

# ROLE OF MICROBIOTA IN ACNE: A NEW APPROACH

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**Abstract** – Acne is a pathology that affects a large number of people of all ethnicities, becoming one of the main causes of visits to the dermatologist. The pathophysiology of acne is multifactorial and is still not fully understood, however, it is known that *Cutibacterium acnes* plays an important role in its development. The traditional approach in its management has consisted in the use of antibiotics, retinoids and topical treatments that aim to eliminate *C. acnes*, but these treatments collaterally damage other bacteria present in the skin microbiota that help us maintain homeostasis and protect from opportunistic pathogens. This article aims to show the impact of the skin microbiota on the development of acne.

**Keywords:** Microbiota, Acne, Skin diseases, Dermatology.

## INTRODUCTION

Vulgar acne occurs in 44-95% of adolescents, being one of the main causes of dermatological consultation<sup>1</sup>. Spontaneous remission of acne in up to 50% of patients, however, proper treatment helps to reduce sequelae and obtain a more favorable evolution. The pathophysiology of acne involves multiple factors including inflammation, excessive sebum production, hormonal surge, and microbial overgrowth, especially *Cutibacterium acnes*<sup>2,3</sup>. Severe forms of acne can cause disfigurement and scarring, resulting in low self-esteem, difficulties in social interaction, and anxiety. In this article we will focus on the review of the different advances that have been made in recent years in the description of the skin microbiota and the factors that modify it, causing acne, as well as an overview of the different treatments that exist and their impact on the microbiota<sup>4</sup>.

## SKIN ARCHITECTURE

The skin is the largest barrier of the human body to the outside world, necessary for protection against external agents. In this region it is important to maintain a symbiotic relationship with its microbiome, with which it is strictly in contact, thus avoiding pathological reactions. The skin consists of three zones: epidermis, dermis and subcutaneous tissue. The epidermis is the area that is in direct contact with the outside, its main cells are keratinocytes. The outer part of the epidermis, known as the stratum corneum, is relatively impermeable and, if undamaged, prevents microorganisms and other foreign substances from entering the body. The next area is the dermis, which contains nerve endings, sweat and sebaceous glands, hair follicles, and blood vessels. The sweat secretions produced by the sweat glands have the ability to control heat and produce moisturizing agents, these functions help maintain the elasticity and integrity of the skin. Under physiological



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conditions, the dermis contains multiple immune cells that form an important defense of the body. Beneath the dermis we can find the subcutaneous tissue, which mainly helps to provide protective padding and energy storage<sup>5-7</sup>.

## HEALTHY SKIN MICROBIOTA

The skin microbiota refers to the set of microorganisms (mainly bacteria, fungi and viruses) found in and on the skin<sup>8</sup>. Most of the microbiota is made up of non-harmful organisms, however, a limited number of microbes are able to take advantage of the conditions offered by the skin and break its homeostasis<sup>9,10</sup>.

The method by which the skin sample is obtained impacts its analysis<sup>11</sup>. These samples were usually cultured, however, less than 1% of the bacterial species achieved proper growth under standard laboratory conditions, making those easily cultured appear to be more abundant on the skin than they actually were. Currently there are methods, such as DNA sequencing and amplification that allow us to obtain a more complete and impartial result of the skin microbiota<sup>12</sup>. The most recent descriptions of the microbiota in the skin have helped the development of new research to understand the physiology of the skin and diseases<sup>13</sup>.

There is constant communication between resident microorganisms and the skin via the immune system<sup>14</sup>. The colonization of the skin begins from the moment of birth and evolves over the time, achieving stabilization during the first years of life<sup>1</sup>. The diversity of the microbiota in these stages is very low, and regulatory T lymphocytes develop an immune tolerance towards them<sup>6,7</sup>. The mode of delivery plays a fundamental role in the colonization of the skin. The vaginal microbiota passes part of its organisms to the baby's skin, on the other hand, those born by cesarean section likewise get part of their microbiota from their mother, by being in contact with her skin. The same happens during lactation by having direct contact between both skins<sup>15</sup>. During this period the immune system evolves in conjunction with the microbes<sup>1</sup>. In adults, the diversity of the microbiota increases significantly, mainly due to the different exposures that each person presents. Recent studies<sup>6</sup> have shown that individuals residing in the same house contain a similar microbiota, just as pet owners have a striking similarity to the bacteria present on their pets.

External factors such as weather, humidity, use of antibiotics, skincare routine, frequency of hygiene and other environmental factors influence the habitat provided for microbes, as well as internal factors of each individual, such as age and their immune system<sup>8</sup>. This combination can lead to differences in the skin microbiome of each individual.

Several factors can affect the homeostasis of the microbiota and the skin, causing a state called dysbiosis. Dysbiosis causes a direct alteration in the relationship between the host and the microbe, producing diseases. It is generally believed that a greater diversity in the microbiota is beneficial by making it more resistant to changes<sup>1</sup>.

The normal resident skin microbiota includes *Cutibacterium*, Coagulase-negative *Staphylococci*, *Micrococci*, *Corynebacteria* and *Acinetobacter*<sup>8,9</sup>. The loss of the diversity of the skin's microbiota, as well as changes in its natural composition, promote the development of inflammatory skin diseases, such as acne<sup>14</sup>. This is because there are bacteria that protect the skin by preventing the disproportionate growth of other more harmful organisms; this is the case of *Staphylococcus epidermidis*, which is frequently obtained from healthy skin<sup>8</sup>. A relationship between *S. epidermidis* and *C. acnes* has been identified, revealing an inhibitory action against *C. acnes*, which is known as the main pathogen of acne. This inhibition is carried out through the fermentation of glycerol into short-chain fatty acids by *S. epidermidis*<sup>2</sup>. Similarly, *S. epidermidis* has been found to protect against other pathogens, including *S. aureus*, through increased host immunity with Toll receptor 2 and increased expression of  $\beta$ -defensins 2 and 3, as well as other antimicrobial peptides<sup>6</sup>.

Most microbiome studies focus on the study of bacteria, however, other microorganisms apart from these reside on the skin. Viruses, fungi and arthropods are also important in the development of skin diseases. Of these, the fungi are the ones that can be grown in traditional media, so a little more is known about them. The difficulty of amplifying viruses limits the knowledge about them, in the same way the new detection methods focus on the metagenomic sequencing of the DNA, so it is unlikely that those viruses with RNA will be identified<sup>13</sup>.

## PATHOPHYSIOLOGY OF ACNE

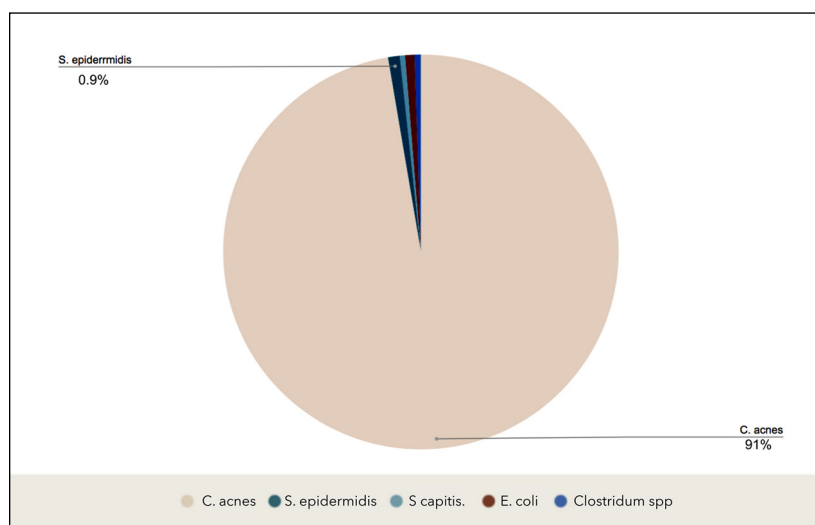
Acne is a chronic inflammatory disease that affects the sebaceous unit. Although its pathophysiology is not exactly known, three main factors are involved in its development: 1. Increased sebum production caused by the stimulation of various receptors, including those for androgens, neuropeptides, IGF-1 and PPAR. 2. Abnormal keratinization of the sebaceous duct 3. An inflammatory immune response produced by the immune system towards bacteria, mainly *C. acnes*. This causes activation of the Toll-like receptor 2 on monocytes, resulting in the production of IL-12 and IL-8. IL-12 is the major proinflammatory cytokine produced by monocytes in response to invasion by Gram-positive organisms<sup>14</sup> (Figure 1).

## MICROBIOTA IN THE SKIN WITH ACNE

As previously mentioned, new methods for analyzing skin samples have given us a broader description of its microbiota. Multiple bacteria have been found in individuals with acne, mainly *Cutibacterium*, *Pseudomonas*, *Staphylococcus* and *Klebsiella*<sup>3</sup>. We know that acne is closely related to the disproportionate presence of some strains of *Cutibacterium*<sup>8</sup>. In acne, dysbiosis in the skin could be attributed to the increase in sebum caused by the stimulation of receptors, such as androgen receptors<sup>11</sup>. During childhood there is a clear dominance in the microbiome by *streptococcus* species, however, during puberty and adolescence hormonal changes with the subsequent overproduction of sebum create a new environment<sup>16</sup>. Different species benefit from this new environment, producing an acceleration in their growth; this is the case with bacteria such as *Cutibacterium* and *Corynebacterium*. Sebum itself has inflammatory potential, but the repentant change in the composition of the microbiota increases the inflammatory response, leaving behind the previous homeostasis and giving rise to the appearance of acne<sup>1</sup>.

This shift towards an inflammatory state is believed to occur in the follicles, thus increasing their keratinization with subsequent closure of the infundibulum and development of comedones, it is believed that *C. acnes* further increases this keratinization with its biofilm. These comedones would be the first visible signs of acne, evolving to the production of papules, pustules and nodules. The mRNA data demonstrate that cytokines produced during dysbiosis, such as IL-6, IL-12, IL-23, TNF- $\alpha$ , IFN- $\gamma$ , increase acne lesions in conjunction with the proinflammatory cytokines IL-1 $\alpha$  and  $\beta$ , IL-10, AMP and IL-17<sup>1,14</sup>.

The role of *C. acnes* in acne has been investigated for several years. Today we still do not fully understand this relationship. However, thanks to new sequencing of the skin microbiota together with metagenomic analyses, we know that each strain of *C. acnes* works differently, and not all of them contribute to the formation of acne<sup>11</sup>.

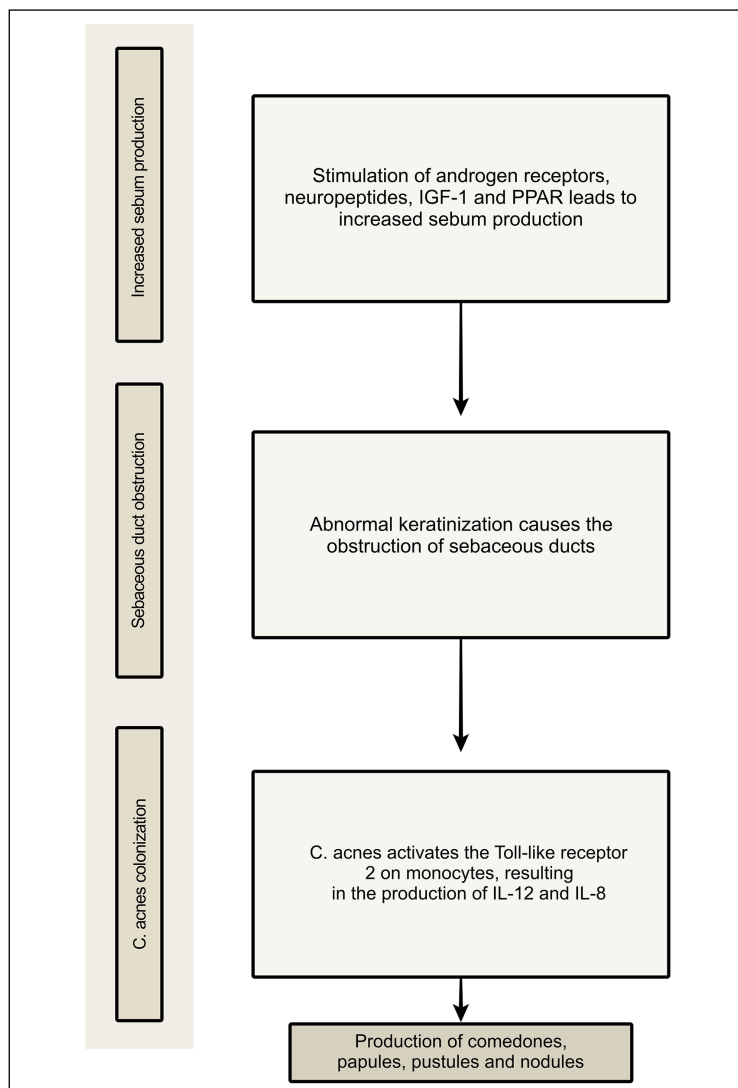


**Figure 1.** Flow diagram of pathophysiological factors of acne.

*C. acnes* is a gram-positive, anaerobic, pleomorphic bacillus belonging to the phylum Actinobacteria. Different methods are known by which it participates in the production of acne; Jarrousse et al<sup>15</sup> demonstrated that the presence of *C. acnes* increases filaggrin expression in keratinocytes in cell culture medium, forming comedones. Similarly, it induces and aggravates inflammation via the MAPK and NF-κB pathways. Subsequently, keratinocytes and macrophages produce proinflammatory cytokines. Together with TLR-2 and TLR-4, CD36 recognizes *C. acnes* and stimulates ROS production from keratinocytes to kill bacteria and induce inflammation. The adaptive immune response induced by *C. acnes* involves Th1 and Th17 lymphocytes, with the subsequent increase in their cytokines<sup>4</sup>.

In a recent study by Barnard et al<sup>17</sup> *C. acnes* was the most prevalent and abundant in patients with acne, it was found in all 68 individuals with an average relative abundance of 91.0%. Other bacterial species frequently identified in the follicle microbiota include *Staphylococcus epidermidis* (0.9%), *Staphylococcus capitis* (0.4%), *Escherichia coli* (0.7%), and *Clostridium sp.* (0.5%) (Figure 2).

However, not only bacteria are responsible for the production of acne. Fungal microorganisms generally do not cause facial acne unless they grow in large numbers. Numata et al<sup>18</sup> found that the total number of *Malassezia* species in women with acne was approximately ten times that of healthy women. The data suggested the remarkable relationship between the presence of acne vulgaris and the quantitative difference of the *Malassezia* flora<sup>19</sup>. Still, there is a long way to go to understand other pathogens involved, including viruses.



**Figure 2.** Main bacteria in the microbiota of acne-prone skin.

## INTESTINAL MICROBIOTA AND ITS RELATIONSHIP WITH ACNE

Changes in intestinal microbiota have been reported in 54% of patients with acne<sup>20</sup>. Currently, the study on the intestinal microbiota and its impact on the skin microbiota has been expanded, although the relationship is not yet fully understood<sup>10</sup>.

One of the latest trends in cosmetics and supplements focuses on the skin microbiome and its interconnection with the gut-skin axis (GSA), which could represent an improvement in skin pathologies<sup>19,20</sup>. The mechanism by which the intestine and skin interact is still not fully understood, it is believed to be due to immune and endocrinological factors. As there is dysbiosis in the intestinal microbiota, immunosuppressive cytokines are inhibited, which produces chronic inflammation unable to self-regulate in the intestine and in other organs, such as the skin<sup>10</sup>.

Different studies<sup>10</sup> have shown the presence of an increase in intestinal bacterial DNA in the bloodstream of patients with chronic skin pathologies, bringing the theory of intestinal permeability. In a recent study conducted by the Journal of the American Academy of Dermatology<sup>21</sup>, it showed a significant increase in *Firmicutes* in acne vulgaris patients with a low *Bacteroides* to *Firmicutes* ratio compared to control. It is necessary to do more studies on the impact of the bacteria present in the intestine and its impact on the skin<sup>21</sup>.

The neuroendocrine theory explains the ability of intestinal microorganisms to stimulate neuronal pathways through the production of neurotransmitters. This triggers the abnormal release of hormones, which have direct effects on skin inflammation. For example, an increase in acetylcholine and norepinephrine levels has been found to promote sebum production. This increased production is also believed to be caused by IGF-1 being stimulated by a high glycemic diet<sup>10</sup>.

The effects of diet on acne have always been controversial. It is believed that by managing Western habits and decreasing the consumption of carbohydrates and whey proteins would have a favorable impact on acne. This would decrease IGF-1 stimulation and the subsequent decrease in sebum and acne-promoting compounds. In addition, several studies have shown that daily consumption of probiotics, especially those containing *Lactobacillus* strains, for 12 weeks reduces inflammatory lesions of the acne by 30-67% and also decreases IGF-1 levels by 32%<sup>10</sup>. This is an example of how knowledge of the microbiota can help us treat acne outside of the traditional approach.

## ACNE TREATMENTS AND ITS IMPACT ON THE SKIN MICROBIOTA

The fact that acne is a multifactorial inflammatory disease makes many different treatment options available that try to target the underlying causes. Here is a review of the main treatments, with updates and their relationship with the microbiota.

### Isotretinoin

Isotretinoin is the only drug available that targets all of the known mechanisms involved in the development of acne. It is known to regulate sebum production and normalize the immune response to *C. acnes*. It is logical to think that the decrease in sebum directly affects other microbes, but it is still not sufficiently studied. However, its hepatic and teratogenic side effects limit its use<sup>3,4</sup>.

### Topical treatments

There are multiple topical treatments focused on eliminating the bacteria that cause acne, such as benzoyl peroxide and azelaic acid. Benzoyl peroxide has a comedolytic action, killing *C. acnes* by releasing oxygen free radicals. Topical azelaic acid has anti-inflammatory and antibacterial properties<sup>4,11</sup>.

Novan Therapeutics has begun a Phase III clinical trial for the treatment of acne with a topical nitric oxide-releasing drug called SB204. Phase II trial results report significant clinical improvement. It works by directly killing *C. acnes* and inhibiting the release of proinflammatory cytokines<sup>11</sup>.

## Phototherapy

Ultraviolet light, photodynamic therapy, and ALA-PDT have been found to reduce the density of bacteria in lesions<sup>4,22</sup>. Tao et al<sup>3</sup> showed that ALA-PDT treatment led to clinical improvements in acne severity with a significant reduction in *C. acnes*. ALA-PDT did not show any effect on *S. epidermidis*, which reinforces the theory that this bacterium plays a protective role against acne.

## Antibiotics

Treatment of acne with antibiotics decreases the diversity of the skin microbiota, since they do not only affect *C. acnes*. This raises concerns about how commensal bacteria and their protective effects on the skin could be impaired. Given the excessive use of antibiotics to treat acne, it is important to know its repercussions on the skin microbiota<sup>2,23</sup>.

Recently, Chien et al<sup>4</sup> examined changes in the microbial composition of the skin of acne patients after oral antibiotic therapy. Four weeks of minocycline caused a 1.4-fold reduction of *C. acnes* in acne patients, however, after 8 weeks of discontinuing the drug recolonization occurred. As the protective effects of commensal bacteria decrease, there is an increase in opportunistic microorganisms, such is the case of *Pseudomonas*, which presented a 5-fold increase after taking antibiotics for 4 weeks. This explains the increase in cases of folliculitis in patients using antibiotic therapy for acne.

The indiscriminate use of antibiotics for acne has caused an increase in resistance to them. Resistance to topical macrolides of more than 50% has been reported in *C. acnes*. To reduce this, effective alternative medications to antibiotics are required to treat acne. It can take years for the skin microbiota to recover after antibiotic use, leading to dysbiosis and promoting long-term susceptibility to certain diseases<sup>13,20</sup>.

## Prebiotics and probiotics

Prebiotic strategies allow manipulation of the composition of the microbiota by selectively inhibiting harmful bacteria while conserving beneficial bacteria<sup>9</sup>. For this reason, interest in this therapy has been increasing in recent years.

Some scholars<sup>11</sup> have shown that oral prebiotics and probiotics reduce systemic markers of oxidative stress, inflammation, and insulin resistance, and also regulate the release of inflammatory cytokines, reducing chronic inflammation in the body, including the skin. Gut dysbiosis has been linked to acne and other skin conditions. Oral probiotics such as *Lactobacillus acidophilus*/*Bifidobacterium bifidum* can resolve dysbiosis and help improve skin appearance. With this we can intuit that the addition of probiotics to conventional acne treatment would mean a significant improvement for patients<sup>24</sup>.

The concept of antagonism between *C. acnes* and *S. epidermidis* could be applied to develop topical probiotics against acne<sup>11</sup>. Twice daily application of a cosmetic product containing selected ginseng, black currant or pine plant extracts to human skin for a total of three weeks was found to be effective in inhibiting the growth of *C. acnes*, while *staphylococci* were not affected<sup>9</sup>. Topical probiotics also increase ceramide production, reducing skin inflammation<sup>2</sup>. One clinical trial reported reductions in mild acne lesions and erythema, as well as increases in skin barrier recovery using *Lactobacillus plantarum*<sup>20</sup>.

## Bacteriophages

Bacteriophages are viruses that can infect and kill bacteria but are probably the least understood component of the human microbiome. New studies<sup>11</sup> have shown that *C. acnes* bacteriophages are more abundant in patients with healthy skin. An increase in these has been found in older people, which could explain the decrease in acne in these age groups, together with the decrease in androgens. More research is still needed on this.

## Vaccine

There is currently a line of research on the creation of a vaccine for acne vulgaris. What is intended is to develop an immune response against the CAMP factor, the results have been promising. These antibodies against CAMP would achieve a decrease in the growth of *C. acnes* and proinflammatory cytokines. There is still a long way to go for the full development of a vaccine, however progress is satisfactory<sup>2</sup>.

## Skin microbiota transplants

Just as fecal microbiota transplants have worked to control *Clostridium difficile*, skin microbiota transplants could serve to control the development of *C. acnes*. This method would manage to restore the dysbiosis bringing it to a balance, thus avoiding the overdevelopment of a single bacterium<sup>25</sup>. The microbiome of the transplanted skin has not yet been able to persist long enough, so complementary studies are needed focused on how to optimize the efficiency of colonization<sup>2</sup>.

## CONCLUSIONS

New advances in the description of the skin microbiota have helped to obtain a more comprehensive view of the management of inflammatory skin diseases, such as acne. Due to the physical and psychosocial repercussions of acne, it is necessary to rethink the current management of this pathology. It is important to continue research on the potential modification of this microbiota to achieve a significant and lasting benefit against acne.

## Conflict of Interest

The authors declare no conflict of interest.

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## Authors' Contributions

Diana María Ibarra Tostado: Study design and planning; writing and editing of the manuscript; data collection, analysis and interpretation; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

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