Overview article

DOI: 10.59715/pntjmp.4.2.2

A review of molecular mechanisms in antimicrobial resistance of *Cutibacterium acnes*

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Abstract

Cutibacterium acnes is a Gram-positive, facultative anaerobe that forms the human skin's commensal flora. The microbe plays an important role in the pathogenesis of acne vulgaris, as in endocarditis and prosthetic joint infectious arthritis. In Europe, the resistance rates of *C. acnes* to Clindamycin and macrolides were reported to be relatively high, while in Vietnam, raw data noted the increasing rate of resistance to broad-spectrum antibiotics indicated for acne treatment following the Ministry guideline.

Regarding molecular mechanism, macrolide resistance is associated with point mutations at 23S rRNA and 16S rRNA encoding genes, leading to the alteration in ribosome structure and, thus, inhibition of the bacterium's protein synthesis. Performing routine evaluation of antimicrobial resistance (AMR) and associated mutations is essential. Therefore, this review aims to explore the status and mechanism of AMR to available antibiotics.

Keywords: *Cutibacterium acnes*, antimicrobial resistance, 23S rRNA, 16S rRNA..

Received: 24/02/2025
Revised: 12/3/2025
Accepted: 20/4/2025
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1. INTRODUCTION

Acne vulgaris is a common disease among many skin infections [1]. The responsible microbe for acne vulgaris is *Cutibacterium acnes*, which makes antibiotics one of the first-line treatments. *C. acnes* is found frequently in the human skin, interacting with other microbes to form a rich commensal flora [2]. The metabolites originating from the bacterium are thought to trigger a local immune response, leading to various types of lesions in acne vulgaris. Despite being one of the four mechanisms causing acne vulgaris, the bacterium has received much research attention recently. Resistance to available antibiotics has recently risen, and data varies in different regions [3–5]. One of the most essential reasons explaining the resistance rate is the alterations in the target genes. These mutations have been demonstrated *in silico* to confer resistance to antibiotic effects; however, the role of gene mutations and antibiotic resistance characteristics in actual clinical practice remains unclear.. In this review, we will discuss the status of antimicrobial resistance in *C. acnes* in Vietnam and the world, and present some of the most associated gene mutations to facilitate potential investigations into the bacterium's response to treatment.

2. REVIEW

2.1. Overview of *Cutibacterium acnes*

Cutibacterium acnes (formerly *Propionibacterium acnes*) is the most frequent species among the *Cutibacterium* genus. The bacterium is in rod shape, positive-gram stained, and typically aerotolerant anaerobic. It is commonly found in the skin, ear canal, oral cavity, and digestive tract. *C. acnes* is polymorphic, which can be described in diphtheroid or coryneform; this explains why the bacterium has been first included in the genus *Bacillus* (as *Bacillus acnes*), then in the genus *Corynebacterium* (as *Corynebacterium acnes*). Due to its ability to produce propionic acid, the bacterium was renamed *Propionibacterium acnes* in the genus *Propionibacterium* until it was finally assigned to the genus *Cutibacterium* with the current name of *Cutibacterium acnes* [6].

The bacterium grows slowly in microaerophilic conditions (environment with 2% to 10% oxygen level) or an anaerobic setting for the best result; its enzyme system allows the microbe to survive in an environment with very little oxygen. Hence, *C. acnes* presents either beneath the follicles or the skin surface, particularly in sebaceous-rich areas [7]. A recent study noted a shift in *C. acnes* density related to human age [8]: By comparing acne and non-acne groups in various age groups, the authors concluded that before puberty, not much *C. acnes* was detected in the skin, but the microbe escalated rapidly in quantity when a person reached puberty. Secreted lipases are believed to contribute to pathogenesis, as the enzymes help break free fatty acid on the skin into smaller molecules, playing an important role in the skin barrier but also resembling mediators and leading to local inflammation on the skin. *C. acnes* can also form a biofilm, making it possible to cause medical device-associated infections, including prosthetic heart valves and prosthetic joints [9–11]. The role of these virulent factors will be presented in the next part.

2.2. Clinical role of *Cutibacterium acnes*

C. acnes is a part of the commensal microbiota on the skin, but it can become an opportunistic pathogen under certain conditions [2]. Studies have shown that *C. acnes* can produce various virulence factors, such as biofilm formation [12–14]. This helps the bacteria adhere to and survive on surfaces, enhancing immune evasion and antibiotic resistance. In post-surgical infections, *C. acnes* is often found on implanted devices (prosthetic joints, orthopedic instruments) [10]. Symptoms may include pain, swelling, redness, and reduced function at the implant site. Infections may not manifest immediately but can appear long after surgery. This is due to the microbe's ability to form biofilms, allowing it to adhere to and survive on medical device surfaces. Biofilms protect the bacteria from the immune system and antibiotics, leading to persistent and difficult-to-treat infections [15]. The biofilm may damage the implant wholly or partially, causing dysfunction in the organ. Sometimes, the biofilm may tear apart, releasing a tremendous amount of bacteria into the blood and turning the patient into a critical condition [15].

Additionally, *C. acnes* produces extracellular enzymes involving lipase, protease, and hyaluronidase, facilitating tissue invasion and host tissue destruction

[2]. Furthermore, peptidoglycan and lipoteichoic acid on the cell wall can trigger inflammatory responses in the body [16]. However, the expression levels of these virulence factors may vary among different *C. acnes* strains, which, in turn, may have various abilities to invade different tissues. This explains why *C. acnes* type IA is associated with inflammatory acne on the skin, while type IB/II is linked to deep soft tissue infections. A study in India (2024) on 38 *C. acnes* strains isolated from acne patients showed that 36.8% had moderate biofilm-forming ability, while 63.2% had weak biofilm-forming ability [17]. This means not all strains are pathogenic, highlighting the importance of studying virulence factors and mechanisms of *C. acnes* to develop effective treatments. The interaction between *C. acnes* and other microbes in the human skin leads to a selection of several virulent strains adapting to the host.

C. acnes plays a particularly significant role as a causative agent of acne. Its lipase enzyme breaks down sebum into free fatty acids, altering skin pH and creating favorable conditions for bacterial growth. Combined with proteinase, which degrades structural proteins in the skin, it weakens hair follicles and surrounding tissues. Hyaluronidase breaks down hyaluronic acid in connective tissue, allowing the bacteria to penetrate deeper into the skin and cause more extensive damage. The byproduct, propionic acid, activates keratin differentiation, aggravating the comedone formation. *C. acnes* can also activate Toll-like receptor 2 (TLR-2) on immune cells (macrophages, monocytes, keratinocytes), stimulating the production of pro-inflammatory cytokines [2]. With its biofilm-forming ability, *C. acnes* can persist long-term in hair follicles, causing prolonged inflammation and antibiotic resistance, making acne treatment more challenging.

Although *C. acnes* is a resident on the skin and mucous membranes, it can become a significant pathogen under certain conditions; that is how *C. acnes* is classified as an opportunistic pathogen. When *C. acnes* enters the bloodstream, it can cause endocarditis, particularly in patients with prosthetic heart valves or other cardiovascular abnormalities [18]. After orthopedic surgeries or bone trauma, *C. acnes* can persist as a latent infection in bones or implant surfaces without causing acute symptoms [19]. This results in delayed-onset osteomyelitis caused by *C. acnes*, which is often difficult to diagnose and can persist for months to years before symptoms become apparent. Due to its biofilm-forming ability and antibiotic resistance, treatment is typically prolonged and requires specialized regimens, including surgical removal of infected tissue combined with long-term antibiotics.

2.3. The antimicrobial resistance of *Cutibacterium acnes*

Antimicrobial resistance (AMR) is a global health concern that requires serious attention. Inappropriate use of antibiotics has played a significant role in contributing to the rise of AMR. In recent years, the resistance rate of *C. acnes* has been increasing, particularly against macrolides (primarily erythromycin) and tetracyclines (mostly tetracycline and doxycycline), which are first-line indicated in treatment guidelines. The primary cause of this resistance stems from the prolonged misuse of antibiotics in acne treatment, creating

selective pressure and promoting the emergence of virulent *C. acnes* strains capable of forming protective biofilms that can resist antibiotic attacks. Moreover, the widespread use of antibiotics in acne treatment has led to cross-resistance and the failure of topical antibiotic treatments, highlighting the potential negative consequences of antibiotic use for acne. Another hypothesis is the poor-control use of broad-spectrum antibiotics (cephalosporins and fluoroquinolones) in many common infections. The antibiotics have caused a high resistance rate in enteric gram-negative rods, and many of the substances can remain in the skin tissue. The phenomenon may lead to concurrent selection of resistant *C. acnes* strains [20].

Resistance of *C. acnes* to antibiotics used in acne treatment was first reported in 1979 [21]. Overall, resistance rates to Clindamycin and erythromycin are higher, while resistance to doxycycline remains lower, as evidenced by studies published from 1990 to 2022 in Europe, the United Kingdom, and other countries [3], [5], [17], [22–24]. A systematic review and meta-analysis of 39 eligible articles on the susceptibility of *C. acnes* has revealed relatively high rates of AMR [25]. In the macrolide group, M. Beig et al. reported that the proportion of erythromycin and azithromycin resistance was 36.6% and 14.9%, respectively. 31% of *C. acnes* strains were resistant to Clindamycin, which was alarming. Other tetracycline antibiotics showed relatively low proportions of resistance: tetracycline (6.2%), doxycycline (7.9%), and minocycline (2.5%). The results address the need to revise first-line antibiotics and promote dose-tailored practice in the clinical setting [25].

Depending on the epidemiology of each region and local treatment practices, the drug resistance of *C. acnes* varies, influenced by treatment factors (topical or systemic, dosage, combinations, and duration) or microbiological characteristics (skin metagenome). In acne patients, macrolide resistance rates ranged from 35% in Colombia to nearly 90% in Spain, as described by previous investigations [23], [26]. In France, the resistance rate to erythromycin was 75.1%, significantly higher than the 9.5% resistance rate to tetracyclines [26]. Resistance patterns to tetracyclines appeared more favorable, with rates below 10% in France and up to nearly 50% in India [3], [26]. Meanwhile, articles from Asian countries reported relatively high resistance rates to erythromycin of *C. acnes* strains isolated from acneic lesions, ranging from 15.5% to 98%, followed by clindamycin resistance rates of 19% to 90.4%, and tetracycline resistance rates of 3.3% to 30.8% [17], [22], [24], [27], [27–29]. Unfortunately, there were few adequate studies in Vietnam on the antibiotic resistance characteristics of *C. acnes* despite the widespread use of long-term antibiotic treatment for acne [30]. There is a need for routine assessing the resistance status and exploring molecular mechanisms underlying drug resistance.

2.4. Molecular mechanism of AMR in *Cutibacterium acnes*

The mechanism of bacterial resistance to antibiotics is classified based on the site of action of the antibiotic. Macrolide antibiotics inhibit bacterial protein synthesis by blocking peptidyltransferase

from forming peptide bonds with the tRNA of the following amino acid. Resistance to macrolides occurs at the post-transcriptional level: abnormalities in the 23S rRNA (part of the 50S subunit) are the primary mechanism allowing bacteria to evade the effects of these drugs. Key alterations in this region include mutations in the 23S rRNA gene and methylation of the 23S rRNA by the *erm(X)* gene encoding ribosome methylase [31]. Mutations in the 23S rRNA arise from prolonged antibiotic exposure [32], while the *erm(X)* gene (located on the transposon Tn5432) can be horizontally transferred to other *C. acnes* strains [33]. S. Aoki et al. (2020) analyzed eight *C. acnes* strains highly resistant to macrolides and Clindamycin, identifying a plasmid DNA (named pTZC1) containing the *erm(50)* gene conferring resistance to macrolides and Clindamycin, as well as the *tet(W)* gene conferring resistance to tetracycline [34]. This raises concerns about the potential spread of resistance factors among *C. acnes* strains, potentially impacting clinical treatment.

Macrolides bind to the 23S rRNA at the P site of the ribosomal subunit; another antibiotic, Clindamycin, belonging to the lincosamide group, also targets the 23S rRNA by binding to the A site. Thus, the key question is whether resistance to macrolides and Clindamycin can co-occur due to similar mutations. I. B. Lomakin et al. (2024) analyzed 33 cryopreserved *C. acnes* strains to detect resistance to macrolide-clindamycin-streptogramin B (MLSB) [35]. The authors identified three distinct mutation patterns at the 23S site, leading to varying levels of resistance:

1. A point mutation substituting G for A at position 2240 (G2240(2057)): low-level resistance to erythromycin;

2. A point mutation substituting A for G at position 2241 (A2241(2058)): found in most MLSB-resistant strains. This mutation creates a weak hydrogen bond between Clindamycin's galactose ring and the 23S rRNA.

3. A point mutation substituting A for G at position 2242 (A2242(2059)): high-level resistance to macrolides and low-level resistance to Clindamycin.

Another significant finding in this study is that cross-resistance occurs because Clindamycin's galactose ring overlaps with the desosamine moiety of macrolides at the 23S rRNA binding site. This explains the relatively high resistance rates of C. acnes to Clindamycin and macrolides reported in systematic reviews and meta-analyses. This finding also raises a clinical concern: Does the use (combination or substitution) of macrolides and Clindamycin achieve optimal treatment efficacy? This question requires confirmation from future clinical trials.

Tetracycline antibiotics also inhibit protein synthesis. These drugs block transcription by binding to the 30S ribosomal subunit, specifically the 16S rRNA. Some studies have also reported that tetracycline can bind to 16S and 23S rRNA. This reversible binding prevents tRNA from attaching subsequent amino acids to the peptide chain. From 16 susceptible and 21 resistant strains of *C. acnes*, J. I. Ross et al. (1998) documented a nucleotide change (G to C) at position 1058 (known as helix 34), significantly impacting *C. acnes*' tetracycline resistance [36]. Helix 34 is a conserved region involved in polypeptide

chain termination and ensuring transcription accuracy. Mutations in helix 34 may weaken tetracycline-ribosome binding or allow tRNA to attach amino acids to the peptide chain despite tetracycline's presence [36]. K. Nakase et al. (2017) reported that doxycycline-resistant strains carried a G-to-C substitution at position 1036 on the 16S rRNA gene, along with an amino acid substitution in the ribosomal protein S10 (encoded by the rpsJ gene) [32]. The authors suggested that *C. acnes* strains with both mutations exhibit strong doxycycline resistance, while the S10 protein substitution only contributes to increased resistance risk.

2.5. New directions in *C. acnes* research

As a component in the pathogenesis of acne, *C. acnes* interacts with the histological structure and resident microbiota of the skin. This interaction generates numerous important skin metabolites, which may play protective or risky roles in skin health [37]. Research projects on human skin microbiota are increasingly gaining attention due to the vast information they provide and the use of new investigative techniques. This information holds microbiological epidemiological significance, contributing significantly to the development of cosmetic and pharmaceutical products in the beauty industry.

The phylotype composition of *C. acnes* strains on human skin is also particularly interesting. Anthropometric, sociological, and epidemiological factors influence the distribution of bacterial phylotypes. Identifying the phylotype composition within local communities provides a foundation for assessing the differential virulence expression among strains, potentially aiding clinicians in selecting appropriate treatment and bacterial control strategies. Furthermore, phylotype characteristics help monitor changes in bacterial population structure over time.

Regarding antibiotic resistance, *C. acnes* is increasingly resistant to first-line acne treatments due to selective pressure on the bacterial population. Resistant strains are becoming more prevalent, eventually leading to clinical impacts. Therefore, periodic screening for mutations in the *C. acnes* population is necessary to limit the emergence of new mutations, especially horizontally transferable ones like *erm(X)* [34], [38].

3. CONCLUSION

Within the limited scope, this review aims to summarize some important issues regarding C. acnes in clinical practice, with the hope of drawing the attention of microbiologists and clinicians to this often overlooked pathogen. Research on *C. acnes* is receiving increased attention in microbiology due to the growing prevalence of antibiotic resistance and related genetic mutations. Alongside investigating drug resistance, new directions focusing on the interactions within microbial communities and clinical responses are also crucial to managing and optimizing the use of antibiotics.

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