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Acne, the Skin Microbiome, and Antibiotic Treatment

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Abstract

Acne vulgaris is a chronic skin disorder involving hair follicles and sebaceous glands. Multiple factors contribute to the disease, including skin microbes. The skin microbiome in the follicle is composed of a diverse group of microorganisms. Among them, *Propionibacterium acnes* and *Malassezia* spp. have been suggested in acne development through influencing sebum secretion, comedone formation and inflammatory response. Antibiotics targeting *P. acnes* have been the mainstay in acne treatment for the past four decades. Among them, macrolides, clindamycin and tetracyclines are the most widely prescribed. As antibiotic resistance becomes an increasing concern in clinical practice, understanding the skin microbiome associated with acne and the effects of antibiotic use on the skin commensals is highly relevant and critical to clinicians. In this review, we summarize recent studies of the composition and dynamics of the skin microbiome in acne and the effects of antibiotic treatment on skin microbes.

1 Introduction

Acne vulgaris (commonly called acne) is a common, chronic skin disease that arises in the hair follicle and often involves inflammation. Approximately 85% of adolescents and young adults are affected by the disease [1], while moderate and severe acne accounts for 15%–20% of cases [2]. Based on the data from the global burden of disease study in 2013, acne accounted for 0.29% of all skin conditions, which contributed 1.79% to the global burden of disease. Acne ranks the second among the most common dermatological conditions after dermatitis [3].

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Compliance with Ethical Standards

Conflicts of interest: The Regents of the University of California is the owner of three patent applications related to acne and/or healthy skin, which list H.L. as one of the inventors. H.L. is a co-founder and shareholder of SkinomiX Biosciences Inc. and Naked Biome Inc. H.X. states no conflict of interest.

Four factors have been thought to contribute to acne: hyper-secretion of sebum, abnormal proliferation and differentiation of keratinocytes in the hair follicle, bacterial colonization, and host inflammatory response [4]. Among these factors, the skin commensal *P. acnes* is thought to mediate inflammatory response and lead to sub-clinical and inflammatory acne lesions [5].

Skin is colonized by hundreds of microorganisms, which occupy different cutaneous environmental niches and form various communities [6]. When the normal flora is disturbed or the host immune defense is weakened, opportunistic microorganisms may trigger or aggravate certain skin diseases [7]. The relationship between skin microorganisms and acne has long been implicated but not fully elucidated. With the rise of the microbiome field in recent years, new findings from the studies of the skin microbiome provided improved understanding of the role of skin microorganisms in health and acne [8–12].

Antibiotics have been an effective and widely used treatment for acne in the past four decades. However, worldwide increase of antibiotic resistance due to frequent and long-term use of antibiotics raises significant concern regarding how the commensal skin microbiome and its protective role for the skin are affected. A better understanding of the relationship among acne, the skin microbiome, and antibiotic treatment may provide new insight on the treatment of the disease while restoring a healthy microbiome.

2 The skin microbiome and acne

Skin is the largest organ in the body. The average area of the skin in adults is $1.8 - 2 \text{ m}^2$. If considering hair follicles, sweat gland ducts, and other skin appendages, the body surface area can reach to 30 m^2 according to Meisel *et al.* [13]. Various heterogeneous communities of microorganisms, including bacteria, viruses, fungi, and mites, occupy different skin environmental niches and appendages [6, 14].

Bacteria are the most dominant and best studied members of the skin microbiome. More than 40 bacterial genera have been identified on human skin, mainly belonging to four phyla, Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [8–10]. The proportions of these bacteria in each community vary depending on individuals, body sites, as well as skin micro-environments [9, 11, 15]. *Propionibacteria*, *Staphylococcus* and *Corynebacteria*, and Gram-negative bacteria are predominant in the sebaceous area, moist skin, and dry skin, respectively. Skin bacteria are not only diverse in taxonomy, but also vary in quantities. Culture-based methods suggest that the total colony-forming units per cm^2 skin varies from 3.7×10^4 to 1.2×10^6 [16]. It has been estimated that 10^6 aerobic bacteria are present per cm^2 of moist skin, whereas less than 10^2 aerobic bacteria and up to 10^6 anaerobes are present per cm^2 of dry skin [17]. The balance of the skin microbiome and its interaction with the host affect the states of skin health and disease.

2.1 *P. acnes* and acne

P. acnes was first observed by Unna in 1896 and later isolated by Sabouraud from acne lesions in 1897 [18, 19], which led to the speculation of its involvement in acne pathogenesis. *P. acnes* was initially named as *Bacillus acnes*, and was changed to

Corynebacterium acnes, as it is morphologically similar to *Corynebacteria*. The name was changed again in 1940s to *Propionibacterium acnes* due to its production of propionic acid [20]. With the identification of distinct phylogenetic groups based on multi-locus sequence typing (MLST) and whole genome sequencing, it was proposed in 2015 to name the three major types as three subspecies known as *P. acnes* subsp. *acnes*, *P. acnes* subsp. *defendens*, and *P. acnes* subsp. *elongatum* [21]. In 2016, a new genus, *Cutibacterium*, was proposed for the cutaneous propionibacteria [22], as such, *P. acnes* is renamed again to *Cutibacterium acnes*, although the name of *P. acnes* continues to be used in the field in an effort to reduce the confusion between *Cutibacterium* and *Corynebacterium* [23].

In the pilosebaceous unit, where acne arises, *P. acnes* is the most prevalent and abundant species accounting for ~90% of the microbiome [10, 12]. The scalp and facial skin harbor the highest density of *P. acnes* ($\sim 10^5$ to $10^6/\text{cm}^2$), followed by the upper limbs and torso, and the lower limbs have the lowest density of *P. acnes* ($\sim 10^2/\text{cm}^2$) [24]. The abundance of *P. acnes* also varies with age. It is low on the skin of children before puberty, but gradually increases with age starting from adolescence to adulthood, and then decreases in older persons of age above 50 years [24–26].

Several mechanisms of acne pathogenesis involving *P. acnes* have been proposed, including changes in sebaceous gland activity, comedone formation, and host inflammation.

- Increasing sebum secretion: The colony-forming units of *P. acnes* in the pilosebaceous unit are correlated with the total amount and composition of the lipids on the skin. The secreted sebum is used by *P. acnes* as metabolic substrates to promote its growth [24, 27]. *P. acnes* further enhances sebum secretion by increasing the activity of diacylglycerol acyltransferase, and exacerbates preexisting androgen-related seborrhea [28].
- Promoting comedone formation: *P. acnes* breaks down triglycerides secreted from sebaceous glands and releases free fatty acids. Porphyrins secreted by *P. acnes* are catalytic factors for the oxidation of squalene, a main component of sebum. Free fatty acids and oxidized squalene promote comedogenesis [29]. Comedones form due to retention of hyper-proliferating

keratinocytes/corneocytes in the follicular duct. Studies have shown that *P. acnes* not only forms biofilm to increase keratinocyte adhesion [30, 31], but also activates the insulin-like growth factor 1 (IGF-1)/IGF-1 receptor signaling pathway to up-regulate filaggrin expression. The up-regulation of filaggrin expression leads to increased levels of integrin- $\alpha 3$, $\alpha 6$ s, and $\alpha 6\beta 6$, and thereby affects keratinocyte proliferation and differentiation [32, 33] and comedone formation.

- Inducing/aggravating inflammation: Upon binding to toll-like receptors (TLR) $\alpha 2$ and $\alpha 4$ on the surface of keratinocytes, *P. acnes* induces monocytes and other cells to produce interleukin (IL)- 1α , IL- 1β , IL-6, IL-8, IL-12, tumor necrosis factor (TNF)- α , interferon, chemotactic factors, β -defensin, and other cytokines and polypeptides, thereby triggering and/or aggravating inflammatory responses [34–37]. *P. acnes* also activates the classical and alternative complement pathways to form C3a and C5a, which increase the vascular permeability and the

involvement of chemotactic leukocytes in inflammatory responses [38, 39]. Furthermore, *P. acnes* stimulates sebocytes and promotes the conversion of naïve T cells into Th17 cells by secreting transforming growth factor- β , IL-1 β , and IL-6. *P. acnes* can also activate the NLRP3 inflammasome to induce the release of IL-1 β , IL-8, and TNF- α from sebocytes [40]. *P. acnes* produces lipases, proteases, hyaluronidases, and phosphatases, and induces multiple cells to produce matrix metalloproteinases, thus directly impairing hair follicles, sebaceous glands, and dermal extracellular matrix, and ultimately aggravating inflammation [41–43].

While a causal role of *P. acnes* in acne pathogenesis remains to be proven, *P. acnes* is also considered an important commensal for skin health. It releases free fatty acids through triglyceride hydrolysis to maintain low skin pH and inhibits the colonization of pathogenic bacteria, such as *Staphylococcus aureus* and *Streptococcus* [44–46]. *P. acnes* typing and genome sequencing efforts suggest that *P. acnes* can function as a commensal or an opportunistic pathogen depending on the strains and the disease [10, 47, 48]. *P. acnes* was previously classified into two types, I and II, based on serum lectin response, cell wall sugar content, and susceptibility to phages [49]. Later, an additional phylotype, type III, was defined [50]. Within type I, *P. acnes* can be further separated into clades IA1, IA2, IB, and IC based on the Belfast MLST scheme [51] or I-1a, I-1b, and I-2 based on the Aarhus MLST scheme [52]. With the whole genome sequencing of a large number of *P. acnes* isolates [48], higher resolution of the phylogeny became available. Based on the single nucleotide polymorphisms (SNP) identified throughout the core genome regions, *P. acnes* can be classified into phylogenetic clades IA-1, IA -2, IB-1, IB -2, IB -3, IC, II, and III [10, 48]. Table 1 summarizes the corresponding nomenclatures of the phylogenetic clades based on the whole genome sequences and different MLST schemes [48, 51, 52]. Additionally, based on the 16S ribosomal RNA (rRNA) sequences, *P. acnes* can be classified into multiple ribotypes (RTs) with RTs 1–10 being the most common ribotypes found in the population [10]. These classifications are useful in understanding the associations between *P. acnes* strains and disease or healthy skin (Table 1). Strains from clades IA-2, (mainly RT4 and RT5), IB-1 (RT8), and IC (RT5) are strongly associated with acne. Type II strains, including RT2 and RT6, are associated with healthy non-acne skin. Strains from clades IA-1, IB-2, and IB-3 have been found in both healthy individuals and acne patients [10, 48, 53]. Type III strains are rarely found on the facial skin, however, are abundant on the back and have been linked to the skin condition progressive macular hypomelanosis [54, 55].

Recent studies of *P. acnes* and the skin microbiome have shed new light on the strain-level differences in the roles of *P. acnes* in health and acne. Fitz-Gibbon *et al.* revealed that certain *P. acnes* strains were enriched in acne patients while some other strains were mostly found in healthy skin [10]. Tomida *et al.* further compared the genomes of *P. acnes* strains isolated from healthy individuals and patients with acne, and identified that the non-core genomic regions of *P. acnes* strains associated with acne contain extra virulence-related genes [48] when compared to other strains. Johnson *et al.* showed that acne-associated strains produce more porphyrins, which are a group of proinflammatory molecules inducing inflammation in keratinocytes and aggravating tissue damage by producing reactive oxygen species [56]. Kang *et al.* further demonstrated that vitamin B₁₂ supplementation alters the transcriptional

activities and increases porphyrin production in acne-associated *P. acnes* strains, while health-associated *P. acnes* strains do not respond to vitamin B₁₂ supplementation [57]. Furthermore, several recent studies have shown that acne-associated *P. acnes* strains induce significant inflammatory responses in keratinocytes, sebocytes, and peripheral blood mononuclear cells, while health-associated strains do not [58–61]. These studies suggest that different strains of *P. acnes* may play different roles in skin health and acne pathogenesis.

Multiple other skin bacteria colonize the external surface of the skin, some of which may play a role in maintaining skin health or exacerbating diseases. *Staphylococcus epidermidis*, *Staphylococcus hominis*, and other coagulase-negative staphylococcal species can be found on the skin of healthy and acne individuals [62]. In acne skin, the relative abundance of *S. epidermidis* increases at the expense of *P. acnes* [49]. Several studies suggest that *P. acnes* can be inhibited by *S. epidermidis*. Wang *et al.* showed that *S. epidermidis* strains could produce succinic acid which has anti-*P. acnes* activity [63]. The study by Christensen *et al.* suggested that *S. epidermidis* possessed a functional ESAT-6 secretion system, which could inhibit *P. acnes* growth through polymorphic toxins that are antibacterial [64]. Additionally, it was shown that *S. epidermidis* secretes staphylococcal lipoteichoic acid, which could reduce *P. acnes*-associated inflammation by inducing expression of miR-143 and inhibiting TLR-2 expression in keratinocytes [65]. These studies suggest that Staphylococci, especially *S. epidermidis*, may protect skin against acne. However, this hypothesis requires further examination.

2.2 *Malassezia* and acne

Malassezia has been thought to induce acne [66]. *Malassezia* is the most abundant fungal organism on the skin, co-existing with *P. acnes* and other bacterial species. In a study by Hu *et al.*, acne lesions were significantly reduced after administration of antifungal drugs. The authors suggested that *Malassezia*, not *P. acnes*, was potentially the cause of refractory acne [67]. The findings from several other studies are in support of this hypothesis. Song *et al.* and Numata *et al.* reported that *Malassezia restricta* and *Malassezia globosa* can be isolated from young acne patients [68, 69]. Akaza *et al.* showed that the lipase activity of *Malassezia* is ~100 times higher than that of *P. acnes* [70]. *Malassezia* can also hydrolyze triglycerides in the sebum to produce free fatty acids, which may affect the abnormal keratinization of hair follicular ducts, chemotize polymorphonuclear neutrophils [71, 72], and promote secretion of pro-inflammatory cytokines from keratinocytes and monocytes [73, 74]. The role of *Malassezia* in acne pathogenesis remains to be further investigated.

3 Antibiotics in acne treatment

Bacterial factors and inflammation are both thought to contribute to acne pathogenesis. Although acne is not a typical infectious disease, the use of antibiotics has been the mainstay in acne treatment for over 40 years. Topical antibiotics are largely used for their bactericidal effects against *P. acnes*. Oral antibiotics have anti-inflammatory effects in addition to antimicrobial effects, which target both *P. acnes* and host immune response [4, 75, 76].

Based on several treatment guidelines and expert consensus documents, macrolides, clindamycin, and tetracyclines are recommended as the first-line therapy in acute

inflammatory phase of acne [77–82]. Erythromycin, clarithromycin, roxithromycin, and azithromycin are macrolides. Clindamycin belongs to lincosamides. Tetracyclines for acne treatment mainly include tetracycline, doxycycline, and minocycline. The effects of macrolides, clindamycin, and tetracyclines on the skin microbiome, including the target bacterium *P. acnes* and other non-target bacteria, and associated issue of antibiotic resistance are discussed below. Several other antibiotics, such as trimethoprim-sulfamethoxazole, levofloxacin, rifampin, dapson, and metronidazole, may also be used in acne treatment. However, current data on the effects of these antibiotics are limited in scope and quality. Additional studies are needed to address multiple knowledge gaps regarding these antibiotics.

3.1 Influence of antibiotic use on *P. acnes*

3.1.1 Effect of macrolides and clindamycin—Erythromycin and clindamycin are widely used in the last 40 years in acne treatment, and are still frequently prescribed by physicians. Long-term use of oral macrolides for acne treatment facilitates the increase of macrolide-resistant *P. acnes* strains [83]. In recent years, increasing levels of resistance of *P. acnes* to macrolides and clindamycin have been reported in several major regions of the world [83]. In some countries, the resistance of *P. acnes* to erythromycin is over 50% [83, 84], and the resistance to azithromycin reaches 82%–100% [85, 86]. Similarly, the resistance of *P. acnes* to clindamycin increased from 4% in 1999 to 90.4% in 2016 [85, 87]. There is a high proportion (52%) of acne patients who carried at least one *P. acnes* strain resistant to clindamycin [88]. When topical clindamycin is administered for 16 weeks for acne treatment, the amount of resistant *P. acnes* is increased by 16 times from the baseline [89]. After antibiotic treatment is ended, tolerant *P. acnes* strains may remain on the skin for a considerable long period of time, and the presence of resistant *P. acnes* strains manifests as a re-occurrence of acne [4]. Furthermore, when patients are treated again with antibiotics, the efficacy of such drugs is reduced or voided [4, 90].

Different *P. acnes* strains exhibit varying degree of antibiotic-resistance. Based on multiple recent studies of *P. acnes* isolates collected from different geographic areas including Italy, Sweden, UK, Australia, USA [10, 47, 51, 91], Denmark [88], and Greece [92], RT4 and RT5 strains, which mostly are clonal complex 3 (CC3) strains and some CC18 strains based on MLST [51, 88], accounted for 85%–95% of the antibiotic resistant strains [47, 51, 91, 92]. The underlying molecular mechanisms for resistance include point mutations G2057A, A2058G, and A2059G in the domain V of 23S rRNA, as well as the presence of the *erm(X)* gene [92–96]. It is common that resistance to erythromycin is associated with cross-resistance to clindamycin [93]. Cross-resistance to erythromycin and clindamycin of *P. acnes* isolates from acne patients varies from 11.6% to 100% as reported in different studies [51, 97–100].

To reduce the emergence of antibiotic resistance, it is currently recommended to use topical antibiotics in combination with benzoyl peroxide (BPO) or retinoid in acne treatment [83]. Studies have shown that combining clindamycin with BPO or retinoid for topical application not only significantly reduced the total number of *P. acnes* on the skin, but also lowered antibiotic resistance of *P. acnes* to erythromycin and clindamycin [101].

3.1.2 Effect of tetracyclines—Tetracyclines are another class of antibiotics frequently used for treating moderate to severe acne. Although this group of antibiotics is still largely active against the majority of *P. acnes* isolates, antibiotic resistance is rising and needs attention of the medical field. The rate of resistance to tetracyclines differed from 2% to 30% in studies from different regions in recent years [86, 97, 99, 101]. In parallel, resistance to doxycycline among isolated *P. acnes* strains varied between 2% and 44.2% [85, 86, 97, 101]. The combined resistance to tetracycline and doxycycline ranged from 1.2% to 100% in different groups of patients [99, 102]. In contrast to high resistance rate to tetracycline and doxycycline, lower resistance rate to minocycline (less than 2%) was observed in Europe, Latin America, Northern American and parts of Asia. This makes minocycline the most effective agent in the tetracycline class for acne treatment [85, 92, 97]. The resistance mechanism against tetracyclines is a G1058C mutation in *P. acnes* 16S rRNA gene [96]. Additionally, an amino acid substitution in the ribosomal S10 protein contributes to reduced doxycycline susceptibility [103].

3.2 Influence of antibiotic use on other skin bacteria

3.2.1 Effect of macrolides and clindamycin—The use of macrolides and clindamycin in acne treatment results in resistance in other skin bacteria in addition to *P. acnes*. At least 30% of the *S. epidermidis* isolates from acne patients were resistant to erythromycin, roxithromycin, and clindamycin [104]. Harkaway *et al.* reported that after 12-week treatment with topical erythromycin alone, erythromycin-tolerant *S. epidermidis* became predominant on skin surface, and the relative abundance of *S. aureus* at nostrils rose from 15% to 40% [105]. Similarly, Mills *et al.* reported that in acne treatment with topical erythromycin, the proportion of patients with erythromycin-tolerant staphylococci on the face was 87% at the baseline, and increased to 98% at week 12 of treatment [106]. Furthermore, the proportion of patients with resistant staphylococci was only slightly reduced 12 weeks after drug withdrawal. The average density of tolerant bacteria at non-treated sites, such as the back, increased at the end of the treatment. Transmission of such bacteria to different sites may cause serious consequences [106]. Like macrolides, clindamycin exerts selection pressure on both *P. acnes* and staphylococci. The study by Nakase *et al.*, which analyzed the correlation of antimicrobial resistance between *P. acnes* and *S. epidermidis*, reported that clindamycin-resistant *S. epidermidis* strains were isolated from more than 80% of the patients who also carried clindamycin-resistant *P. acnes* [95].

3.2.2 Effect of tetracyclines—There are few established data on the effect of tetracyclines on the skin bacteria besides *P. acnes*. Doxycycline 40 mg modified-release has been used for the treatment of inflammatory lesions in moderate and severe acne. Limited evidence suggested that this dose showed no effect on the normal skin flora as well as the rate of antibiotic resistance while being effective in reducing acne lesions [76, 107].

Lymecyclin and sarecycline are new members of tetracyclines in acne therapy. A recent study based on 16S rRNA sequencing demonstrated that six weeks after lymecyclin treatment, the relative abundance of *Propionibacterium* on the cheeks of patients decreased, but the relative abundances of *Streptococcus*, *Staphylococcus*, *Micrococcus*, and *Corynebacterium* increased. However, changes in the above microbial community after drug

withdrawal were not investigated [108]. Sarecycline (two Phase 3 clinical trials completed in 2017) has a narrow antibacterial spectrum relative to other tetracyclines. It might have less selective pressure on enteric gram-negative bacteria, but there are no available data on its influence on the skin microbiome [109].

3.3 Applications of antibiotics in acne treatment

Growing prevalence of antibiotic resistance in *P. acnes* and other skin commensal bacteria becomes increasingly alarming. For mild-to-moderate acne, topical antibiotic monotherapy is not recommended. Topical retinoid, BPO, or a combination therapy (topical retinoid + BPO, topical antibiotic + BPO, topical retinoid + topical antibiotic + BPO) is recommended [110]. For moderate-to-severe acne, recommended first-line treatment is oral antibiotics combined with BPO and/or a topical retinoid. Oral antibiotic monotherapy is not recommended [111]. To reduce antibiotic resistant microorganisms on the skin, as alternative treatments, BPO can be used for at least 5–7 days between antibiotic courses [5]. Oral contraceptives or anti-androgens may be another alternative for some female patients. To obtain a better clinical efficacy and reduce antibiotic resistance, information of past exposure to macrolides or clindamycin should suggest avoidance of prescription of these antibiotics. Given that some acne patients are colonized by antibiotic-resistant *P. acnes* strains, Sinnott *et al.* recommended that swabbing, culturing, and testing for resistant strains may be one way to help avoid chronic use of ineffective antibiotics [112].

The recommended minimum course of acne treatment with oral antibiotics is 6–8 weeks. Oral antibiotics may continue to be used after taking effect, but should not be used for longer than 12 weeks [83, 113]. However, it is reported that in practice, 17.5% of antibiotic treatments last 6 months and 7% of the treatments last over 9 months, with an average treatment time of 125–129 days [114, 115]. The long-term use of antibiotics may significantly alter the skin microbiome and increase drug resistance. Future longitudinal studies of long-term use of antibiotics may shed light on its effect on the composition and dynamics of the microbiome [83].

4 Conclusions and outlooks

Although the pathogenesis mechanisms of acne have not yet been fully elucidated, it is recognized that *P. acnes* and inflammatory response play important roles in the development of the disease. The use of bactericidal and anti-inflammatory antibiotics remains an important strategy for treating acne. Thus, rational selection of antibiotics according to the classification of *P. acnes* strains and corresponding drug susceptibility is preferred. However, this recommendation has not yet gained sufficient attention in clinical practice.

Given the rapid emergence of antibiotic resistance on the global scale and considering the effects of antibiotic use on the human microbiome, alternative clinical practice to antibiotic prescription in treating microbe-related diseases has become urgent. A recently published study suggested a potential vaccination approach against acne by targeting Christie-Atkins-Munch-Petersen (CAMP) factor as an antigen [116].

Meanwhile, other studies showed promises in microbiome-based therapies, which may shift the balance among the microbial members, influence the function of immune cells, and prevent diseases while restoring a healthy microbiome [117–119]. In one such study, Nakatsuji *et al.* showed that reintroduction of coagulase-negative Staphylococcus (CoNS) strains, which produce antimicrobial peptides, to patients with atopic dermatitis decreased *S. aureus* colonization on the skin. The study demonstrated how commensal skin bacteria can defend against pathogens and suggested that correcting microbiome dysbiosis may potentially be used to treat or improve certain conditions. Future studies on how to effectively reduce the load of pathogenic microorganisms and inflammation while preserve the balance of the commensal microflora may lead to potential new therapies.

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Key Points:

Acne vulgaris is a common and multi-factorial skin disease, affecting 85% of adolescents and young adults.

P. acnes is the dominant component of the skin microbiome in the pilosebaceous unit. Certain strains of *P. acnes* have been linked to acne pathogenesis. Other microorganisms such as *Malassezia* may also play a role in acne.

Antibiotics, mainly macrolides, clindamycin, and tetracyclines, have been the mainstay for acne treatment, and influence the composition and dynamics of the skin microbiome. Antibiotic resistance has become increasingly prevalent worldwide and thus there is an urgent need for new acne therapies.

Table 1Classifications and associations of *P. acnes* strains with acne and healthy skin

Clade (based on whole genome sequence comparison)	Clade (based on Belfast eMLST [51])	Clade (based on Aarhus MLST [52])	Ribotype (RT) [10]	Acne	Healthy skin
IA-1	IA1	I-1a	RT1		
IA-2	IA1	I-1a	RT4, RT5		
IB-1	IA1	I-1b	RT8		
IB-2	IA2	I-1a	RT3		
IB-3	IB	I-2	RT1		
IC	IC	n/a	RT5		
II	II	II	RT2, RT6		
III	III	III	NA		

NA: Not available.