# Journal Pre-proof

The emerging utility of the cutaneous microbiome in the treatment of acne and atopic dermatitis

Taylor E. Woo, MSc, Christopher D. Sibley, MD, PhD, FRCPC

PII: S0190-9622(19)32686-6

DOI: https://doi.org/10.1016/j.jaad.2019.08.078

Reference: YMJD 13802

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 14 May 2019

Revised Date: 21 August 2019

Accepted Date: 28 August 2019

Please cite this article as: Woo TE, Sibley CD, The emerging utility of the cutaneous microbiome in the treatment of acne and atopic dermatitis, *Journal of the American Academy of Dermatology* (2019), doi: https://doi.org/10.1016/j.jaad.2019.08.078.

**Title: The emerging utility of the cutaneous microbiome in the treatment of acne and atopic dermatitis**

**Authors:** Taylor E. Woo MSc [1] and Christopher D. Sibley MD, PhD, FRCPC[2]

1. Cumming School of Medicine, University of Calgary, AB, CAN
2. South Ottawa Medical Centre, Ottawa, ON, CAN

**Corresponding Author:**

Mr. Taylor Woo

University of Calgary

E: tewoo@ucalgary.ca

**Funding Sources:** None

**Conflict of Interest:** None disclosed

**Word Count:**
**Abstract (168), Capsule Summary (37), Text (2254), Figures (1), Tables (2), References (52)**

**Keywords: microbiome, biotherapy, acne vulgaris, atopic dermatitis**

**Abstract**

The cutaneous microbiome has potential for therapeutic intervention in inflammatory-driven skin disease. Research into atopic dermatitis and acne vulgaris has highlighted the importance of the skin microbiota in disease pathogenesis, prognostication and targets for therapeutic intervention. Current management of these conditions aims to control the inflammatory response thought to be associated with specific pathogens using both topical and systemic antimicrobials. However, commensal microbiota found naturally on the skin have been shown to play an important role in the resolution of disease flares. While often efficacious, the mainstay treatments are not without side effects and raise concerns regarding the development of antimicrobial resistance. Augmentation of microbial communities with targeted biotherapy could revolutionize the way inflammatory conditions of the skin are treated. Herein, we review evidence for the role of the cutaneous microbiome in atopic dermatitis and acne vulgaris and suggest that these conditions highlight the potential for microbiome-directed therapeutics.

**Capsule Summary**

- Cutaneous microorganisms are implicated in the pathophysiology of both acne and atopic dermatitis.
- Interventions targeting the cutaneous microbiome are a promising area of therapeutics in acne vulgaris and atopic dermatitis.

## Introduction

Rapid advances in nucleic acid sequencing technologies have enabled the detection of a large number of eukaryotes, bacteria, viruses and other microorganisms, which collectively compose the human microbiome. Skin is the largest human organ (~1.8 $m^2$) and serves as a physical and immunological barrier to the environment. This interface, with plentiful folds, invaginations and specialized niches, is a harsh environment for microbes with its cool temperature, an acidic pH and a milieu of host defense molecules (proteases, lysozyme and antimicrobial peptides)[1,2]. Despite these conditions, human mucosal surfaces and skin harbor more commensal microbes than the number of eukaryotic cells in the body[3]. To maintain human health an interplay between the host's innate immune system and the microbial communities must transpire[2,4]. A wide breadth of microbial species is organized into complex microbial communities on the skin. The density of these communities is an estimated one million bacteria per centimeter squared[5] and their demographics vary depending on the body site involved[6]. Areas such as hair follicles, sebaceous and glandular structures represent unique environmental niches for the colonization of microorganisms. Nineteen phyla represent the core skin microbiome[6] including Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%) and Bacteroidetes (6.3). At the genus level, *Corynebacterium*, *Propionibacterium* and *Staphylococcus* are most commonly identified.

Both commensal and pathogenic microorganisms have been suggested to play an important role in the pathogenesis of inflammatory skin conditions[7]. Recent evidence suggests that commensal microbial metabolites contribute to local homeostasis by influencing host cell gene expression[8]. Disruption of the balance between the microbiome

and the host can lead to a pro-inflammatory environment and the development of clinical disease[9]. The transition to a pro-inflammatory state in the skin is often associated with changes in the microbial richness (total number of bacterial species) and evenness (the relative proportion of microorganisms in a community)[10]. Disruption of the normal microbiome homeostasis manifests in atopic dermatitis and acne vulgaris as decreased richness, a decrease in the total bacterial load, or altered evenness [11,12]. As such, targeted interventions focused on restoring the microbial community to a stable anti-inflammatory state are of great interest and represent a shift in the way we manage and treat inflammatory skin disease (Figure 1).

**Atopic dermatitis is a disease of microbial dysbiosis**

Atopic dermatitis is a chronic condition contributing to significant morbidity in approximately 7% of the general population[13]. It's pathogenesis is multifactorial, with important genetic and environmental factors. Atopic dermatitis is highly heritable[14] and most often secondary to loss-of-function mutations in the filaggrin gene[15]. A notable modifiable environmental risk factor, which has been implicated in the exacerbation of disease is the composition and dynamics of commensal skin microbiota that can be associated with more severe clinical presentations[11]. Specifically, an inverse relationship between baseline Shannon diversity (a measurement which takes into account both species richness and evenness of a sample) and the severity of atopic dermatitis has been well documented. For instance, individuals who have lower measures of diversity have more severe disease as compared to healthy controls, which coincides with an overgrowth of *Staphylococcus aureus*[11]. This corresponds with a decrease in the relative abundance of *Streptococcus*, *Corynebacterium* and *Propionibacterium*. Moreover,

resolution of acute flare correlates with the reestablishment of a commensal community with a rich and even structure.

*S. aureus* has a diverse range of virulence factors that contribute to the pathogenesis of atopic dermatitis[16–18]. Virulence factors include superantigen production, which promotes inflammatory pathways through the activation of interleukin-mediated T cell responses[19,20]. While the role of *S. aureus* in invoking inflammatory responses is clear, understanding how *S. aureus* interacts with the resident commensal microbiota is of great clinical interest. Milder forms of atopic dermatitis are seen in patients when *S. aureus* is not the predominant organism[21]. In these cases, patients are colonized predominantly by *S. epidermidis*, suggesting a broader antagonistic relationship between coagulase-negative *Staphylococcus* and *S. aureus*[22]. In addition, *Cutibacterium acnes* also appears to have an antagonistic relationship with *S. aureus*[23]. Likely, these observations are due to the ability of commensal microbiota to inhibit the growth of *S. aureus* through the fermentation of compounds occurring naturally on the skin. Many of the members of the cutaneous microbiome can metabolize glycerol into antimicrobial compounds, which inhibit *S. aureus* growth[22–24]. This degree of interaction extends beyond the context of atopic dermatitis, suggesting that commensal organisms may attenuate the virulence of *S. aureus* in polymicrobial diabetic foot infections[25].

**Acne vulgaris is a clinical morphology of pro-inflammatory microbial communities**

The pathogenesis of acne highlights the interplay between skin microbiota and inflammatory disease. The pathophysiology of acne involves abnormal follicular hyperkeratinization, excessive sebum production, colonization by *C. acnes* (recently reclassified from *Propionibacterium acnes*[26]) and subsequent activation of an inflammatory cascade[27]. Formation of comedones or inflammatory papules, pustules and nodules are a significant source of morbidity and are associated with depressive symptoms, including lower self-attitude, feelings of uselessness, lower self-worth and lower body satisfaction[28].

It has been demonstrated that the overall microbial community between involved and uninvolved skin at the same location is similar[29]. While acne microbiology research has mainly focused on *C. acnes*, recent studies have highlighted the important role played by the commensal microbiota as significant differences in phyla are noted in the following cases. First, Proteobacteria are under-represented in comedone and papulo-pustular lesions as compared to clear skin. Additionally, *Cutibacterium* and *Staphylococcus* are abundantly found on sebum-rich areas of the skin and are associated with disease flares[29].

Treatment of acne with antimicrobials (often used for their anti-inflammatory properties) decreases the richness and evenness of the cutaneous microbiome[29,30]. In addition to the impact on *C. acnes*, the collateral damage to the resident microflora may also impact acne pathogenesis. A relevant relationship between *S. epidermidis* and *C. acnes* has been identified. Screening of genotypic isolates of *C. acnes* revealed an inhibitory effect of *S. epidermidis* against a majority of *C. acnes* strains[31]. The

mechanism of this inhibition is propagated through the fermentation of glycerol into short-chain fatty acids, including succinic acid by *S. epidermidis* [32]. Topical use and intralesional injections of succinic acid have been shown to inhibit the growth of *C. acnes*[32]. Likely, the production of these potent inhibitory compounds reduces the clinical inflammation observed by others studies[33].

**Recent developments in the treatment of acne and atopic dermatitis**

Acne and atopic dermatitis are promising diseases for the development of microbiome-specific biomarkers to guide clinical intervention[12]. Targeted therapies aimed at optimizing the health of a microbial community have the potential to be used as adjuvant or maintenance therapy. Notably, they could avoid adverse consequences typically associated with long-term use of topical corticosteroids[34] or aid in mitigating the ongoing development of antimicrobial resistance associated with the use of topical antimicrobials[35]. Furthermore, evidence suggests that long-term antimicrobial treatment used in an attempt to eradicate exacerbating pathogens such as *S. aureus* is not possible. While short-term use of antimicrobials effectively clears *S. aureus* during treatment periods (using traditional culture-based approaches), re-colonization is typically seen within four to eight weeks[36]. This is likely a result of the ubiquity of the organism on the skin and in areas such as the nares. These treatments appear to only provide short-term benefit and also disrupt the commensal microbiota. Therefore, therapies that maintain and promote a stable healthy microbial diversity may reduce the frequency of exacerbations and improve outcomes in these patients in the long term. This resembles what is seen in chronic airways disease, including cystic fibrosis, whereby periods of clinical stability are punctuated by exacerbations that require acute and maintenance therapy. In the context of

cystic fibrosis, new evidence shows changes to the specific organization of the lung microbiome and overgrowth of anaerobic pathogens being associated with pulmonary exacerbations[37].

**New Therapeutic Developments in Atopic Dermatitis**

Existing and emergent therapeutics in atopic dermatitis are targeted towards the inflammatory response in active disease (Table 1). Established therapies have already been shown to influence the skin microbiota and improve disease outcomes. In atopic dermatitis, the use of narrow band ultraviolet-B (UVB) therapy has been shown to significantly reduce the concentration of *S. aureus* and decrease superantigen production (pro-inflammatory peptides)[38,39]. Recent studies in atopic dermatitis have focused on the clinical utility of modulating the microbiota[22]. Nakatsuji *et al.* treated five patients with strains of *S. epidermidis* or *S. hominis* with antimicrobial properties against *S. aureus*. These strains were formulated into a vehicle and applied topically to lesions, which significantly decreased the abundance of *S. aureus* at the application site. Moreover, Myles *et al.* have shown that that topical transplantation with *Roseomonas mucosa* in 10 adults with no preexisting gram-negative bacilli is associated with clinical improvement in both adult and pediatric patients[40]. These data provide the basis for rational development of bacteriotherapy.

209 Table 1. **Microbiome therapeutics under development for atopic dermatitis.**

| Study | Intervention | Outcome |
|---|---|---|
| Totté *et al*. 2017 | Bacteriolysin targeted against *S. aureus* | Trial in progress |
| Nakatsuji *et al.* 2017 | Antimicrobial peptides produced by coagulase-negative S*taphyloccocus* | Decreased colonization by *S. aureus* |
| Nakatsuji *et al.* 2018 | Autologous application of antimicrobial peptide producing coagulase-negative *Staphylococcus* | Decreased colonization of *S. aureus* and increased microbial diversity |
| Myles *et al.* 2018 | Transplantation with *Roseomonas mucosa* | Decreased disease severity, *S. aureus* burden, and topical corticosteroid use |
| Gallo *et al* 2017 (NCT03151148) | Allogenic Targeted Microbiome Transplant | Trial in progress |

210

211

212

213

214

215

216

217

218

219

220

221

222

223

**New Therapeutic Developments in Acne Vulgaris**

Acne vulgaris is a promising disease for the advent of unique microbiome therapeutics (Table 2). Ongoing therapies in development include utilizing a targeted bacteriophage endolysin selective for causative organisms without disrupting the commensal microbiota. Whereas the use of bacteriophage therapy against *S. aureus* is of current investigation in atopic dermatitis [41], bacteriophage therapy targeted against *C. acnes* in the treatment of acne vulgaris has also shown promising results *in vitro*[42]. Though resistance to phage therapy is a concern, the inclusion of multiple phage strains may help reduce the development of resistance. Furthermore, the requirement of refrigeration or storage requirements for this therapy may limit its utility to an in-office treatment. Though preliminary evidence remains optimistic, further trials are required to evaluate its efficacy.

More broadly, the use of prebiotics (carbohydrates utilized by commensal microbiota) and probiotics (beneficial commensal microorganisms) have shown promise as treatments for acne and atopic dermatitis.. In addition to the modulation of the microflora, topical probiotics are able to contribute to barrier function by increasing ceramide production. This may reduce inflammatory lesions and lend their widespread applicability in many inflammatory skin diseases[43,44]. It is also clear that exploiting the biology of the members of the cutaneous microbiome could be therapeutically useful given their role in *C. acnes* inhibition by anti-microbial proteins[45,46]. Indeed, many commensal organisms can breakdown natural skin products to produce nitric oxide, which displays antimicrobial and anti-inflammatory properties[47]. As such, exploiting this mechanism will likely lead to advancements in the treatment of disease flares.

Development of a vaccine for acne vulgaris is an active area of research. Current attempts to develop a long-lasting immune response against the Christie-Atkins-Munch-Petersen (CAMP) factor have shown promising results in *ex vivo* mouse models[48]. The CAMP factor contributes to *C. acnes* colonization and the inflammatory response. The antibodies directed against the CAMP molecule resulted in decreased *C. acnes* growth and two pro-inflammatory interleukins (IL-1 and IL-8). Further research could yield similar molecular targets that contribute to the function of microbial communities residing in the sebaceous gland.

Table 2. **Microbiome therapeutics under development for acne vulgaris.**

| Study | Intervention | Outcome |
|---|---|---|
| Wang *et al.* 2014 | Topical application of *Staphylococcus epidermidis* | Fermentation of glycerol and inhibition of *C. acnes* |
| Brown *et al.* 2016 | Bacteriolysin against *C. acnes* | Lysis of *C. acnes* |
| Baldwin *et al.* 2016 | Suspension of Topical Nitric Oxide-releasing drug | Nitric oxide production and decreased inflammatory lesions |
| Wang *et al.* 2018 | Vaccine against CAMP Factor | Decreased production of interleukin IL-8 and IL-1β (pro-inflammatory cytokines) |
| Taylor *et. al* 2019 (NCT03709654) | Topical application of Healthy Bacterial Strains | Trial in Progress |

Skin microbiota transplants could potentially be used in the future, similar to how fecal microbiota transplants have revolutionized the management of recurrent *Clostridium difficile* infections[49]. Fecal microbiota transplants work because the inoculum consists of entire intact communities and contain organisms that cannot be effectively cultured in the laboratory. These microbial communities harbor all the necessary microbe-microbe and microbiome-host interactions capable of restoring the dysbiotic, pathogenic state to a balanced immunologic equilibrium that prevents domination by a single pathogen. Similar to the recurrent infections of *C. difficile*, current therapies are aimed at addressing the manifestation of many cutaneous diseases without addressing the underlying etiology as microbial dysbiosis. Evidence suggests that repeated antibiotic exposure impacts the commensal microbiota[50]. Overreliance on antimicrobial treatments may lead to a higher rate of recalcitrant disease due to the development of antimicrobial resistance. Moreover, the relative failure of anti-*Staphyloccocus* therapies for long-term control of atopic dermatitis should prompt the development of alternative personalized therapies such as cutaneous microbiota transplantation.

**Conclusion**

Next-generation sequencing has allowed for the detection and characterization of numerous components of the cutaneous microbiome. However, ongoing research focused on understanding how these complex communities function is still in its early stages. As we learn more about the function of the cutaneous microbiome, it has become clear that these complex communities play a fundamental role in inflammatory skin disease[7]. Furthermore, a change in dermatology clinical practice may occur with the advent of a

new treatment paradigm reliant on the appreciation of the role of the cutaneous microbiome in chronic inflammation. This could change the way patients presenting with common skin conditions such as atopic dermatitis and acne vulgaris are managed. Bacteriotherapy, selective bacteriophages, vaccines, improved pro and prebiotics and perhaps even skin microbiota transplants, could one day be incorporated into the treatment arsenal[22,42,45,46,51]. With refinement in these therapies, clinical practice may shift towards the treatment of acute flares with bacteria instead of antibiotics.

**Figure Legends**

**Figure 1. The transition between healthy and dysbiotic microbial communities are reflected by a change in the community structure and microbial diversity and clinically manifests as an exacerbation of disease.** Several broad therapeutic targets exist that offer mechanisms to shift the dynamic balance from a proinflammatory environment to a balanced and diverse community. The data represented in the figure is an example of the mean abundance of the cutaneous phyla of healthy and cutaneous disease.

**Table 1. Developments of potential microbiome therapeutics in atopic dermatitis.**

**Table 2. Recent developments in potential microbiome therapeutics in acne vulgaris**

354 **Literature Cited**


355 1. Chiller K, Selkin BA, Murakawa GJ. Skin Microflora and Bacterial Infections of
356 the Skin. *J Investig Dermatology Symp Proc*. 2001;6(3):170-174.
357 doi:10.1046/j.0022-202x.2001.00043.x
358 2. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? *Br*
359 *J Dermatol*. 2008;158(3):442-455. doi:10.1111/j.1365-2133.2008.08437.x
360 3. Foxman B, Goldberg D, Murdock C, Xi C, Gilsdorf JR. Conceptualizing human
361 microbiota: from multicelled organ to ecological community. *Interdiscip Perspect*
362 *Infect Dis*. 2008;2008:613979. doi:10.1155/2008/613979
363 4. Segre JA. Epidermal barrier formation and recovery in skin disorders. *J Clin*
364 *Invest*. 2006;116(5):1150-1158. doi:10.1172/JCI28521
365 5. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol*.
366 2018;16(3):143-155. doi:10.1038/nrmicro.2017.157
367 6. Grice EA, Kong HH, Conlan S, et al. Topographical and Temporal Diversity of the
368 Human Skin Microbiome. *Science (80- )*. 2009;324(5931):1190-1192.
369 doi:10.1126/science.1171700.Topographical
370 7. Balato A, Cacciapuoti S, Di Caprio R, et al. Human Microbiome: Composition and
371 Role in Inflammatory Skin Diseases. *Arch Immunol Ther Exp (Warsz)*.
372 2018;67(1):1-18. doi:10.1007/s00005-018-0528-4
373 8. Meisel JS, Sfyroera G, Bartow-McKenney C, et al. Commensal microbiota
374 modulate gene expression in the skin. *Microbiome*. 2018;6(1):1-15.
375 doi:10.1186/s40168-018-0404-9
376 9. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. *Science*.

2014;346(6212):954-959. doi:10.1126/science.1260144

10. Kong HH, Segre JA. Skin microbiome: Looking back to move forward. *J Invest Dermatol*. 2012;132(3):933-939. doi:10.1038/jid.2011.417

11. Kong H, Clay J, Conlan S, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22:850-859. doi:10.1101/gr.131029.111

12. Niemeyer - van der Kolk T, van der Wall HEC, Balmforth C, Van Doorn MBA, Rissmann R. A systematic literature review of the human skin microbiome as biomarker for dermatological drug development. *Br J Clin Pharmacol*. 2018;84(10):2178-2193. doi:10.1111/bcp.13662

13. Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. *Dermatol Clin*. 2017;35(3):283-289. doi:10.1016/j.det.2017.02.002

14. Elias PM, Steinhoff M. "Outside-to-inside" (and now back "Outside" Pathogenic Mechanisims in Atopic Dermatitis. *J Invest Dermatol*. 2009;128(5):1067-1070. doi:10.1038/jid.2008.88.

15. Irvine AD, McLean WHI, Leung DYM. Filaggrin Mutations Associated with Skin and Allergic Diseases. *N Engl J Med*. 2011;365(14):1315-1327. doi:10.1056/NEJMra1011040

16. Geoghegan JA, Irvine AD, Foster TJ. Staphylococcus aureus and Atopic Dermatitis: A Complex and Evolving Relationship. *Trends Microbiol*. 2018;26(6):484-497. doi:10.1016/j.tim.2017.11.008

17. Foster TJ, Geoghegan JA, Ganesh VK, Höök M. Adhesion, invasion and evasion: the many functions of the surface proteins of Staphylococcus aureus. *Nat Rev*

*Microbiol*. 2014;12(1):49-62. doi:10.1038/nrmicro3161

18. Cho SH, Strickland I, Boguniewicz M, Leung DYM. Fibronectin and fibrinogen contribute to the enhanced binding of Staphylococcus aureus to atopic skin. *J Allergy Clin Immunol*. 2001;108(2):269-274. doi:10.1067/mai.2001.117455

19. Liu H, Archer NK, Dillen CA, et al. Staphylococcus aureus Epicutaneous Exposure Drives Skin Inflammation via IL-36-Mediated T Cell Responses. *Cell Host Microbe*. 2017;22(5):653-666.e5. doi:10.1016/j.chom.2017.10.006

20. Alomar A. Can microbial superantigens influence atopic dermatitis flares? *Chem Immunol Allergy*. 2012;96:73-76. doi:10.1159/000331887

21. Byrd A., Deming C, Cassidy SKB, et al. Staphylococcus aureus and Staphylococcus epidermidis strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med*. 2017;9(397):1-13.

22. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9(378):S205.2-S206. doi:10.1126/scitranslmed.aah4680

23. Francuzik W, Franke K, Schumann RR, Heine G, Worm M. Propionibacterium acnes abundance correlates inversely with staphylococcus aureus: Data from atopic dermatitis skin microbiome. *Acta Derm Venereol*. 2018;98(5):490-495. doi:10.2340/00015555-2896

24. Shu M, Wang Y, Yu J, et al. Fermentation of Propionibacterium acnes, a Commensal Bacterium in the Human Skin Microbiome, as Skin Probiotics against Methicillin-Resistant Staphylococcus aureus. *PLoS One*. 2013;8(2).

doi:10.1371/journal.pone.0055380

25. Ramsey MM, Freire MO, Gabrilska RA, Rumbaugh KP, Lemon KP. Staphylococcus aureus Shifts toward commensalism in response to corynebacterium species. *Front Microbiol*. 2016;7(AUG):1-15. doi:10.3389/fmicb.2016.01230

26. Scholz CFP, Kilian M. The natural history of cutaneous propionibacteria, and reclassification of selected species within the genus propionibacterium to the proposed novel genera acidipropionibacterium gen. Nov., cutibacterium gen. nov. and pseudopropionibacterium gen. nov. *Int J Syst Evol Microbiol*. 2016;66(11):4422-4432. doi:10.1099/ijsem.0.001367

27. Dréno B. What is new in the pathophysiology of acne, an overview. *J Eur Acad Dermatology Venereol*. 2017;31:8-12. doi:10.1111/jdv.14374

28. Dalgard F, Gieler U, Holm JØ, Bjertness E, Hauser S. Self-esteem and body satisfaction among late adolescents with acne: Results from a population survey. *J Am Acad Dermatol*. 2008;59(5):746-751. doi:10.1016/j.jaad.2008.07.013

29. Dreno B, Martin R, Moyal D, Henley JB, Khammari A, Seité S. Skin microbiome and acne vulgaris: Staphylococcus, a new actor in acne. *Exp Dermatol*. 2017;26(9):798-803. doi:10.1111/exd.13296

30. Coughlin CC, Swink SM, Horwinski J, et al. The preadolescent acne microbiome: A prospective, randomized, pilot study investigating characterization and effects of acne therapy. *Pediatr Dermatol*. 2017;34(6):661-664. doi:10.1111/pde.13261

31. Christensen GJM, Scholz CFP, Enghild J, et al. Antagonism between Staphylococcus epidermidis and Propionibacterium acnes and its genomic basis.

*BMC Genomics*. 2016;17(1):1-14. doi:10.1186/s12864-016-2489-5

32. Wang Y, Kuo S, Shu M, et al. Staphylococcus epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of Propionibacterium acnes: Implications of probiotics in acne vulgaris. *Appl Microb Biotechnol*. 2014;98(1):411-424. doi:10.1097/MCA.0000000000000178.Endothelial

33. Xia X, Li Z, Liu K, Wu Y, Jiang D, Lai Y. Staphylococcal LTA-Induced miR-143 Inhibits Propionibacterium acnes-Mediated Inflammatory Response in Skin. *J Invest Dermatol*. 2016;136(3):621-630. doi:10.1016/j.jid.2015.12.024

34. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. *Indian Dermatol Online J*. 2014;5(4):416-425. doi:10.4103/2229-5178.142483

35. Adler BL, Kornmehl H, Armstrong AW. Antibiotic resistance in acne treatment. *JAMA Dermatology*. 2017;153(8):810-811. doi:10.1001/jamadermatol.2017.1297

36. Gilani SJK, Gonzalez M, Hussain I, Finlay AY, Patel GK. Staphylococcus aureus re-colonization in atopic dermatitis: Beyond the skin. *Clin Exp Dermatol*. 2005;30(1):10-13. doi:10.1111/j.1365-2230.2004.01679.x

37. Layeghifard M, Li H, Wang PW, et al. Microbiome networks and change-point analysis reveal key community changes associated with cystic fibrosis pulmonary exacerbations. *npj Biofilms Microbiomes*. 2019;5(1). doi:10.1038/s41522-018-0077-y

38. Silva SH, Guedes ACM, Gontijo B, et al. Influence of narrow-band UVB phototherapy on cutaneous microbiota of children with atopic dermatitis. *J Eur Acad Dermatology Venereol*. 2006;20(9):1114-1120. doi:10.1111/j.1468-

3083.2006.01748.x

39. Dotterud LK, Wilsgaard T, Vorland LH, Falk ES. The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and healthy controls. *Int J Circumpolar Health*. 2008;67(2-3):254-260. http://www.ncbi.nlm.nih.gov/pubmed/18767345. Accessed February 7, 2019.

40. Myles IA, Earland NJ, Anderson ED, et al. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. *JCI Insight*. 2018;3(9):1-13. doi:10.1172/jci.insight.120608

41. Totté J, de Wit J, Pardo L, Schuren F, van Doorn M, Pasmans S. Targeted anti-staphylococcal therapy with endolysins in atopic dermatitis and the effect on steroid use, disease severity and the microbiome: Study protocol for a randomized controlled trial (MAAS trial). *Trials*. 2017;18(1):1-8. doi:10.1186/s13063-017-2118-x

42. Brown TL, Petrovski S, Dyson ZA, Seviour R, Tucci J. The formulation of bacteriophage in a semi solid preparation for control of propionibacterium acnes growth. *PLoS One*. 2016;11(3):1-16. doi:10.1371/journal.pone.0151184

43. De Simone C, Dimarzio L, Cinque B, Giuliani M, Cifone MG, Cupelli F. Increase of Skin-Ceramide Levels in Aged Subjects following a Short-Term Topical Application of Bacterial Sphingomyelinase from Streptococcus Thermophilus . *Int J Immunopathol Pharmacol*. 2017;21(1):137-143. doi:10.1177/039463200802100115

44. Kang BS, Seo JG, Lee GS, et al. Antimicrobial activity of enterocins from Enterococcus faecalis SL-5 against Propionibacterium acnes, the causative agent in

acne vulgaris, and its therapeutic effect. *J Microbiol*. 2009;47(1):101-109. doi:10.1007/s12275-008-0179-y

45. Bowe WP, Filip JC, Dirienzo JM, Volgina A. Inhibition of Propionibacterium acnes by Bacteriocin-Like Inhibitory Substances (BLIS) Produced by Streptococcus Salivarius. *J Drugs Dermatology*. 2006;5(9):868-870. doi:10.1016/j.ydbio.2009.10.046.Hippo

46. Oh S, Kim S-H, Ko Y, et al. Effect of bacteriocin produced by Lactococcus sp. HY 449 on skin-inflammatory bacteria. *Food Chem Toxicol*. 2006;44(8):1184-1190. doi:10.1016/j.fct.2005.08.008

47. Baldwin H, Blanco D, McKeever C, et al. Results of a phase 2 efficacy and safety study with SB204, an investigational topical nitric oxide-releasing drug for the treatment of acne vulgaris. *J Clin Aesthet Dermatol*. 2016;9(8):12-18.

48. Wang Y, Hata TR, Tong YL, et al. The Anti-Inflammatory Activities of Propionibacterium acnes CAMP Factor-Targeted Acne Vaccines. *J Invest Dermatol*. 2018;138(11):2355-2364. doi:10.1016/j.jid.2018.05.032

49. Kelly CR, Ihunnah C, Fischer M, et al. Fecal Microbiota Transplant for Treatment of Clostridium difficile Infection in Immunocompromised Patients. *Am J Gastroenterol*. 2014;109(7):1065-1071. doi:10.1016/j.chemosphere.2012.12.037.Reactivity

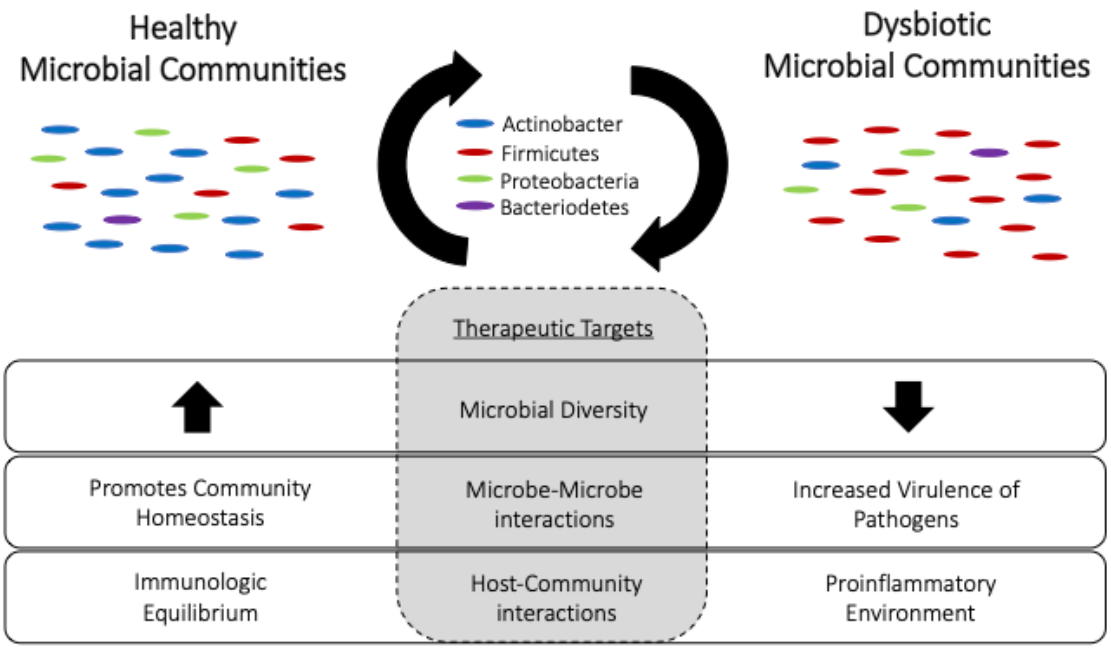
50. Chien AL, Tsai J, Leung S, et al. Association of Systemic Antibiotic Treatment of Acne With Skin Microbiota Characteristics. *JAMA Dermatology*. 2019;21287:1-10. doi:10.1001/jamadermatol.2018.5221

51. Castillo DE, Nanda S, Keri JE. Propionibacterium (Cutibacterium) acnes

515 Bacteriophage Therapy in Acne: Current Evidence and Future Perspectives.

516 *Dermatol Ther (Heidelb)*. 2018;9(1):19-31. doi:10.1007/s13555-018-0275-9

517


Healthy
Microbial Communities
Actinobacter
Firmicutes
Proteobacteria
Bacteriodetes
Dysbiotic
Microbial Communities
Therapeutic Targets
Microbial Diversity
Promotes Community Homeostasis
Microbe-Microbe interactions
Increased Virulence of Pathogens
Immunologic Equilibrium
Host-Community interactions
Proinflammatory Environment