Cutibacterium acnes Dysbiosis

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This research presents the virulence factors, clinical relevance, and current treatments of *C. acnes*, highlighting its association with AV, post-surgical infections, and other diseases. It also explores alternative innovative therapies such as phage therapy in development/research that are gaining prominence, with a growing focus on personalized medical approaches.

Keywords: Cutibacterium acnes ; antibiotic resistance ; personalized medicine ; phage therapy

1. Taxonomy and Nomenclature

C. acnes was firstly described as a member of the *Bacillus* species and of the *Corynebacterium* species [1]. Ever since its first isolation, *C. acnes* has suffered multiple taxonomic reclassifications due to the technological improvements in research and diagnosis, such as proteomic and genomic analysis. In 2016, *C. acnes* was included in the *Propionibacterium* genus. However, the known genus was later divided into four genera, namely, *Propionibacterium*, *Cutibacterium*, *Acidipropionibacterium*, and *Arachnia*. *C. acnes* was included in the genus *Cutibacterium,* alongside with *Cutibacterium avidum*, *Cutibacterium granulosum*, *Cutibacterium namnetense,* and *Cutibacterium modestum* [2]. Nowadays, *C. acnes* is often described by the following subspecies: acnes (*C. acnes* type I), *defendens* (*C. acnes* type II), and *elongatum* (*C. acnes* type III) [2].

2. C. acnes Infection and Virulence Factors

Cutibacterium acnes, or *C. acnes*, was firstly isolated from a patient with chronic acne vulgaris (AV) in the 1900s. It constitutes a healthy human commensal, Gram-positive, and anaerobic facultative bacterium [3]. *C. acnes* has a broad distribution on the human body, including face, supra, subgingival plaque, back, chest, groin, bend of elbow, intestine, inguinal canal, forearm, palm, plantar heel, and toe, as part of the skin's microbiota [2][4]. Under normal circumstances, *C. acnes* does not cause harm and coexists peacefully with other microorganisms. In some situations, however, there can be an overgrowth that can occur when factors like excess sebum production, hormonal changes, or inflammation create conditions favorable for bacterial proliferation. This proliferation permits the formation of biofilms that allow the bacterium to adhere to surfaces, including hair follicles and sebaceous glands on the skin. These biofilms constitute one of several virulence factors that bacteria possess as part of their defense mechanism (**Figure 1**) [3].

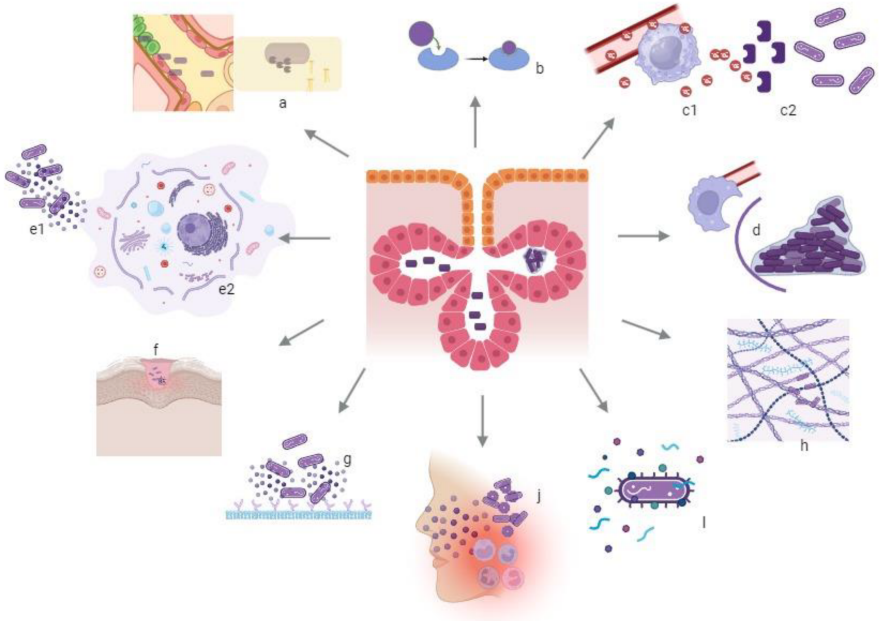

Figure 1. *C. acnes* virulence factors allow the bacteria to cause an infection and to survive the host defenses. There are several mechanisms in *C. acnes* to promote the infection, the evasion of the host defenses, host tissue damage, and invasion, such as a—Lipases can break down sebum and release the free fatty acids, influencing the bacterial capacity to adhere to other cells and surfaces which leads to the formation of comedones; b—Polyunsaturated Fatty Acid Isomerase promotes the catalyzation and the isomerization of linoleic acid; c—Reactive oxygen species (ROS) produced by macrophages (c1) are reduced by *C. acnes*' radical oxygenase, inactivating its deadly effects (c2); d—Bacterial biofilms consist of an extracellular matrix composed of proteins, polysaccharides, and/or extracellular DNA. Biofilm production protects *C. acnes* against the host immune system, most likely by creating a barrier that protects the bacteria from harmful environments such as antibiotics; e—Christ–Atkins–Much–Petersen Factors (CAMP factors) produced by *C. acnes* (e1) lead to tissue damage by creating membrane pores that promote the lysis of the host cells (e2); f—Hyaluronate lyase promotes the degradation of the host epidermis and dermis extracellular matrix components, such as glycosaminoglycans and hyaluronic acid, allowing the bacterial invasion in the host tissues by the degradation of the skin layers and dissemination of the inflammation; g—Glycosidase enzymes break carbohydrate structures such as host glycolipids and glycoproteins, which permits *C. acnes* to use host carbohydrates to grow; h—*C. acnes*' DsA1 binds to the dermatan sulfate and to fibrinogen protein, involved in the biofilm formation; j—Sialidases remove sialic acid within sialoglyco conjugates, a highly immunogenic protein, although their function in the bacteria pathogenicity is still not clear; l—Sortases F permit the attachment to different proteins, like adhesion factors. These en-zymes are produced in the cytoplasm and promote the transportation of proteins to the bacterial wall.

The virulence ability comprises several molecular mechanisms that microorganisms use to infect the host cells and tissues. These virulence factors, summarized in **Table 1**, are associated with bacterial adhesion and tissue invasion/degradation of the host tissues, allowing the microorganism to overrun the host's immune system and antibiotic treatments [3].

Table 1. *C. acnes* virulence factors and respective function.

Virulence Factors	Function
Lipases	Enzymes involved in the metabolization of sebum and free fatty acid release and triglycerides.
Polyunsaturated Fatty Acid Isomerase	Catalyzation and isomerization of linoleic acid.
Hyaluronate Lyase	Promotes the degradation of hyaluronic acid andolaolablablaother glycosaminoglycans, such as chondroitin-4-sulfate, chondroitin-6-sulfate, and dermatan sulfate, of the extracellular matrix in the epidermis and dermis.
Glycosidase	Disruption of carbohydrate and glycan structures that constitute the eukaryotic host glycolipids and glycoproteins.
Sialidase	Discard the sialic acid from sialoglycoconjugates.
Radical oxygenase	Reduction of the oxygen free radicals.
Sortase F	Capacity to covalently attach to various proteins, including adhesion factors.
Porphyrin	Fluorescent molecules that can stimulate inflammatory host reactions.
Biofilm	Matrix that provides bacterial resistance to adverse compounds, such as antibiotics
Adhesin dermatan-sulfate protein	Molecular surface components that recognize adhesive molecules of the matrix.

Virulence Factors	Function
Christie–Atkins–Munch–Petersen Factors	Promote the formation of pores in host cells membranes.

It is important to note that not all individuals carrying *C. acnes* will develop this pathogenicity. The transition from commensal to pathogenic depends on various factors, including host genetics, the local microenvironment, and the immune response. The mechanisms underlying these transitions are complex and are an active area of research in dermatology, immunology, and microbiology.

3. C. acnes Clinical Relevance

In acne, *C. acnes* can influence hair follicles, causing them to become plugged with sebum, dead skin cells, and bacteria. This creates an ideal environment for the formation of comedones (blackheads and whiteheads). Virulence factors, such as lipases and proteases, can then exacerbate inflammation and tissue damage, breaking down lipids and proteins, hence contributing to the pathogenesis of acne lesions [3]. In post-surgical infections, *C. acnes* may enter sterile tissues during surgical procedures through contaminants from the patient's skin, the air in the operating room, surgical instruments, or even the surgical team [5]. Considering that biofilms can be formed on surgical implants, tissues, or medical devices, the treatment can become a challenge, as the access to the bacteria is limited, due to the biofilm barrier, leading to bacteria proliferation and localized infections [6].

Since *C. acnes* can metabolize the lipids produced by the human's sebaceous glands, the density of this bacterium tends to be higher in lipid-rich areas of the human body, such as the face and upper thorax [7]. This distribution is correlated with the risk of infections observed in iatrogenic procedures (post-surgical procedures in shoulders, heart, hip, and others) and to the manifestation of AV. In fact, a study performed on the University affiliated with the Hospital Network in Wisconsin identified 77 patients from post-operative cultures that tested positive for *C. acnes*: 61% were neurosurgical, 17% orthopedic, 9% cardiothoracic, 8% general surgery, and 5% from other departments [7]. The infections caused by *C. acnes* were associated with a significant morbidity in these patients and are often underestimated due to the difficulties regarding growth and detection of this bacterium in cultures [6]. Although post-surgery shoulder infections can happen due to several other microorganisms, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, studies regarding post-surgical infections, such as shoulder arthroplasty, detected *C. acnes* as the main cause in 50 to 60% of the cases [8]. Moreover, infective endocarditis, i.e., the occurrence of an infection on a heart valve and endocardial surfaces, that can lead to a systematic infection, thus raising the risk of patient mortality [9], showed that *C. acnes* has been responsible for up to 3.5% of the infection endocarditis cases [10].

Due to the capacity of *C. acnes* to modulate the inflammatory system of the host, it is also often related to sarcoidosis (SC) and prostate cancer [7].

SC is a granulomatous disorder that forms granulomas with Th1 and Th17.1 cells and constitutes a pathological condition that can affect multiple organs, often affecting the lungs and the peripheral lymph nodes. Recently, researchers mentioned the possibility of *C. acnes* infection being on the list of possible causes for the development of SC in humans, since *C. acnes* has been detected in tissues affected by SC with high frequency [11].

In prostate cancer, the inflammatory modulation has been related with prostate carcinogenesis [12]. Indeed, it has been described that the presence of *C. acnes* in patients with prostate cancer correlates to a higher infiltration of regulatory T CD4(+), FoxP3(+) cells in prostatic tissues. Scientists discovered also that this infiltration correlates to the aggressiveness of the prostatic cancer in patients positive for *C. acnes* [13].

Acne Vulgaris (AV)

AV is a multifactorial disease that affects pilosebaceous units, leading to inflammation and keratinization. AV is developed by the androgen increase in the puberty, consequent increase in the sebum production, and *C. acnes* colonization in the skin follicle [14]. This colonization leads to the activation of local inflammation and increases the host's tissue damage [14]. Patients with AV usually begin by presenting comedones (noninflammatory lesions) that may consequently evolve to papules (inflammatory lesions), pustules, nodules, and abscesses, presenting, in severe cases, skin scars [15]. There is not a clear and unique accepted scale for rating acne. However, there are some general tools that can be useful to define or classify the severity of the observed lesions. Two of these tools are the Investigator Global Assessment of acne (IGA)

(**Table 2**), which is accepted by the American Food and Drug Administration (FDA), and the Global Acne Grading System (GAGS) (**Table 3**), that also takes into consideration the location of the counted lesions [16][17].

Table 2. Investigator Global Assessment of acne (IGA) score, acne severity denomination, and type of lesions observed [17].

Score	Acne Severity Denomination	Type of Lesions Observed
0	Clear skin	No lesions observed.
1	The skin is almost unchanged	Few comedones and less, or 1, small inflammatory lesion.
2	Mild severity	12 comedones and less or equal severe inflammatory lesions.
3	Moderate severity	Many comedones and more several inflammatory lesions and less, or 1, nodule.
4	Severe severity	Many comedones and inflammatory lesions, less or equal several nodules and cysts.

Table 3. Global Acne Grading System (GAGS) scale for AV severity rating [16].

Global Score	**Lesions Count**
	None: 0
	Mild: 1 to 18
	Moderate: 31 to 38
	Very severe: >39
Local score = Factor × Grade (0–4)	
Factor (1–3)	Grade (0–4)
	No lesions: 0
Nose/chin: 1	One or more comedone: 1
Forehead/right cheek/left cheek: 2	One or more papule: 2
Chest and upper back: 3	One or more pustule: 3
	One or more nodule: 4

Even though there are different phylotypes and subspecies of *C. acnes* in healthy skin, the phylotype IA1 is the one associated with the lesions observed in AV [18].

4. C. acnes Antibiotic Treatment

Antibiotics have been used for more than 40 years to control and promote the elimination of bacterial infections. In clinical practice, there are currently prescribed topical and oral antibiotics to control infections [19].

Topical antibiotics include clindamycin and erythromycin. These drugs work by binding to the 50s ribosomal subunit of the bacteria, disrupting protein synthesis and, ultimately, compromising cell integrity and the replication process. These antibiotics are often used in the treatment of moderate to severe acne, particularly when other topical treatments have been ineffective, and are frequently combined with other active ingredients, such as benzoyl peroxide, to improve therapeutical efficacy [20][21].

Regarding oral treatment, tetracycline antibiotics, such as doxycycline, minocycline, and tetracycline, and macrolide antibiotics, such as erythromycin, are the most commonly used. These antibiotics constitute therapeutics in cases of moderate to severe *C. acnes* infection and/or when the infection is observed in a larger area of the body. Trimethoprim-Sulfamethoxazole (TMP-SMX) is also prescribed, especially when other antibiotics are ineffective or not well tolerated [22].

However, over the last decade, *C. acnes*, much like other bacteria, has shown an increase in antibiotic resistance mechanisms, due to its overuse and/or incorrect use, with over 50% of *C. acnes* strains showing resistance to antibiotic treatments [19]. This alarming increase in bacterial survival created the necessity to search for alternative strategies with similar outcomes regarding treatment efficacy, whether by reducing antibiotic concentration or using alternative compounds. Several studies have been conducted with that goal in mind [23][24][25][26][27]. According to the most recent American recommendation, benzoyl peroxide (BPO) should be used as the first-line treatment for mild to moderate AV, along with a topical retinoid and/or antibiotics [23]. Moreover, other compounds have been considered (**Table 4**), particularly regarding their use in post-surgery infections as topical antiseptics.

Table 4. The positive and negative aspects of compounds used as antiseptics described in clinical studies for Cutibacterium acnes infections in post-surgery contexts [23][24][25][26][27].

Compound	Antibacterial Mechanism	Positive Factors	Negative Factors
Benzoyl peroxide (BPO)	The discharge of reactive oxygen intermediates oxidizes the proteins in the bacterial cell membrane.	No bacterial resistance to BPO has emerged despite decades of use. Keratolytic and anti-inflammatory properties are an additional component of BPO.	BPO is expensive and is a skin irritant, especially in darker skin types.
Clindamycin	Inhibits the bacterial 50S ribosome-mediated protein production.	Has a synergetic effect when used with BPO. Fox–Fordyce illness, folliculitis, periorificial face dermatitis, and rosacea have all been treated successfully with topical clindamycin, according to reports.	*C. acnes* isolates was shown to be resistant to clindamycin. Topical clindamycin side effects generally take the shape of dryness, stinging, burning, and erythema.
Micozanole Nitrate (MN)	Antifungal drug that affects the integrity of fungal cell membranes.	Annihilates Malassezia furfur, a fungus that provides an optimal environment for the growth of *C. acnes*.	May provoke allergic reactions, skin irritation such as erythema, pruritus, and occasionally exudation.

Compound	Antibacterial Mechanism	Positive Factors	Negative Factors
Hydrogen Peroxide (HP)	Is known by its powerful antiseptic activity against the vast known microorganisms in the skin. It can be used in the concentrations of 3 to 6% of (*v*/*v*). Even though the precise mechanism of action of hydrogen peroxide is unknown, it is widely thought that it is connected to its oxidizing activity.	No cases of acquired bacterial resistance to HP have been reported. PVP–I and HP interact positively.	HP concentrated solutions (20–30% or more) are extremely irritating to the skin and mucous membranes and should be handled carefully.
Chlorhexidine (CHX)	CHX has an antibacterial activity by affecting the integrity of cell membranes.	Being a highly safe topical medication, chlorhexidine is also commonly found in wound dressings and central line catheters. Chlorhexidine has a broad spectrum of activity and persistent residual effects.	Associated with poor efficacy, chlorhexidine side effects are uncommon but include minor skin irritation and, less often, allergic responses such as severe anaphylaxis.
Povidone-iodine (PVP-I)	It is hypothesized that PVP–I mechanisms include the inhibition of the electron transportation and cellular and inhibiting protein synthesis.	It is considered, among the antiseptics, the one with the broadest spectrum of activity against viruses, bacteria, molds, fungi, yeasts, and protozoa.	Low solubility, poor chemical stability, and shows local toxicity if not used in a soluble polymer matrix. PVP–I should not be used in patients with thyroid diseases and applicated iodine radiotherapy and it is also contraindicated to pregnant women or during lactation, and to newborns, and to young children.
Isopropanol	It is hypothesized that alcohols promote the protein denaturation or inhibition of mRNA and protein synthesis.	Rapid bacterial activity and broad spectrum of activity (vegetative bacteria, including mycobacteria, viruses, fungi, but not against bacterial spores). No reported allergic reactions.	Alcohols' antimicrobial properties are brief, so they are commonly combined with compounds such as chlorhexidine, which keep working after the alcohol has evaporated.

5. New Therapeutic Strategies

To overcome bacterial resistance concerns, there are strategies being explored, not only envisioning therapy efficacy but also a personalized medical approach [28]. Improvements in the treatment of *C. acnes* rely on the development of novel therapies that maximize efficacy while reducing side effects, as well as issues in public health, such as antibiotics prescriptions.

Since a healthy skin flora can be influenced by exogenous and endogenous factors causing pathological conditions for the host, one of the strategies is the use of bacterial extracts and compounds. This strategy aims to help recover the healthy state of the skin in different pathological conditions such as AV [29]. Ho et al. studied the effects of fermented postbiotics (TYCA06, AP-32 and CP-9 and collagen gel) in the growth inhibition of *C. acnes*, as well as an in vivo assay on the skin of patients with oily skin and severe AV. The postbiotics displayed a good growth inhibition for *C. acnes,* and in clinical trials no adverse effects was observed, showing significant reduction in redness, inflammation, and accumulation of porphyrins in skin brown spots. Moreover, there was a significant improvement in the skin hydration and in the AV lesions (in only one

week of treatment), even though there was no significant reduction in the sebum skin [30]. Han et al. studied the effects of the *E. faecalis* CBT SL-5 extract, isolated from healthy Korean human fecal samples in patients with mild to moderate AV. The treatment significantly reduced the phylogenetic diversity in the patient's skin and was well tolerated by the patients. However, no significant difference was observed in the treatment and in the vehicle lotion in the improvement of AV [31]. Tsai et al. applied a base cream including heat-killed *L. plantarum*-GMNL6 on one side of the face in 15 females. The treatment significantly reduced the amount of *C. acnes* and reduced, inclusively, the red areas and the porphyrin [32]. Karoglan et al. performed a microbiome transplantation of beneficial strains of *C. acnes* to the patient's skin. The results were not statistically significant but clinical improvements in the noninflammatory lesions were observed. The major limitation of the study was the absence of a control or placebo group and the small participant sample, highlighting the need for further studies with larger groups to correlate the microbiome transplantation with beneficial outcome in AV patients [33].

More recently, phage therapy has been increasingly studied as an innovative approach in bacterial infection treatments.

Phage therapy, short for bacteriophage therapy, is a type of treatment that uses bacteriophages to target and kill specific bacteria. Bacteriophages, often referred to as phages, are viruses that infect and replicate within bacteria, ultimately leading to the bacterial cell's death [34]. This way, phage therapy constitutes a potential approach for treating bacterial infections, including those caused by bacteria like *C. acnes,* and involves identifying and isolating specific bacteriophages that can target and infect *C. acnes* bacteria. Once suitable phages are isolated, they can be purified and used to treat the infection [35]. The phages attach to the surface of *C. acnes* bacteria, inject their genetic material, and then replicate inside the bacterial cell. This replication ultimately leads to the lysis (bursting) of the bacterial cell, killing it, and releasing more phages to attack other bacteria [35].

Phage therapy entails several advantages, such as (a) specificity, as phages are highly specific to the target bacteria, reducing the risk of harming beneficial bacteria in the body; (b) reduced antibiotic resistance, since phages can be effective against bacteria with multiresistant profile and help overcome virulence mechanisms such as the production of biofilms; and (c) potential for personalized treatment, since it constitutes a therapy that can be tailored to a specific strain that is causing infection [28][34]. This therapy has been considered an optimistic possibility to provide specific treatment in infections with pathogenic bacteria and in dysbiosis conditions when compared to the use of antibiotics [28]. As such, several studies have been conducted, using phages as the vehicle to treat *C. acnes* bacterial infection.

An important therapeutic aspect is phages' temperate nature, allowing coexistence with their host and enabling gene transfer, including antibiotic resistance genes. The safety of phage therapy relies on understanding these dynamics. A study conducted with antibiotic treated mice was found to increase phage integration into bacterial genomes, enriching the phage metagenome with stress-specific functions, shaping the phage–bacterial network. This enrichment also included functions related to host metabolism, such as a broader carbohydrate pathway in ampicillin-treated mice [36]. Such strategies could provide a protective effect in the gut microflora during antibiotic treatments.

Despite all the advantages in this innovative approach, phage therapy also entails some challenges that make its applicability not straight forward.

Identifying and isolating appropriate phages can be challenging and time-consuming, since the affinity towards a specific strain is essential to an effective treatment. Another challenge is the regulatory approval. In many countries, phage therapy is considered experimental, failing to check all the necessary bureaucracies for clinical application and, therefore, not reaching global population. One more challenge, that somewhat correlates with the former, is the lack of clinical data. This limitation constricts the flexibility in terms of phage therapy as a personalized treatment, due to its regulatory limitations that, in the end, result in few clinical trials.

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