Calming the Inflammation of ACNE and ROSACEA

The Microbiome in Acne: Where are We Now?

As research reveals connections of the microbiome to skin disease, clinicians may discover new approaches to managing the disease.

BY DHARM SODHA, BS AND PETER LIO, MD

Acne vulgaris is an extremely common, multifactorial, chronic inflammatory skin disorder that affects the sebaceous glands and comprises sebum production, abnormal keratinization, inflammation, and bacterial colonization. Acne can cause disfigurement and scarring, resulting in low self-esteem, difficulties in social interaction, and emotional distress.

The microbiome is defined as the community of microorganisms (such as bacteria, fungi, and viruses) that inhabit a particular environment and especially the collection of microorganisms living in or on the human body. There may be as many 10 times more microbial cells colonizing the human body, and studies are now finding that each individual’s unique microbiome contributes to immunologic, hormonal, and metabolic functions.

The interaction between skin microbes and host immunity plays an important role in this disease. *Cutibacterium acnes* (*C. acnes*; formerly called *Propionibacterium acnes*) is commonly found in sebum-rich areas, and its over-proliferation has long been thought to contribute to acne. Treatment of acne vulgaris often depends on its severity, the presence or absence of inflammatory nodules, and response to treatment. Topical therapies most commonly used by patients include alpha-hydroxy acids, benzoyl peroxide, retinoid analogues, keratolytics, azelaic acid, and topical antibiotics. For patients with more severe or extensive disease, isotretinoin or oral antibiotics may be required. Tetracyclines, erythromycin, and trimethoprim/sulfamethoxazole have all been used to inhibit *C. acnes* specifically however, it has been difficult to disentangle the anti-inflammatory effects of these agents that also may contribute to lesion reductions.5,6 As increasing amounts of research is done into the human microbiome, it seems to be significantly more complex from a microbial perspective, and simply focusing on one strain of bacteria may be overly simplistic.

THE RELATIONSHIP OF THE SKIN MICROBIOME AND ACNE

Most of the microorganisms that are present on the skin are harmless and live in symbiosis along with host cells. The most common colonies of bacteria that form on the surface of our skin are *S. epidermidis*, *S. saprophyticus*, *S. hominis*, *S. warneri*, *S. haemolyticus*, and *S. capitis*, bacteria of the genus *Cutibacterium*, and bacteria of the genus *Micrococcus*. The bacteria in the inner dermal layer are most often: *Actinobacteria*, *Firmicutes*, *Staphylococci*, *Clostridium spp.*, hemolytic *Streptococci*, *Enterococci*, and *Proteobacteria*.5,6 Bacterial composition varies depending on many factors, including environmental ones, such as the use of cosmetics, exposure to UV radiation, humidity, antibiotic use, lifestyle, and profession.7-9

Human skin contains many bacteria, viruses, fungi, and even mites. Over the past several decades, researchers have searched for the relationship between the microbiota and *C. acnes*. *C. acnes* is an anaerobic, Gram-positive, pleomorphic rod that belongs to the *Actinobacteria phylum*. Several

Many conventional acne therapies can cause a deleterious effect on the gut and skin flora. The use of probiotics either alongside treatments or by themselves may provide additional benefit, perhaps even synergy. The intestinal microbiome is increasingly found to be important in the pathology of acne and many other diseases. Thus, clinicians should begin to acknowledge and advise patients suffering from acne on the importance of diet and its possible role in health and disease, almost certainly mediated through the microbiome to some degree. As research regarding different probiotic treatments expands, more individualized probiotic therapies can be recommended for patients, hopefully with more robust data on safety and efficacy.

The bottom line
mechanisms have been proposed by which C. acnes aggravates acne, including augmentation of lipogenesis, comedone formation, and host inflammation. Recent studies have shown that C. acnes strains dominate in acne vulgaris, but limitations and methods of skin sampling indicate the need for more extensive research in this area. Although C. acnes seems to be common among patients with acne, it is also seen in patients not affected by acne. Thus, the interaction between skin microbes and host immunity is more complex than initially thought.

Though the role of C. acnes in the pathophysiology of acne is not fully understood, its main role seems to be that it helps maintain an acidic skin pH by releasing free fatty acids and inhibiting the multiplication of S. Aureus and Streptococcus. The population of C. acnes strains is diverse, depending on the characteristics of cohorts of examined patients. A large degree of genetic variance can occur between strains resulting in either acne prone or acne free skin. Although C. Acnes is a focus of acne treatment, studies have also demonstrated that C. granulosum is more virulent than C. acnes, and Malassezia (a fungus) is also believed to be an acne-causing organism due to hydrolysis of triglycerides in the sebum producing free fatty acids that can cause abnormal keratinization of hair follicular ducts and inflammation.

THE IMPORTANCE OF THE GUT MICROBIOME

While the skin microbiome seems obviously involved, the gut microbiome also appears to play an important role, as an increasing number of studies implicate the health of the intestines in the health of the skin. The intestinal microbiota is likely involved in the immune response to pathogens on the skin surface that can contribute to acne. Acne and the condition of the digestive tract are both associated with the quality of the microbiome inhabiting intestines. Emerging data suggest that dietary factors may influence acne development due to effects on the gut microbiome. A typical Western diet that includes foods with a complex mixture of fats, generally has a high glycemic index, and contains abundant dairy may aggravate acne by raising the levels of insulin-like growth factor-1 (IGF-1) and insulin. The Western diet specifically has been found to disturb the balance between beneficial and pathogenic organisms in the microbiome of the human digestive tract. Though knowledge of the human microbiome has significantly expanded in recent years, the microbiological environment in humans is complex and individualized.

The microbiota also causes modifications in the creation of short chain fatty acids that are utilized in the functions of nourishing cells and modulating brain activity. One such acid is propionic acid, which exhibits an antimicrobial effect against bacteria such as S. Aureus and may provide resistance to acne causing agents. The integrity of the gut itself and diversity within its microbiome carry an important role in the development of inflammatory skin diseases, though we still have much to learn.

PROBIOTIC THERAPIES FOR ACNE

While we have relatively sparse evidence, especially a lack of the robust studies required to make sound clinical recommendations, we do have some compelling data for both cutaneous and gastroenterologic microbiome manipulation with probiotic treatments. The most well-known probiotic organisms that are shown to have therapeutic health effects are Lactobacillus and Bifidobacterium. In order for therapies to be safe and effective, the organisms utilized must also be nonpathogenic and nontoxic. A study completed by Di Marzio et al demonstrated that the use of Streptococcus thermophilus for seven days increased the production of ceramides. This may be beneficial in the treatment of acne as ceramides, beyond their role in the skin barrier, can provide an anti-inflammatory and antimicrobial effect towards C. acnes.

Jung et al studied 45 women being treated with minocycline and examined whether probiotic supplementation would reduce side effects and provide a synergistic effect. Their investigation found that, “there was a synergistic anti-inflammatory effect, while probiotics minimized the appearance of side effects resulting from the use of antibiotic therapy.”

A study completed in 2010 found konjac glucomannan hydrolysates and probiotics significantly reduced the growth of C. acnes as well. Additionally, there have been a few studies that suggest the use of supernatant, heat killed bacteria, and/or topical administration of probiotic derived cream can reduce skin inflammation and lesions of acne vulgaris. These studies have provided hope and future outlook for the development of treatments to improve symptoms and treat acne vulgaris.
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**FURTHER DIRECTIONS AND CONCLUSION**

Acne remains a very common disease that is multifactorial in nature. Many conventional therapies can cause a deleterious effect on the gut and skin flora. Despite these treatments often leading to disease improvement, there may be unintended side effects, and the use of probiotics either alongside treatments or by themselves may provide additional benefit, perhaps even synergy.

The intestinal microbiome is increasingly found to be important in the pathology of acne and many other diseases. Thus, clinicians should begin to acknowledge and advise patients suffering from acne on the importance of diet and its possible role in health and disease, almost certainly mediated through the microbiome to some degree.

As clinicians and researchers better understand the mechanism behind different probiotic treatments, more individualized probiotic therapies can be recommended for patients, hopefully with more robust data on safety and efficacy. Specifically, for patients who may not respond well to current treatments or suffer side effects from current acne treatments, probiotics and their ilk may provide relief when used instead of or alongside current therapies. Oral or topical probiotics may be indicated during and after use of antibiotics in order to maintain gut microbiome integrity.

Future research must consider nutritional factors, skin integrity, oral and topical probiotics, as well as commensal application, among others. With this in mind, the human microbiome is clearly a complex system and further trials and research will hopefully allow clinicians to integrate new knowledge and advance the understanding of these relationships.

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Dharm Sodha is a medical student at the University of Illinois at Chicago and is interested in Dermatology. Specifically, Dharm is interested in working collaboratively with clinicians to find treatments and diagnostic tools for skin conditions such as acne, hidradenitis suppurativa, and skin cancer.

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11. Polak SG, Siriwardana N, Dissanayake D, Fujisawa T, Takeda Y. Oral or topical probiotics may be indicated during and after use of antibiotics in order to maintain gut microbiome integrity.