effectively shown to abolish VFB-induced gene stimulation.²² The moisturizer may offer benefits in atopic patients, in which antioxidant, antibacterial, and appropriate immune activities are important therapeutic strategies (Table 1).^{19,21-24,30} More clinical studies are needed to confirm possible benefits.

The skin microbiome may be “the newest frontier” in preventive health and may impact on the approach to AD treatment.^{23,30} However, we are currently at the “hypothesis” stage in this area of research, and further robust studies are needed to confirm the value for inflammatory skin disease treatment.

Conclusions

In AD patients, the skin microbiome of lesional atopic skin is different from adjacent nonlesional skin. Worsening AD and

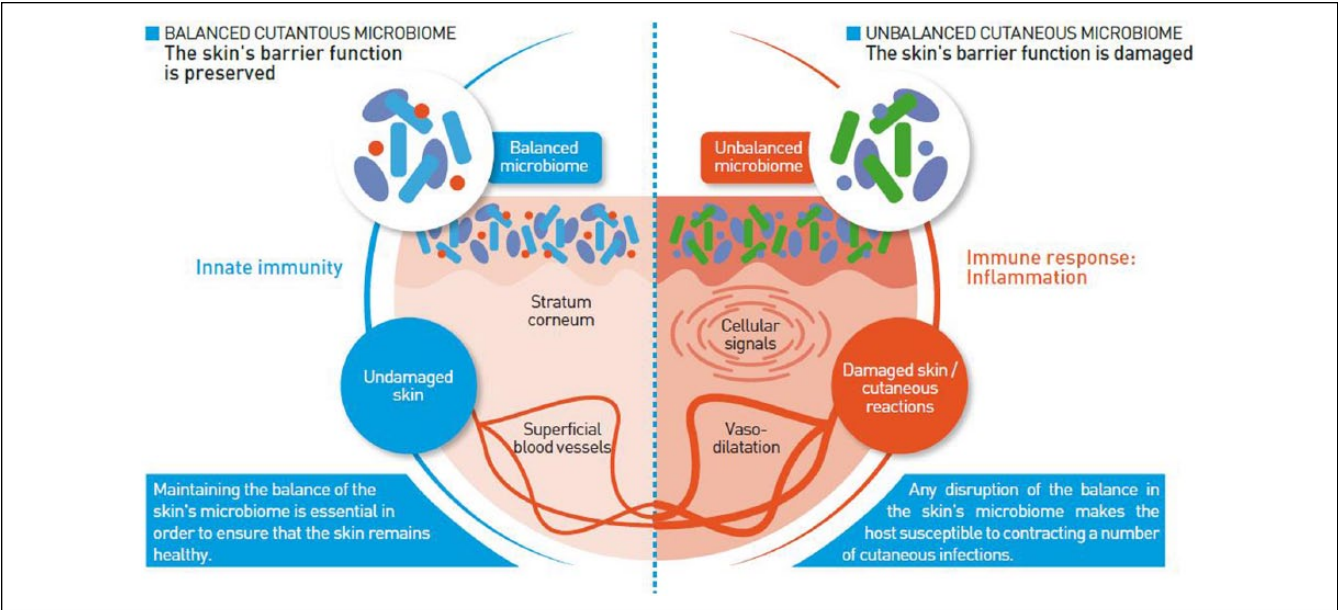


Figure 7. Restoring skin microbiome and skin barrier function.

Table 1. Skin Microbiome and Skin Care.

How Skin Microbiota Affect Human Skin Cells	How Human Skin Cells Affect Skin Microbiota	How Skin Care Routines/Products May Affect Skin Microbiota
Proteases may affect corneocyte desquamation.	Provide nutrients.	Surfactants in skin cleansers may interact with microbial membranes.
Lipases break down skin surface lipids with irritant byproducts.	Control growth through innate immunity (antimicrobial peptides, lipids) and by controlling the skin surface pH.	Moisturizers affect local microenvironments, potentially shifting microbial compositions.
May provide antigens to the skin-residing immune cells.	Control virulence by creating a physical barrier to penetration.	Barrier creams may fortify the skin surface against microbial penetration.
Help with defences against “common enemies.”	Control population composition by creating local microenvironments (moist, dry, sebaceous).	Possible preservative effects
Quorum-sensing molecules may affect skin cells?		Product pH effects?

Adapted from Stamatas and Capone. New findings and the impact of infant skin microbiota on product development. *Cosmetics and Toiletries*. 2014;129(2):54.²³

dysbiosis on the skin are strongly associated. Application of certain emollients can increase microbiome diversity in atopic skin and may offer benefits for patients with inflammatory skin diseases beyond moisturizing.

Declaration of Conflicting Interests

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for Allergan, Galderma, Kythera, LaRoche-Posay, Merz, Procter & Gamble, and Valeant. Dr Skotnicki is a consultant/speaker for Procter & Gamble, Valeant, Roche Pharmaceuticals, and Johnson and Johnson. Dr Weinstein is a consultant/speaker for La Roche-Posay and has received support for a clinical teaching project for patients with eczema. Dr Zip is a consultant/speaker for La Roche-Posay, Valeant, and Galderma.

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