

# New Treatments for Acne in The Context of Antibiotic Resistance

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**Abstract.** Acne has long been recognized as a widespread skin condition, and its prevalence is currently increasing. One of the top 10 epidemics in the world right now, it has a serious psychological toll on its victims. Four interconnected processes, including inflammation, increased sebum production, follicular infundibular hyperkeratosis, and *Chlamydia acne* growth, make up the disease's complicated pathophysiology. Antibiotics that target *P. acnes* have been a successful and popular way to treat acne for the past 40 years, even though the pathophysiology of acne is not entirely understood. The emergence of antibiotic resistance, however, is a persistent issue with a variety of negative consequences. Isotretinoin and antiandrogen therapy are frequent therapies for certain of them. This article summarizes the effectiveness and safety of oral antibiotics for acne treatment in recent years as well as some other recent treatment research, operating under the premise that the current domestic and international clinical trials of *acne vulgaris* are insufficient. The goal is to raise awareness of *acne vulgaris*.

**Keywords:** Acne; antibiotics; resistance; new treatments.

## 1. Introduction

Commonly referred to as acne, *acne vulgaris* is a persistent skin disorder that starts in the hair follicles and frequently results in inflammation. The infectious illness affects 85% of adolescents and young adults. 15% to 20% of all cases of acne are moderate or severe. While severe cases leave scars like acne, mild cases heal quickly. Acne makes up 0.29% of all skin conditions and 1.79% of the world's disease burden, according to the 2013 Global Burden of Disease Study. After dermatitis, acne is the second most prevalent skin condition.

Adapalene, benzoyl peroxide, adapalene and benzoyl peroxide combination pharmaceuticals, clindamycin, and benzoyl peroxide combination drugs such as antibiotics are medications and ointments that are strongly advised in the Japanese Academy of Dermatology's guidelines for treating acne. Adapalene and benzoyl peroxide are two of them that can both improve pore blockage and efficiently combat acne-causing germs. Additionally, antibiotics are used aggressively in conjunction with many treatments or with combination medications that already contain both drugs to treat acne bacteria. Standard treatment involves stopping oral antibiotics and topical lotions once the red pimples have healed and using adapalene or benzoyl peroxide to avoid recurrence (maintenance therapy). Additionally, there are procedures known as acne extractions in which the sebum that has built up in the pores is pierced and forced out with needles, as well as other do-it-yourself procedures like chemical peels and more. Retinoids and some antibiotics are covered by health insurance in the United States and other nations, but in Japan, the situation is still unclear.

Excessive sebum production, aberrant keratinocyte proliferation and differentiation, bacterial colonization, and host inflammatory response are thought to be four of these components that cause acne. Among these elements, it is believed that cutaneous commensal *P. acnes* mediates the inflammatory response and contributes to inflammatory and subclinical acne lesions. The hormonal etiology of acne can be successfully treated with spironolactone and combined oral contraceptives (including estrogen and progestin). Their use is restricted to females, though, and there is a chance that it could have negative systemic effects like hyperkalemia or thrombosis. Notably, it's important to point out that there are currently no topical treatments for acne that focus on the hormonal causes of acne.

Some previously used antibiotics (such as erythromycin and clindamycin) are no longer used clinically due to high resistance rates, and antibiotic resistance has become a growing concern in clinical practice. The problem is so serious that the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) are actively advocating programs to address antibiotic resistance. Improper use of antibiotics can produce many bad phenomena. According to the World Economic Forum, 99,000 annual hospital-acquired infection deaths in North America were largely attributed to antibiotic-resistant bacteria in 2013, costing healthcare systems \$210-\$3.4 billion.

To sum up, this article first summarizes the latest clinical trial results of some common drugs and conducts a literature review on these various antibiotic problems at home and abroad, to raise everyone's vigilance against antibiotic resistance and provide some latest treatment methods.

It is hoped that the way of treating acne in the future can slowly change from the mainstream form of oral acne treatment to a new model.

## 2. Literature References

### 2.1. The Discovery of Traditional Healing Modalities

Acne is one of the most common reasons for patients to visit a dermatologist in both African American and Caucasian patients (both over 20%), and it affects many people of all races and colors, including those with darker skin.

Adapalene, antibacterial substances, antiandrogens, benzoyl peroxide (BPO) preparations, and isotretinoin specifically target this and have bactericidal and bacteriostatic effects, limit inflammation, and effectively reduce sebum production as a result of changes in the activity of the sebaceous glands [1-2].

Therefore, in response to this phenomenon, in the study by Janet DuBois et al., 0.3% adapalene and 2.5% benzoyl peroxide gel (0.3% A/BPO) is useful. The subjects included people of different skin colors, including white, yellow, and black, from Mauritius, Singapore and the United States. Within 16 weeks, not only the subjects were required to use the drug (0.3% A/BPO) once a day, but also the patients were required to use foam lotion and sunscreen with oil control effect, and nearly 80% of the patients felt that the treatment effect was good or very good, on average, PIH was reduced by nearly 30% with no adverse events. Additionally, quality of life (QoL) and subject questionnaires, IGA, Investigator's Assessment of Global Improvement (GAI), post-inflammatory hyperpigmentation, and safety issues were also assessed, confirming the benefits of the treatment modality in patients with skin of color. Most patients are highly satisfied, and the symptoms of acne and PIH have been effectively improved. Another point is that 0.3% A/BPO is also well tolerated [3].

### 2.2. Antibiotic Clinical Trials

To clarify the impact of antimicrobial use on resistance, define resistant strains, and address the issue that the use of antimicrobial drugs for acne is linked to an increased occurrence of resistant *C. acnes*. A multicenter investigation was carried out by Keisuke Nakase and Sae Aoki in dermatological offices that frequently saw new acne, and Vulgaris patients. They examined acne strains using samples from 264 acne sufferers. Antimicrobial susceptibility tests revealed that the resistance rates to tetracyclines, macrolides, and clindamycin among *Chlamydia acnes* strains isolated from patients treated with antibacterial agents for acne were significantly higher than those of patients who did not use tetracyclines, macrolides, and clindamycin. Particularly, clindamycin-resistant bacteria were frequently seen in patients with severe/moderate acne and a higher median age (24 years). Transposed clindamycin resistance genes, *erm(X)* or *erm(50)*, were discovered in 14 strains after 15 high-level clindamycin-resistant strains were examined for their resistance mechanism. By using single-site sequence typing of *Chlamydia acnes*, the strains encoding *erm(X)* or *erm(50)*, multidrug resistance plasmid pTZC1, and tetracycline resistance gene *tet(W)* were grouped into clade F. Their findings demonstrated the use of patient information in determining if a patient carried drug-resistant *C. acnes*,

including antimicrobial use, age, and acne severity. Additionally, our findings imply that clade F strains are highly susceptible to developing multidrug resistance [4].

Another group of antibiotics frequently used to treat moderate to severe acne is tetracyclines. Antibiotic resistance is on the rise and calls for medical intervention, even if this class of antibiotics continues to be mainly effective against the majority of *P. acnes* isolates. In recent years, investigations in various regions have found that the frequency of tetracycline resistance varies from 2% to 30%. Between 2% and 44.2% of isolated *P. acnes* strains were resistant to doxycycline. Tetracycline and doxycycline combination medication resistance rates in various patient populations ranged from 1.2% to 100%. Low rates of resistance to minocycline (less than 2%) were found across Europe, Latin America, North America, and some areas of Asia, in contrast to the high rates of resistance to tetracycline and doxycycline. The G1058C mutation in the 16S rRNA gene of *P. acnes* is the cause of the organism's tetracycline resistance. Additionally, altered ribosomal S10 protein amino acid composition affects doxycycline sensitivity. There are some potential concerns related to long-term tetracycline usage, because of the increased antibiotic resistance linked to the rising use of oral tetracyclines. The use of doxycycline is linked to a higher risk of inflammatory bowel illness, irritable bowel syndrome, and gut dysbiosis. According to one study, taking doxycycline for acne treatment increased the risk of developing Crohn's disease by a factor of 2.25. Long-term usage of antibiotics has also been linked to an increased risk of breast and colon cancer, according to research.

However, more information is now required before conclusions can be made. Additionally, phototoxicity, urticaria, and lupus-like condition are side effects of tetracyclines. Tinnitus, pseudotumor brain, and vertigo are three side effects of these antibiotics that prevent military pilots from taking minocycline. The increased risk of vertigo and dizziness may be explained by the fact that minocycline passes the blood-brain barrier. Oral minocycline does not make the reduced resistance promise found on the label of topical minocycline. The use of tetracyclines is also known to cause candidiasis or vulvovaginal fungal infections [5].

### 2.3. New Treatment

In their review of the literature, they found that vaccines made by *Staphylococcus cephalus* E12 had been produced and studied for their capacity to prevent *P. acnes* overgrowth. Vaccination with antibodies against the Christie-Atkins-Munch-Petersen (CAMP) factor (associated with *Bacillus acnes* cytotoxicity) reduced the growth of *Bacillus acnes* and MIP-227 in mice. Because eliminating *P. acnes* causes inflammatory cytokines to be released, monoclonal antibodies that inhibit cytokines were necessary to control inflammation. However, it was anticipated that vaccines created by *S. capitis* would both prevent and eradicate *P. acnes* overgrowth. The possibility of developing an acne vaccination that specifically targets *Clostridium acnes*-released virulence factors, such as secreted Christie-Atkins-Monk-Petersen, was suggested by Sunita Keshari and Manish Kumar (CAMP).

Therefore, major measures can be taken to prevent future cases of acne vulgaris by launching public immunization campaigns at an early stage. The risk of secreted virulence factors disrupting the microbial ecosystem in the human skin microbiome is low. Therapeutic monoclonal antibodies could be developed in the future to precisely neutralize *C. acnes* virulence factors like CAMP factors without disrupting the ideal balance of *C. acnes* in the human skin microbiome and preventing the emergence of resistant *C. acnes*. Acne vulgaris treatment may now include a focus on secreted virulence factors without disrupting the host symbiosis [6].

Salicylic acid is a topical medication that can be used as a treatment. Haibo Liu and Haiyan Yu examined the effectiveness of topical acne treatments including azelaic acid, salicylic acid, plus a few other chemicals. Comparing multiple topical treatments with each other, placebo and randomized controlled clinical trials comparing no treatment with another topical treatment. More than 3,800 people participated in the trial, which was conducted in clinics and academic institutions around the world (Europe, Asia, and the United States). Many of the participants were female, aged 12 to 30 (range: 10 to 45), and had mild to moderate acne. More than half of the treatments lasted longer than eight weeks. The study, which lasted from three months to three years, concluded that treatment

responses to azelaic acid may not be as good as those to benzoyl peroxide, as determined by the PGA. Azelaic acid may not have as great an effect on treatment response as tretinoin, but unfortunately the quality of evidence for the various comparisons and outcomes was low or very low [7].

A new alternative therapy that provides a special acne treatment is light therapy. Currently, intense pulsed light (IPL) and photodynamic therapy (PDT) are two high-irradiance light approaches used to treat mild to moderate inflammatory acne (PDT). When compared to traditional treatments like BPO, Mara Licia Gonçalves Diogo and Thalita Molinos Campos showed that LED and blue light device treatments can effectively improve acne with little to no side effects. Red light combined with blue light initially produced superior success in reducing acne lesions (76%), which did not happen at the end of therapy. At the end of the course of treatment, blue light alone was still quite beneficial, with an average improvement in acne lesions of 54% (comedone 45%, inflammatory lesions 63%). This finding shows that exposing *C. acnes* colonies to visible blue light causes photoexcitation of bacterial porphyrins, the generation of singlet oxygen, and ultimately bacterial destruction, implying that blue light can be used to treat acne. It also backs up the majority of studies that look at the impact of blue light on acne treatment. The use of visible light phototherapy proved effective [8].

The US FDA authorized Krascoprogestrone 1% Cream in August 2020 as a brand-new treatment for acne vulgaris in patients 12 years of age and older. Krascoprogestrone 1% Cream demonstrated superior acne vulgaris treatment efficacy in comparison to the carrier cream with fewer side effects. Clascoprogestrone 1% cream is a brand-new and promising therapeutic option for treating acne vulgaris in patients under the age of 12. Clarascodone appears to be a safe and effective treatment, with the most frequent side effects being erythema, dryness, and itching, according to the evidence supporting its usage. Notably, no appreciable systemic effects of systemic anti-androgens were seen with this topical drug, and there is no proof that clascoprogestrone is safe to use while pregnant or nursing, that it is effective with current combination therapies, or that it is comparable to other topical and systemic treatments for acne. The effectiveness of claricogestrone 1% cream compared to its comparator, tretinoin 0.05% cream, was demonstrated in a prior small trial ( $n = 77$ ), however further research is needed to confirm these results on a wider scale. Subgroup analysis may help direct the clinical application of clascoprogestrone in particular patient populations. More research is required to determine the long-term safety and efficacy of clascoprogestrone paired with other medications [9].

Diet is closely related to acne because it is a fundamental part of being human. Jerry Tan and Hilary Baldwin examine the limitations of diet and acne research and the supporting data on how diet affects acne and how it can be treated. When omega-3 fatty acids are consumed regularly, along with some low-fat dietary options, acne can be successfully reduced. Milk may also increase the frequency and severity of acne lesions, according to numerous studies. That said, low-glycemic diets often improve acne outcomes. But the fact that low-glycemic diets have produced variable results in acne patients may require further treatment beyond dietary changes to minimize acne. Also, there have been reports that probiotics are effective in reducing acne lesions, but more research is needed to confirm these preliminary results. Since there is so little research in this area, more research into the effects of vegan/vegetarian and ketogenic diets on acne is warranted [10].

For one thing, food seems to have a major impact on the effectiveness of acne treatments like tetracycline antibiotics. There is strong evidence that dairy-free treatment promotes optimal absorption. Studies have demonstrated that lip sugar-isotretinoin does not require a high-fat meal for maximum absorption, despite the prescribing instructions for isotretinoin indicating that coadministration with a high-fat meal promotes bioavailability. As a result, more recent isotretinoin formulations, like lidose-isotretinoin, might not call for coadministration with a particular diet. Healthcare professionals should tell patients about how their food choices can improve the efficacy of their treatment and possibly lower the risk of relapse when treatment is ended for all prescribed medications [10].

### 3. Conclusion

This article presents some of the most recent treatments after first summarizing the most recent clinical trial findings for a few widely used medications. There are still numerous new therapeutic options available due to the development of new antibiotic resistance. Future acne treatments may include topical antiandrogens, melanocortin receptor antagonists, IGF -1 inhibitors, PPAR modulators, acetylcholine inhibitors, topical retinoic acid, and metabolic blockers, and However, there is also a tendency to gradually switch from oral treatment to external treatment in addition to oral drugs. Topical treatment not only brings effective therapeutic effects but also has much fewer side effects than oral treatment. However, the crux of the matter now is that there is so little clinical trial data on these topical treatments that it will be a great challenge to use them as medical coverage in the future. Finally, scarring is the most troublesome complication of acne. However, there is a problem there is a serious lack of clinical data. The prevention of acne marks and how to effectively treat wounds after they appear are the key. In addition, the negative effects of topical treatment are far lower than those of oral medication, in addition to having excellent therapeutic results. The problem presently, though, is that there are so few clinical trial results available for these topical medicines that it will be extremely difficult to use them as medical insurance in the future. Finally, the most difficult acne problem to treat is scar formation. The major treatments to avoid acne scars will be immune induction and wound healing therapy, but they also struggle with the serious issue of a lack of clinical data.

Acne, as a skin disease that is very difficult to cure and almost impossible to cure, often plagues patients. Although there are some very powerful drugs, drug resistance will appear after long-term use, and even the damage to the human body will be transferred from the skin to the internal organs. . But once you stop taking it, the acne will reappear. This article summarizes these clinical trials and literature reviews, which will have a positive impact on the treatment of acne in the future. It is hoped that there will be more experimental data in the future to promote the development of acne treatment. In addition, I also hope to provide clinicians with new treatment ideas and treat acne in different ways for patients with different races, skin colors, different causes, and different degrees of severity. It is also hoped that the promotion of acne vaccines will be further transformed into practical actions.

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