**The Open Dermatology Journal**
*DOI: 10.2174/0118743722279314240219091938, 2024, 18, e18743722279314*
**ISSN: 1874-3722**
*1*

**REVIEW ARTICLE** **OPEN ACCESS**

# Assessment of *Cutibacterium acnes*: Acne Biofilm, Comedones, and Future Treatments for Acne

Craig G. Burkhart[1,*]

[1]*Department of Medicine, University of Toledo College of Medicine, Toledo, Ohio, OH, USA*

**Abstract:**
*Cutibacterium acnes* (*C.acnes*) is a skin commensal organism that controls the growth of *Staphylococcus aureus* and *Streptococcus pyogenes*. Additionally, the organism can become an opportunistic pathogen, causing acne and post-surgical prosthetic infections. The outcome of acne depends on *Cutibacterium* subtypes, virulence factors, and microbial equilibrium. This organism makes a biological glue that is essential for biofilm formation, but its overabundance makes its way into the sebum. This sebum slowly reaches the upper layer of the hair unit along with dead cells from the keratinocyte layer, causing comedones. Treatments in the pipeline include tumor necrosis factors (biologics), various agents attacking biofilm viability, phage therapy, and vaccinations against virulence factors produced by *C. acnes*.

**Keywords:** Acne, *Cutibacterium acnes*, Acne biofilm, Treatment, Phage therapy, Acne vaccinations.

© 2024 The Author(s). Published by Bentham Open.
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: https://creativecommons.org/licenses/by/4.0/legalcode. This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

*Address correspondence to this author at the Department of Medicine, University of Toledo College of Medicine, Toledo, Ohio, OH, USA; Tel: 419-885-3403 (o), 410-885-3401 (f), 419-466-7244 (c);
E-mail: cgbakb@aol.com

*Cite as:* Burkhart C. Assessment of *Cutibacterium acnes*: Acne Biofilm, Comedones, and Future Treatments for Acne. Open Dermatol J, 2024; 18: e18743722279314. http://dx.doi.org/10.2174/0118743722279314240219091938

Received: October 23, 2023
Revised: January 16, 2024
Accepted: January 30, 2024
Published: February 29, 2024

***Send Orders for Reprints to***
***reprints@benthamscience.net***

## 1. INTRODUCTION

Acne vulgaris is a frequent condition in dermatology as it affects 20 million people, most of whom are in their teen years or early 20s. The standard literature has proclaimed that the major causative factors are excess keratin formation in the upper hair units, sebaceous gland obstruction, irregular maturation of cells in the upper follicular units, expanded production of sebaceous fluids secondary to androgenic production, and overgrowth in the number of *Cutibacterium acnes* (*C. acnes*). *C. acnes* was formerly named *Propionibacterium acnes.* Traditionally, the major areas of pathophysiology have been stated to be hyperkeratinization and obstruction of sebaceous follicles resulting from abnormal desquamation of the follicular epithelium, an androgen-stimulated increase in the production of sebum, and proliferation of *Cutibacterium acnes* (*C. acnes*), previously known as *Propionibacterium acnes* [1]. This dogma has been altered by the development of the acne biofilm.

## 2. FEATURES OF *CUTIBACTERIUM ACNES*

*C. acnes* is a gram-positive bacterium that causes inflammatory acne. Its cell wall and envelope are different as they consist of two unusual lipids, namely phosphatidylinositol and triacylglycerol [2]. *C. acnes* is a commensal organism and has a definite role in maintaining homeostasis. In short, it produces virulence factors that regulate the growth of several potentially harmful pathogens, such as *Staphylococcus aureus* and *Streptococcus pyogenes*. However, it can also protect from these bacteria by hydrolyzing lipids and maintaining a low pH [3, 4]. Additionally, it affects skin T helper 17 cell responses and immunomodulatory IL-10 [5]. Metabolic features allow *C. acnes* to break down sebum-consistent triglyceride into smaller molecules of fatty acid. One of these is propionic acid whose presence leads to keeping the skin acidic. Due to the identification of lipase genes not found in other cutaneous *Propionibacterium* and other genomic adaptive changes, its name was changed to *Cutibactrium* species.

*C. acnes* prefers to live on the face, back, and chest, where it can enjoy an environment abundant in sebum. The number of such bacteria in one single hair follicle unit can approach $10^8$ colony-forming units [3]. The bacteria is also found in the conjunctiva, intestinal tract, stomach, lungs, prostate, oral mucosa, external auditory canal, and urinary tract [3, 6, 7]. It is a facultative anaerobic bacteria, but it does have the genetic ability to produce the needed factors to also live in oxygen-rich conditions.

The *C. acnes* genome is quite large. It consists of a single circular chromosome. On this single chromosome, there are 2,560,265 base pairs with 2333 potential genes [8], making it equivalent to about 8% of the human genome by comparison. There are 100 different strains of *C. acnes*, and it is classified into eight phylotypes. Two of these phylotypes are found commonly in more severe acne cases, namely IA-1 and IA-2 [9]. Some may act as opportunistic pathogens, such as phylotypes II and III, which are often identified in infections that extend farther down into the skin [9]. Many of the other phylotypes may not have any pathogenic tendencies and merely maintain homeostasis. It is challenging to make direct comparisons of specific phylotypes to disease states as there can be variances in how one follicle behaves, given the interplay of various external factors [10].

The skin surface is host to *Corynebacteria, Cutibacteria*, and *Staphylococci* [11]. The major inhabitant is *S. epidermis*, making up 27% of the population of bacteria [12]. *C. acnes* is less than 2%, as it mostly resides deep within the sebaceous gland [3]. *S. epidermidis* controls the *C. acnes* growth-induced inflammation through the release of succinic acid [13].

*C. acnes* can be an opportunistic pathogen, with acne being the most common example. In the hair follicle with acne, it can release lytic enzymes, triggering follicular disruption and activation of an immune response. *C. acnes* has also been recognized as a major cause of post-surgical prosthesis infection, endocarditis, endophthalmitis, prostatitis, sarcoidosis, osteitis syndrome, osteomyelitis, and septic arthritis [14].

Certain antibiotics have limited abilities to attack anaerobic bacteria as the molecular means of penetration utilized with aerobic microbials are not present. In the case of *C. acnes,* innate resistance to fosfomycin, metronidazole, 5-nitroimidazole agents (*i.e.*, metroni- dazole), aminoglycosides, sulfonamides, and mupirocin has been found [15]. Moreover, the resistance of *C. acnes* to various other antibiotics has been gradually increasing. For example, resistance to erythromycin and clindamycin are reported to be 21% and 70%, respectively [15, 16]. Interestingly, both antibiotics are tertiary amines and have been shown to activate benzoyl peroxide topically into its radical state with therapeutic effects [17, 18]. Thus, topically, these antibiotics prove to be more helpful due to their chemical structure rather than antibacterial properties.

## 3. THE *C. ACNES* BIOFILM AND PRODUCTION OF VIRULENCE FACTORS

Most *C. acnes* in hair follicle units reside in biofilms. A biofilm is a collection of surface-associated microbial cells surrounded by an extracellular polymeric substance matrix that allows adherence to a surface as well as making an exoskeleton [19]. The biofilm allows for numerous different habitats for the bacteria to exist, which leads to *C. acnes* organisms having varied rates of metabolism, replication, and responsiveness to antibiotic therapy. Biofilms make *C. acnes* less susceptible to antibiotics as they greatly reduce the penetration of drugs. Thus, these bacteria residing in biofilms are much more resistant to antibacterial measures than free-floating (planktonic) bacteria. Gene expression clearly proves the innate capacity of *C. acnes* to manufacture biofilms [20]. Biofilms can attach to numerous types of surfaces. In the case of implants, the development of such a biofilm could lead to complications [21]. A biofilm enhances pathogenicity by leading to greater lipase activity implicated in inflammation and upregulation of genes encoding various virulence factors [22].

*C. acnes* are capable of producing several virulence factors, including dermatan-sulfate adhesins (DsA1 and DsA2), Christie-Atkins-Munch-Petersen (CAMP) hemolytic factors, lipases, hyaluronate lyase, sialidase, poly-unsaturated fatty acid isomerase, HtaA iron acquisition protein and GehA lipase, and heat-shock proteins, such as HSP20, DnaK, DnaJ, GrpE, and groEL [8, 23, 24]. *C. acnes* makes some of these virulence factors for forming a biofilm, cell adhesion, and adapting to its environment. However, the same proteins in higher concentrations can also cause tissue invasion and degradation of other bacteria and or the host. It has been demonstrated that *C. acnes* releases high levels of specific virulence factors and increases its pathogenicity. Other possibilities include environmental changes and/or interaction of *C. acnes* with the skin microbiota [24].

## 4. THE COMEDONE AND ITS FORMATION FROM BIOLOGICAL GLUE FROM *C. ACNES*

For generations, comedone has been considered the primary cause for unraveling acne pathogenesis. The comedone is a keratin plug, and its formation has been thought to be a result of some non-explained change in the epithelium of the upper hair follicle unit. These keratinocytes amass, causing pressure and expansion within the hair follicle unit, ultimately leading to the rupture of the comedone and the resultant dispersion of keratin and sebum into the dermis, which would act as a foreign immunologic material.

The understanding of an acne biofilm led to a different perspective. In short, some of the excess biological glue that *C. acnes* makes to form its biofilm finds itself in the sebum [25]. Genomic studies on *C. acnes* have revealed the existence of UDP-N-acetylglucosamine 2 epimerase and glycosyl transferases, two main adhesive proteins for biofilm formation [20]. The biological glue that finds its way into the sebum leads to the adhesiveness of keratinocytes in the upper hair unit, leading to comedones.

**Table 1. Potential novel therapeutic agents for acne.**

| Class of Agent | Examples of Agents | Mechanism of Action(s) |
|---|---|---|
| **Anti-inflammatory** | | |
| Biologics | Anti-TNF, *e.g.* adalimumab, infliximab, etanercept | Target TNF to reduce inflammation [30] |
| **Modifiers of Acne Biofilm** | | |
| Quorum sensing inhibitors | Azithromycin, bergamottin, usnic acid, quercetin, and ellagic acid | Block genetic factors |
| Degradation of specific proteins | Dispersin B and Deoxyribonuclease | Destroy functional proteins in biofilm formation |
| Surfactants | Poloxamer-188, Tween 20, sodium dodecyl sulfate, and rhamnolipids | Form central hollow cavities in biofilms |
| Signal molecules | Caprylic acid, palmitic acid, and myristoleic acid | Alter chemical compounds essential for biofilm survival |
| Metal chelators | Ethylenediaminetetraacetic acid | Bind to magnesium and calcium from the outer cell wall, upsetting biofilm stability |
| Nitric oxide-generating agents | Glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, and isoamyl nitrite | Reduction of intracellular cyclic dimeric guanosine monophosphate |
| Antimicrobial peptides | Nisin A, human cathelicidin LL-37, human beta-defensin 3, and hepcidin 20. | Make microbial membranes permeable |
| **Bacteriophage Therapy** | | |
| Bacterial viruses | Cuteribacterium acnes phage | Target specific bacterial cells, destroying the bacteria |
| **Molecular Biology** | | |
| Specific antibodies to *C. acnes* virulence factors | Antibodies for new CAMP1-derived peptide | Neutralize effects of virulence factors |

Understanding that *C. acnes* makes this biological glue within the biofilm redirects some of the therapy from comedones. Rather than merely concentrating on topical unplugging agents to unplug the comedonal keratinous plug in the hair units, one might now consider altering the *C. acnes* biofilm or its microenvironment. Factors to consider in altering the *C. acnes* biofilm or its microenvironment would be biological, chemical, and/or physical means. For example, the anecdotal evidence that comedonal acne can be improved by oral medications, such as minocycline, tazarotene, and isotretinoin, can now be explained by their actions on changing the *C. acnes* biofilm or altering the sebaceous gland so that there is less making of biological glue [25, 26].

## 5. CONCLUSION AND FUTURE TREATMENTS: WHAT IS COMING DOWN THE ACNE PIPELINE?

Acne does not simply occur due to increased numbers of *C. acnes*. An alteration in the homeostasis between the microbes on the skin surface and *C. acnes* phylotypes might play an important role in acne onset [4, 27]. Change in the balance of skin microbiota with probiotics to obtain a healthy microbiome may prove helpful [25, 28]. There is concern with the growing resistance of *C. acnes* to various antibiotics. However, standard antibiotic resistance factors may not be significant when dealing with a commensal bacteria that can also assume the role of a pathogen [29]. For example, antibiotics might alter the function of bacteria within biofilms favorably despite showing resistance in *in vitro* studies. Possible new therapies are listed in Table **1**.

Biologics have been used in the treatment of acne. These agents are tumor necrosis factor inhibitors that have been used for numerous inflammatory conditions, including rheumatoid arthritis and psoriatic arthritis. They reduce inflammation and can stop disease progression by targeting TNF. Biologics, including adalimumab, infliximab, and etanercept, have been used in severe acne cases. In a study, 40% of participants achieved acne clearance and 90% experienced improvement [30]. However, there proved to be the actual occurrence of worse acne in certain instances.

Altering the acne biofilm can also result in acne improvement. Some agents can either prevent a biofilm's emergence or attack and/or alter an existing biofilm [28]. These agents alter the surface of *C. acnes*, so they are unable to bind to each other [31, 32]. Agents capable of disrupting biofilm function include:

• Quorum sensing inhibitors: They block signals affecting virulence factors as well as the development of biofilms. Agents that have been implicated as having such abilities include azithromycin, bergamottin, usnic acid, quercetin, and ellagic acid [33-36].

• Substances that degrade functional proteins in biofilm structure: These agents include dispersin B (which lyse a polysaccharide that aids in surface attachment) and Deoxyribonuclease (which acts on nucleic acids that affect cell surface adhesion) [37, 38].

• Surfactants, such as Rhamnolipids made by *Pseudomonas aeruginosa*: These agents form central hollow cavities in biofilms. Their examples include poloxamer-188, Tween 20, sodium dodecyl sulfate, and rhamnolipids [39, 40].

• Agents altering signal molecules essential for biofilm survival: These are specific fatty acids, such as caprylic acid, palmitic acid, and myristoleic acid [41-43].

• Metal chelators, such as ethylenediaminetetraacetic acid (EDTA), bind to magnesium and calcium from the outer cell wall, upsetting biofilm stability [44, 45].

• Nitric oxide generating agents: They cause a reduction in intracellular cyclic dimeric guanosine monophosphate, resulting in bacteria favoring planktonic mode rather than biofilm existence [46, 47].

• Antimicrobial peptides: They damage microbial membranes, making them permeable to liquids and gases, leading to cell death. Examples are nisin A, human cathelicidin LL-37, human beta-defensin 3, and hepcidin 20 [48-50].

• Certain antibiotics: They may not decrease the number of bacteria in a biofilm setting but will decrease or alter its function. Minocycline and Bactrim are involved in this category.

• Agents that shrink the sebaceous gland will affect the nourishment of bacteria, which alters the normal homeostasis of bacteria within the biofilm. Examples would be isotretinoin and spironolactone.

Another method of treating acne would be bacteriophage (phage) therapy. Phages are bacterial viruses that invade specific bacterial cells, thus destroying the bacteria. Such therapy directed against *C. acnes* has proved successful in the animal model [51, 52]. Although phage therapy has shown value in various conditions, including dysentery, sepsis, and meningitis, there is a dearth of research on possible usage with skin bacteria [14].

Molecular biology is now able to make specific antibodies for many of the virulence factors of *C. acnes*. Many new treatments have been developed. For example, there are already antibodies for new CAMP1-derived peptides for clinical evaluation [25]. Thus, any of the virulence factors listed in our previous discussion could have a vaccine made, altering that particular virulence molecule and targeting its destruction. However, these virulence factors at lower concentrations are crucial for the function and normal actions of *C. acnes*. Thus, these virulence factors are protective at low doses and yet can be pathogenic at higher levels. However, neutralizing virulence factors of *C. acnes* without disrupting homeostasis in the human skin microbial environment may be tricky [53].

The outcome of acne depends on subtypes, virulence factors, and microbial equilibrium. Molecular science enables us to have potentially new methods of controlling acne. Given the excellent results seen with isotretinoin, the cost of these newer possible treatments in recalcitrant patients will direct, to some extent, their development and usage.

## ABBREVIATION

EDTA = Ethylenediaminetetraacetic Acid

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

Craig Burkhart is the Editor in cheif of The Open Dermatology Journal.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

[1] Burkhart CG, Burkhart CN, Lehmann PF. Acne: A review of immunologic and microbiologic factors. Postgrad Med J 1999; 75(884): 328-31. http://dx.doi.org/10.1136/pgmj.75.884.328 PMID: 10435165

[2] Jeon J, Park SC, Her J, *et al*. Comparative lipidomic profiling of the human commensal bacterium *Propionibacterium acnes* and its extracellular vesicles. RSC Advances 2018; 8(27): 15241-7. http://dx.doi.org/10.1039/C7RA13769A PMID: 35541326

[3] Christensen GJM, Brüggemann H. Bacterial skin commensals and their role as host guardians. Benef Microbes 2014; 5(2): 201-15. http://dx.doi.org/10.3920/BM2012.0062 PMID: 24322878

[4] Szabó K, Erdei L, Bolla BS, Tax G, Bíró T, Kemény L. Factors shaping the composition of the cutaneous microbiota. Br J Dermatol 2017; 176(2): 344-51. http://dx.doi.org/10.1111/bjd.14967 PMID: 27518483

[5] Agak GW, Kao S, Ouyang K, *et al*. Phenotype and antimicrobial activity of Th17 cells induced by *Propionibacterium acnes* strains associated with healthy and acne skin. J Invest Dermatol 2018; 138(2): 316-24. http://dx.doi.org/10.1016/j.jid.2017.07.842 PMID: 28864077

[6] Delgado S, Suárez A, Mayo B. Identification, typing and characterisation of Propionibacterium strains from healthy mucosa of the human stomach. Int J Food Microbiol 2011; 149(1): 65-72. http://dx.doi.org/10.1016/j.ijfoodmicro.2011.01.028 PMID: 21329995

[7] Fassi Fehri L, Mak TN, Laube B, *et al*. Prevalence of *Propionibacterium acnes* in diseased prostates and its inflammatory and transforming activity on prostate epithelial cells. Int J Med Microbiol 2011; 301(1): 69-78. http://dx.doi.org/10.1016/j.ijmm.2010.08.014 PMID: 20943438

[8] Brüggemann H, Henne A, Hoster F, *et al*. The complete genome sequence of Propionibacterium acnes, a commensal of human skin. Science 2004; 305(5684): 671-3. http://dx.doi.org/10.1126/science.1100330 PMID: 15286373

[9] Mayslich C, Grange PA, Castela M, Marcelin AG, Calvez V, Dupin N. Characterization of a *Cutibacterium acne*s CAMP Factor 1-related peptide as a new TLR-2 modulator in *in vitro* and *ex vivo* models of inflammation. Int J Mol Sci 2022; 23(9): 5065-72. http://dx.doi.org/10.3390/ijms23095065 PMID: 35563458

[10] Flowers L, Campbell A, Uberoi A. *Cutibacterium acnes* evolution: One pore at a time. Cell Host Microbe 2022; 30(2): 144-6. http://dx.doi.org/10.1016/j.chom.2022.01.007 PMID: 35143764

[11] Grice EA, Kong HH, Conlan S, *et al*. Topographical and temporal diversity of the human skin microbiome. Science 2009; 324(5931): 1190-2. http://dx.doi.org/10.1126/science.1171700 PMID: 19478181

[12] Dreno B, Martin R, Moyal D, Henley JB, Khammari A, Seité S. Skin microbiome and *acne vulgaris* : *Staphylococcus*, a new actor in acne. Exp Dermatol 2017; 26(9): 798-803. http://dx.doi.org/10.1111/exd.13296 PMID: 28094874

[13] Xia X, Li Z, Liu K, Wu Y, Jiang D, Lai Y. *Staphylococcal* LTA-induced miR-143 inhibits *Propionibacterium acnes*-mediated inflammatory response in skin. J Invest Dermatol 2016; 136(3): 621-30. http://dx.doi.org/10.1016/j.jid.2015.12.024 PMID: 26739093

[14] Scott E, Burkhart CG. *Cutibacterium acnes* as a cause of post-surgical prosthesis infection. Open Dermatol J 2023; 17

[15] Dessinioti C, Katsambas A. *Propionibacterium acnes* and antimicrobial resistance in acne. Clin Dermatol 2017; 35(2): 163-7. http://dx.doi.org/10.1016/j.clindermatol.2016.10.008 PMID: 28274353

[16] Dréno B. Bacteriological resistance in acne: A call to action. Eur J

Dermatol 2016; 26(2): 127-32.
http://dx.doi.org/10.1684/ejd.2015.2685 PMID: 26711531

[17] Burkhart CN, Specht K, Neckers D. Synergistic activity of benzoyl peroxide and erythromycin. Skin Pharmacol Physiol 2000; 13(5): 292-6.
http://dx.doi.org/10.1159/000029936 PMID: 10940820

[18] Burkhart CG, Burkhart CN, Isham N. Synergistic antimicrobial activity by combining an allylamine with benzoyl peroxide with expanded coverage against yeast and bacterial species. Br J Dermatol 2006; 154(2): 341-4.
http://dx.doi.org/10.1111/j.1365-2133.2005.06924.x PMID: 16433807

[19] Burkhart CN, Burkhart CG. Microbiology's principle of biofilms as a major factor in the pathogenesis of acne vulgaris. Int J Dermatol 2003; 42(12): 925-7.
http://dx.doi.org/10.1111/j.1365-4632.2003.01588.x PMID: 14636182

[20] Burkhart CN, Burkhart CG. Genome sequence of *Propionibacterium acnes* reveals immunogenic and surface-associated genes confirming existence of the acne biofilm. Int J Dermatol 2006; 45(7): 872.
http://dx.doi.org/10.1111/j.1365-4632.2006.02734.x PMID: 16863535

[21] Achermann Y, Goldstein EJC, Coenye T, Shirtliff ME. Propionibacterium acnes: From commensal to opportunistic biofilm-associated implant pathogen. Clin Microbiol Rev 2014; 27(3): 419-40.
http://dx.doi.org/10.1128/CMR.00092-13 PMID: 24982315

[22] Jahns AC, Eilers H, Alexeyev OA. Transcriptomic analysis of *Propionibacterium acnes* biofilms *in vitro*. Anaerobe 2016; 42: 111-8.
http://dx.doi.org/10.1016/j.anaerobe.2016.10.001 PMID: 27725231

[23] Brzuszkiewicz E, Weiner J, Wollherr A, *et al*. Comparative genomics and transcriptomics of Propionibacterium acnes. PLoS One 2011; 6(6): e21581.
http://dx.doi.org/10.1371/journal.pone.0021581 PMID: 21738717

[24] Mayslich C, Grange PA, Castela M, Marcelin AG, Calvez V, Dupin N. Characterization of *Cutibacterium acnes* CAMP factor 1 related peptide as a new TLR-s modulator in *in vitro* and *ex vivo* models of inflammation. Int J Mol Sci 2022; 23(9): 5065-72.
http://dx.doi.org/10.3390/ijms23095065 PMID: 35563458

[25] Burkhart CG, Burkhart CN. Expanding the microcomedone theory and acne therapeutics: *Propionibacterium acnes* biofilm produces biological glue that holds corneocytes together to form plug. J Am Acad Dermatol 2007; 57(4): 722-4.
http://dx.doi.org/10.1016/j.jaad.2007.05.013 PMID: 17870436

[26] Tan JKL, Lew-Kaya D, Walker PS. Oral tazarotene reduces comedones. J Am Acad Dermatol 2004; 50(3): P20.
http://dx.doi.org/10.1016/j.jaad.2003.10.083

[27] Barnard E, Shi B, Kang D, Craft N, Li H. The balance of metagenomic elements shapes the skin microbiome in acne and health. Sci Rep 2016; 6(1): 39491.
http://dx.doi.org/10.1038/srep39491 PMID: 28000755

[28] Shinta Marito, Sunita Keshari, Chun-Ming Huang. Peg-8 laurate fermentation of *Staphylococcus epidermidis* reduces the require dose of clindamycin against *Cutibacterium acnes*. Int J Mol Sci 2020; 21: 5103.
http://dx.doi.org/10.3390/ijms21145103 PMID: 32707723

[29] Burkhart CN, Burkhart CG. Antibiotic-resistant propionibacteria acnes may not be the major issue clinically or microbiologically in acne. Br J Dermatol 2003; 148(2): 365-6.
http://dx.doi.org/10.1046/j.1365-2133.2003.05097_3.x PMID: 12588399

[30] Sandoval AGW, Vaughn LT, Huang JT, Barbieri JS. Role of tumor necrosis factor-alpha inhibitors in the treatment and occurrence of acne: A systemic review. JAMA Dermatol 2023; 159(5): 504-9.
http://dx.doi.org/10.1001/jamadermatol.2023.0269 PMID: 36930143

[31] Feuillolay C, Pecastaings S, Gac CL, *et al*. A *Myrtus communis* extract enriched in myrtucummulones and ursolic acid reduces resistance of *Propionibacterium acnes* biofilms to antibiotics used in acne vulgaris. Phytomedicine 2016; 23(3): 307-15.
http://dx.doi.org/10.1016/j.phymed.2015.11.016 PMID: 26969384

[32] Razdan K, Garcia-Lara J, Sinha VR, Singh KK. Pharmaceutical strategies for the treatment of bacterial biofilms in chronic wounds. Drug Discov Today 2022; 27(8): 2137-50.
http://dx.doi.org/10.1016/j.drudis.2022.04.020 PMID: 35489675

[33] Tang K, Zhang XH. Quorum quenching agents: Resources for antivirulence therapy. Mar Drugs 2014; 12(6): 3245-82.
http://dx.doi.org/10.3390/md12063245 PMID: 24886865

[34] Favre-Bonté S, Köhler T, Van Delden C. Biofilm formation by Pseudomonas aeruginosa: Role of the C4-HSL cell-to-cell signal and inhibition by azithromycin J Antimicrob Chemother 2003; 52: 598-604.

[35] Francolini I, Norris P, Piozzi A, Donelli G, Stoodley P. Usnic acid, a natural antimicrobial agent able to inhibit bacterial biofilm formation on polymer surfaces. Antimicrob Agents Chemother 2004; 48(11): 4360-5.
http://dx.doi.org/10.1128/AAC.48.11.4360-4365.2004 PMID: 15504865

[36] Kim C, Kim J, Park HY, *et al*. Furanone derivatives as quorum-sensing antagonists of *Pseudomonas aeruginosa*. Appl Microbiol Biotechnol 2008; 80(1): 37-47.
http://dx.doi.org/10.1007/s00253-008-1474-6 PMID: 18566810

[37] Ramasubbu N, Thomas LM, Ragunath C, Kaplan JB. Structural analysis of dispersin B, a biofilm-releasing glycoside hydrolase from the periodontopathogen *Actinobacillus actinomycete mcomitans*. J Mol Biol 2005; 349(3): 475-86.
http://dx.doi.org/10.1016/j.jmb.2005.03.082 PMID: 15878175

[38] Qin Z, Ou Y, Yang L, *et al*. Role of autolysin-mediated DNA release in biofilm formation of *Staphylococcus epidermidis*. Microbiology 2007; 153(7): 2083-92.
http://dx.doi.org/10.1099/mic.0.2007/006031-0 PMID: 17600053

[39] Pereira MO, Machado I, Simoes M, Vieira MJ. Preventing biofilm formation using surfactants. Biofilm Club 2007; 10: 167-74.

[40] Coronel-León J, Marqués AM, Bastida J, Manresa A. Optimizing the production of the biosurfactant lichenysin and its application in biofilm control. J Appl Microbiol 2016; 120(1): 99-111.
http://dx.doi.org/10.1111/jam.12992 PMID: 26519210

[41] Dow JM, Crossman L, Findlay K, He YQ, Feng JX, Tang JL. Biofilm dispersal in *Xanthomonas campestris* is controlled by cell–cell signaling and is required for full virulence to plants. Proc Natl Acad Sci USA 2003; 100(19): 10995-1000.
http://dx.doi.org/10.1073/pnas.1833360100 PMID: 12960398

[42] Santhakumari S, Nilofernisha NM, Ponraj JG, Pandian SK, Ravi AV. *In vitro* and *in vivo* exploration of palmitic acid from *Synechococcus elongatus* as an antibiofilm agent on the survival of *Artemia franciscana* against virulent vibrios. J Invertebr Pathol 2017; 150: 21-31.
http://dx.doi.org/10.1016/j.jip.2017.09.001 PMID: 28887169

[43] Nicol M, Alexandre S, Luizet JB, *et al*. Unsaturated fatty acids affect quorum sensing communication system and inhibit motility and biofilm formation of *Acinetobacter baumannii*. Int J Mol Sci 2018; 19(1): 214.
http://dx.doi.org/10.3390/ijms19010214 PMID: 29320462

[44] Percival SL, Kite P, Eastwood K, *et al*. Tetrasodium EDTA as a novel central venous catheter lock solution against biofilm. Infect Control Hosp Epidemiol 2005; 26(6): 515-9.
http://dx.doi.org/10.1086/502577 PMID: 16018425

[45] Raad I, Chatzinikolaou I, Chaiban G, *et al*. *In vitro* and *ex vivo* activities of minocycline and EDTA against microorganisms embedded in biofilm on catheter surfaces. Antimicrob Agents Chemother 2003; 47(11): 3580-5.
http://dx.doi.org/10.1128/AAC.47.11.3580-3585.2003 PMID: 14576121

[46] Barraud N, Schleheck D, Klebensberger J, *et al*. Nitric oxide signaling in *Pseudomonas aeruginosa* biofilms mediates phosphodiesterase activity, decreased cyclic di-GMP levels, and enhanced dispersal. J Bacteriol 2009; 191(23): 7333-42.

http://dx.doi.org/10.1128/JB.00975-09 PMID: 19801410

[47] Howlin RP, Cathie K, Hall-Stoodley L, *et al*. Low-dose nitric oxide as targeted anti-biofilm adjunctive therapy to treat chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. Mol Ther 2017; 25(9): 2104-16.
http://dx.doi.org/10.1016/j.ymthe.2017.06.021 PMID: 28750737

[48] Yasir M, Willcox M, Dutta D. Action of antimicrobial peptides against bacterial biofilms. Materials 2018; 11(12): 2468.
http://dx.doi.org/10.3390/ma11122468 PMID: 30563067

[49] Di Somma A, Moretta A, Canè C, Cirillo A, Duilio A. Antimicrobial and antibiofilm peptides. Biomolecules 2020; 10(4): 652.
http://dx.doi.org/10.3390/biom10040652 PMID: 32340301

[50] Luo Y, Song Y. Mechanism of antimicrobial peptides: Antimicrobial, anti-inflammatory and antibiofilm activities. Int J Mol Sci 2021; 22(21): 11401.
http://dx.doi.org/10.3390/ijms222111401 PMID: 34768832

[51] Gupta M, Anzelc M, Stetkevich S, Burkhart C. Bacteriophages: An alternative to combat antibiotic resistance? J Drugs Dermatol 2022; 21(12): 1311-5.
http://dx.doi.org/10.36849/JDD.6638 PMID: 36468950

[52] Lam HYP, Lai MJ, Chen TY, Wu WJ, Peng SY, Chang KC. Therapeutic effect of a newly isolated bacteriophage against multi-drug resistant *Cutibacterium acnes* infection in mice. Int J Mol Sci 2021; 22(13): 7031-47.
http://dx.doi.org/10.3390/ijms22137031 PMID: 34209998

[53] Keshari S, Kumar M, Balasubramaniam A, Chang TW, Tong Y, Huang CM. Prospects of acne vaccines targeting secreted virulence factors of *Cutibacterium acnes*. Expert Rev Vaccines 2019; 18(5): 433-7.
http://dx.doi.org/10.1080/14760584.2019.1593830 PMID: 30920859