Expert Opinion

Emerging drugs for acne

Kirk A James, Craig N Burkhart† & Dean S Morrell
†*UNC School of Medicine - Dermatology, 410 Market Street, Suite 200 Chapel Hill, NC 27516, USA*

Acne vulgaris is a common skin disorder that affects most individuals at some point in their lives. It may result in significant morbidity, including cutaneous scarring and psychological impairment. Current treatments include topical retinoids, benzoyl peroxide, topical and systemic antibiotics, and systemic isotretinoin. There are growing concerns of rising antibiotic resistance, significant side effects of isotretinoin therapy, and lack of safe and effective treatment for pregnant females. Recent advances in the pathogenesis of acne have led to a greater understanding of the underlying inflammatory mechanisms and the role the *Propionibacterium acnes* and biofilms. This has led to the development of new therapeutic targets. This article reviews emerging treatments of acne, including topical picolinic acid, topical antibiotic dapsone, systemic zinc salts, oral antibiotic lymecycline, new formulations of and synergistic combinations of benzoyl peroxide, photodynamic therapy with topical photosensitizers and potential acne vaccines.

Keywords: acne, acne vulgaris, biofilm, dapsone, new treatments, photodynamic therapy, picolinic acid, synergy, vaccine, zinc

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1. Background

Acne vulgaris is a common skin disorder that is characterized by a spectrum of cutaneous lesions. This spectrum ranges from non-inflammatory comedones, such as blackheads and whiteheads, to inflammatory lesions that may consist of papules, pustules and/or nodules. Adolescence is the most common period in which acne begins and is subsequently diagnosed. Furthermore, it is estimated that > 85% of teenagers are afflicted with the disorder [1,2]. However, acne may initially present during or persist into adulthood. Acne is more common in males than females during adolescence; in contrast, acne is more common in females during adulthood [3]. Acne may result in a distorted body image and visible scarring, which may lead to low self-esteem and influence the development of psychological and social impairment: it has been associated with anxiety, depression and social withdrawal [4]. In the US, the direct cost of acne is high, as it is estimated be greater than $ 1 billion a year, with $ 100 million being attributed to over-the-counter products [5].

Pilosebaceous glands, which arise from hair follicles, are the sites from which acne lesions arise. These glands, corresponding to the areas of the body most commonly afflicted by acne, are found most numerously on the face, back and chest. As the level of circulating androgens increase during puberty, the size and activity of pilosebaceous glands increase and reaches a peak by 20 – 30 years of age [6].

The pathophysiology of acne is associated with four etiological factors, including: hyperplasia of the pilosebaceous duct, increased sebum (the oily substance produced by a pilosebaceous gland) production, colonization with *Propionibacterium acnes*, and inflammatory and immune response of the body. *Propionibacterium acnes* is the principal microorganism found within the pilosebaceous gland. Its role in acne pathogenesis may be related to its ability within the pilosebaceous unit to create and exist as a biofilm [7], which is a population of microorganisms that live within a self-made, extracellular polysaccharide encasement that is adherent to either an artificial or living surface.

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2. Medical need

Acne vulgaris is estimated to affect ~ 17 million people in the US, and 85 – 100% people at some point in their lives [3,8]. Although the prevalence peaks during the teenage years and subsequently decreases during adulthood, 8% of those aged 25 – 34 years and 3% of those aged 35 – 44 years have acne [8]. Acne results in an extremely large number of office visits to both dermatologists and primary care physicians alike. Given that many current treatments have potential for significant side effects, contraindications that preclude use in certain groups and experience-reduced responsiveness, there is a need to develop safer and effective options to treat this common skin disorder.

3. Existing treatment

The current standard treatment of acne vulgaris is targeted towards both the severity and type of lesions involved, and consists of a combination of topical and systemic agents. Based on the type and number of specific lesions present on an individual, acne severity is usually considered comedonal (mild), inflammatory (moderate) or nodulocystic (severe) [9]. Existing treatments target one or more of the four traditional pathogenic factors involved in acne.

3.1 Existing topical therapy

Topical retinoids, benzoyl peroxide and antibiotics are used to treat comedonal and mild to moderate inflammatory acne. These are most commonly used in combination with one another.

The current topical retinoid therapies include tretinoin, adapalene and tazarotene. They are thought to inhibit acne through several mechanisms, including the induction of comedolysis, inhibition of inflammation and normalization of follicular hyperproliferation, and hyperkeratinization [10]. Retinoids are the foundation of topical acne therapy and are considered a first-line treatment of mild to moderate acne. Their side effects are generally limited to local skin irritation, such as peeling or erythema.

Benzoyl peroxide is comedolytic [11] and bactericidal [12] to *P. acnes*. It is the oldest and most widely used topical agent for the treatment of non-inflammatory and inflammatory acne vulgaris. This chemical's main mechanism of action is characterized by the cleavage of oxygen–oxygen bonds, which result in the production of benzoyl free radicals [12]. This triggers a cascade of events, resulting in the formation of more free radicals. These free radicals act as exfoliating agents, which clear pores and increase skin turnover: this helps treat the non-inflammatory comedones of acne. The free radicals also destroy bacteria in both aerobic and anaerobic conditions, which is an important feature considering the primary pathogen responsible for the inflammatory lesions, *P. acnes*, is an aerotolerant anaerobe. Benzoyl peroxide has not been associated with antibiotic resistance[13]. It is the most widely used topical agent for acne as it has proven efficacy, minimal side effects, broad availability and affordability.

Topical antibiotics consist of erythromycin, clindamycin, and less commonly, tetracycline. They act as both antibacterial and anti-inflammatory agents, and are thus reserved for inflammatory acne. Their ability to reduce inflammation is thought to be related to the suppression of leukocyte chemotaxis, reduction of pro-inflammatory free fatty acids within sebum and a decrease in the amount of *P. acnes* organisms [14]. There have been growing concerns about antibiotic resistance, and it is recommended that topical antibiotics be combined with other topical retinoids or benzoyl peroxide to decrease the emergence of drug resistance.

3.2 Existing systemic treatment

Oral antibiotics are used for moderate to severe inflammatory acne. Like topical antibiotics, they have both antibacterial and anti-inflammatory properties. Drugs of the tetracycline class, (doxycycline, minocycline and tetracycline), erythromycin (a macrolide) and trimethoprim are most often prescribed. The lipophilic antibiotics, such as doxycycline and minocycline, are generally more effective than others. They have traditionally been very effective, but according to recommendations of the 'European expert group on oral antibiotics and acne,' use should not exceed 3 months, as the risk of developing antibiotic resistance is known to increase after 3 months of use [15]. In clinical practice, however, use may be continued longer until improvement is noted. In addition to the increased risk of resistance, prolonged systemic antibiotic use can alter the normal flora of the body, subsequently elevating the risk of opportunistic infection. One study found a higher incidence of upper respiratory infections in those on oral antibiotics for acne, but no increased risk of developing a urinary tract infection [16]. Further study is needed to confirm and better understand these findings. Side effects of the tetracycline class include most commonly gastrointestinal complaints, such as nausea or vomiting [17]. Dose-dependent photosensitivity may be noted with doxycycline [18], and this class is contraindicated in pregnancy and children younger than 10, as it may cause yellow discoloration of the teeth and hypoplasia of tooth enamel [10,19]. Erythromycin is associated with nausea, vomiting and abdominal cramps [20].

Isotretinoin, a vitamin A metabolite, is typically reserved for severe nodular acne that is unresponsive to other forms of treatment. It targets all four pathogenic factors of acne, as it decreases sebum production by ~ 70%, reduces the amount of *P. acnes* organisms, inhibits inflammation and normalizes follicular proliferation [3]. This is an effective treatment, but is severely teratogenic [21] and can be associated with multiple side effects. Therefore, its use is restricted by the FDA in the US.

In women, hormonal agents, such as oral contraceptives and spironolactone, can also be considered, especially if ovarian or adrenal hyperandrogenism is suspected. Oral contraceptives are thought to increase the amount of serum sex hormone-binding globulin, which reduces the amount of

circulating free testosterone [22]. This treatment can be rarely associated with severe cardiovascular side effects. Spironolactone decreases androgen production by binding to the androgen receptor, preventing its interaction with dihydrotestosterone [23]. Its most significant side effect is hyperkalemia, and it should be avoided during pregnancy to prevent feminization of the male fetus.

3.3 Limitations of existing treatment

The main limitation of current antibiotic treatment for acne is the rise of antibiotic resistance. Although there have been studies that have been conducted *in vitro* that show increased resistance of *P. acnes* colonies to certain antibiotics, it is important to note that this bacteria is thought to exist as a biofilm within the pilosebaceous unit *in vivo*, not as a freely mobile microorganism [7]. Unfortunately, *P. acnes* does not exist as a biofilm *in vitro*. Therefore, studies that have shown increased antibiotic resistance of the freely movable bacterial colonies *in vitro* do not really provide an accurate assessment of the resistance of the bacteria within the pilosebaceous unit, unless there is a subsequent association to a lack of or diminished clinical response [24]. Nevertheless, a recent review cited studies that have taken *P. acnes* isolates and tested their resistance to various drugs *in vitro* demonstrating that one out of every two acne patients in the UK is colonized with strains that are resistant to erythromycin and clindamycin [25]. Although they found a smaller percentage of patients that had strains that were resistant to tetracycline, these *P. acnes* variants usually had resistance to erythromycin and clindamycin as well. Another study reported a near doubling of the proportion of acne patients with antibiotic-resistant *P. acnes* from 34.5% in 1991 to 64% in 1997[26].

Possible methods to determine antibiotic resistance of *P. acnes* are studies that show either decreased clinically-oriented outcomes with the same concentrations over time, or increased concentration or duration of antibiotic treatment needed to achieve the same clinical results. In order to determine a decreased efficacy in reducing the amount of acne lesions, it is easiest to follow the clinical results of antibiotic treatment over time. For instance, a systemic review revealed that 1.5 – 2% topical erythromycin used for 12 weeks had a 60 – 40% decrease in inflammatory lesion counts from the early 1980s to the early 1990s, but by the late 1990s, the antibiotic only produced a 20% decrease in lesion count [27]. Another study showed a correlation between decreased *in vitro* sensitivity or increased resistance to tetracycline and erythromycin and a poorer clinical response [28].

Although isoretinoin therapy is very effective, it is associated with many potential side effects. These include dry skin, lips, and eyes, headache, decreased night vision, and more rarely, benign intracranial hypertension. It may also lead to an increase in liver enzymes [29] and hypertriglyceridemia [30]; the latter may potentially trigger acute pancreatitis. Additionally, isotretinoin is a highly teratogenic agent, especially if used within the first trimester of pregnancy. It is essential that a female have two negative pregnancy tests before beginning treatment, and must have negative pregnancy tests throughout treatment and 6 weeks after cessation; oral contraceptives are typically prescribed during this period to prevent pregnancy. Furthermore, treating acne, especially moderate to severe inflammatory variants, is especially challenging during pregnancy because most of the systemic antibiotics cannot be safely used during this time period either.

It is a concern for the potential rise in antibiotic resistance, teratogenicity and unfavorable side effect profile of isotretinoin, a lack of safe treatment options during pregnancy and the identification of previously unknown microbiological targets such as the biofilm hypothesis that necessitate the need to explore the potential of evolving alternative treatments for acne vulgaris.

4. Current research goals

Recent advances have led to new potential therapeutic targets, such as the light-absorbing porphyrins produced by *P. acnes* and components of biofilms. Given that the immune system's inflammatory response is a complex interplay between various cells and chemical mediators, our understanding of it will constantly change. As we delve further into the *P. acnes* biofilm and the reason that makes it so difficult to break down and eradicate, we will find new therapeutic targets. There should also be a constant focus on finding new antibiotic treatments or combination treatments to prevent the development of antibiotic resistance, which has been a growing problem. Thus, as our understanding of the complex pathogenesis of acne is improved, more therapeutic targets will be revealed, and these will hopefully lead to more effective treatment options for patients with acne vulgaris. Additionally, there have been studies that have tested the efficacy of *P. acnes* vaccines in animal models of acne.

5. Scientific rationale

Current drug therapies typically target one of the four traditional pathogenic factors of acne mentioned earlier. Advances in the understanding of the pathogenesis of acne have led to two new potential therapeutic targets. As stated before, these include the hypothesis that the *P. acnes* biofilm may be a central event in the acne pathogenesis and the fact that *P. acnes* generates photosensitizing porphyrins within the pilosebaceous unit.

5.1 Four traditional pathogenic factors

5.1.1 Pilosebaceous hyperplasia

Follicles that are affected by acne show increased keratinocyte proliferation with subsequent abnormalities in desquamation, which leads to marked accumulation of these cells within the follicle. The end result is the production of microcomedones which eventually become grossly visible comedones. This is considered to be the first step in the pathogenesis of acne.

Follicular hyperkeratosis is thought to result from several possible factors including a deficiency in linolic acid or the production of certain comedogenic peroxides within sebum [10]. Inflammatory mediators may also play a role, as one study showed that ample concentrations IL-1 within the follicle can induce hyperkeratosis [31]. Recently, with the discovery that *P. acnes* can create and exist as a biofilm, it is thought that the secreted glycocalyx polymer can actually become incorporated into the sebum composition and act as biological glue between keratinocytes, and thus, ultimately lead to the production of comedones [32]. Therefore, it is highly plausible that the initial step may not even be hyperkeratosis of the follicle, but rather colonization with *P. acnes* and subsequent biofilm formation.

5.1.2 Increased sebum production

Excess sebum production can be caused by several different factors. Androgens induce the production of sebum, and their abrupt increase during puberty explains why acne begins during adolescence. It also helps explain why those with hyperandrogenism (e.g., polycystic ovarian syndrome, adrenal tumors) usually have acne manifestations. However, most acne patients have normal circulating levels of androgen within their serum [10]. It is hypothesized that these individuals possess sebocytes that have an increased sensitivity to androgens. Specific neuroendocrine peptides (corticotrophin-releasing hormone and α-melanocortin) have also been shown to stimulate lipid synthesis by sebocytes *in vitro*, which supports an association between stress and acne [33].

5.1.3 Colonization by Propionibacterium acnes

Propionibacterium acnes is an aerotolerant anaerobe that prefers anaerobic areas with increased lipid content. This explains why this bacterium thrives and proliferates in a pilosebaceous unit that has been plugged from hyperkeratosis (and thus, lacking contact with environmental oxygen) and has increased sebum production. Additionally, *P. acnes* possesses the ability to form a biofilm within the follicle.

5.1.4 Immune response and inflammation

Multiple inflammatory mediators are involved in the pathogenesis of acne. *Propionibacterium acnes* binds directly to toll-like receptor-2 (TLR2) on monocytes and neutrophils [34]. TLR2 is a surface-membrane protein receptor involved in immune activation through the release of inflammatory cytokines [35,36]. Thus, these immune cells then produce pro-inflammatory cytokines, including TNF-α, IL-1 and IL-8, which act as chemotactic factors for the migration of more neutrophils and lymphocytes. *Propionibacterium acnes* also releases metabolites, such as lipases and proteases, which result in an inflammatory response by the host's immune system [37]. *Propionibacterium acnes* may also induce the expression and secretion of MMP-9, an inflammatory mediator, by keratinocytes [34]. In addition to the aforementioned secondary immune response, there is mounting evidence that primary immune response may even be the initiating event in acne. Perifollicular leukocytes, such as helper T-cells, could potentially form initial comedones through the release of IL-1 [38]. The study by Jeremy *et al.* demonstrated that there is an increase in the numbers of $CD3^+$, $CD4^+$ T cells in the perifollicular and papillary dermis of follicles from uninvolved skin of acne patients compared to normal skin of non-acne controls. The uninvolved skin follicles of the acne patients did not show microcomedonal features or keratinocyte hyperproliferation. This evidence supports the possibility that inflammation of the follicle precedes the traditional first step of acne pathogenesis. There was also increased upregulation of IL-1 perifollicularly. However, the level of T cells was not as great as those found in papules of early inflamed lesions of acne patients. As these inflammatory mechanisms are further uncovered, they could present new potential therapeutic targets for future acne treatment.

5.2 Other pathogenic factors

5.2.1 Biofilm

The first step in the formation of a biofilm is the adherence of bacteria to a surface, in this case, *P. acnes* attaching to the pilosebaceous gland wall. The attached bacteria then begin to facilitate the attachment of other bacteria and undergo cell division to extend the population. The biofilm is established as the bacteria begin to secrete an extracellular polysaccharide substance that coats the surface of their colony. This coating provides physical protection, as it acts as a barrier between the cell populations underlying the biofilm and the relative exterior environment.

The genome sequence of *P. acnes* has been shown to contain clusters of genes involved the biosynthesis of a glycocalyx polymer [39,40]. The biofilm concept explains why antibiotics must be prescribed for months while treating acne: the biofilm limits and retards the penetration of antibiotics into its microenvironment of organisms. In addition, the microenvironment created by the biofilm also stimulates the production of certain proteins which may enhance antibiotic resistance of the colonies. This framework provides new targets for potential therapies aimed at halting the progress of biofilm formation. These include therapies that prevent the initial attachment step of *P. acnes* to the pilosebaceous wall, inhibit or alter the formation of the extracellular glycolax polysaccharide, target specific components of the biofilm or enhance the penetration of the antibiotic through the extracellular matrix [7].

5.2.2 Porphyrin production

Porphyrins are metabolic products of *P. acnes* with the innate ability to absorb light, which enables them to form free radicals [41]. These free radicals have direct inflammatory effects, as they can help damage and destroy *P. acnes* and the glycocalyx capsule of its biofilm. Additionally, there is evidence that these chemicals may induce the expression of IL-8 by keratinocytes [42]. It is suggested that this cytokine may trigger the production

of inflammatory substances, such as squalene peroxide, which may lead to perifollicular inflammation [43].

6. Competitive environment

6.1 Topical therapy

6.1.1 *Picolinic acid*

Picolinic acid is thought to act as a chelating agent of various transitional metal ions in the human body, such as zinc, iron, chromium and copper. By binding to ions such as zinc, it increases their uptake into the circulatory system and through the gastrointestinal membrane [44]. Furthermore, picolinic acid has been shown to have antiviral, antibacterial and immune-modulating properties [45]. It disturbs zinc binding within zinc finger proteins, which are DNA-binding proteins that usually exist as part of transcription factors [46]. By altering this interaction, picolinic acid leads to the alteration of chemokine expression. Specifically, Bosco *et al.* found that picolinic acid is potent activator of the inflammatory chemokines macrophage inflammatory protein-1 α and β in murine macrophages [47]. Although its action against *P. acnes* has not been formally studied, picolinic acid has been shown to be particularly effective in inhibiting mycobacterial growth both extracellularly and intracellularly [48].

In a recent study, the application of a 10% picolinic acid gel twice a day to the face for 12 weeks reduced the amount of total acne lesions by 58.2%, inflammatory lesions by 55.2% and non-inflammatory lesions by 59.7% in 20 patients with mild to moderate acne vulgaris by the end of the study [49]. The side effects were considered mild, and the most common was burning at the application site. Although the results of the study are encouraging, it is still necessary to confirm these with a randomized control study.

6.1.2 *Anti-inflammatory/antibiotic therapy*

6.1.2.1 *Dapsone*

Dapsone is an antibacterial medication traditionally used to treat *Mycobacterium leprae* infections; however, two recent studies have shown that a 5% dapsone topical gel solution is effective in reducing the amount of both non-inflammatory and inflammatory acne lesions when used as a monotherapy and applied twice a day for 12 weeks [50]. The most pronounced effect was in treating the inflammatory lesions, which decreased by 47.5% after 12 weeks of treatment.

It is thought that dapsone possesses anti-inflammatory properties that are especially beneficial in treating inflammatory acne. Proposed mechanisms of action include the inhibition of leukocyte migration and subsequent release of cytokines, and altering of the action of *P. acnes* in the pilosebaceous unit [50].

The side effect profile is considered safe, with the most abnormal events being local site reactions such as dryness and erythema. Unlike dapsone delivered by the oral route which may cause dose-dependent hemolysis and should be used cautiously in those with glucose-6-phosphatase deficiency (G6PD), [51] the topical preparation resulted in no changes from baseline hematologic status in those with or without G6PD deficiency, most likely attributable to limited systemic absorption [52].

6.2 Systemic therapy

6.2.1 *Systemic minerals*

6.2.1.1 *Zinc salts*

Zinc salts have been proposed to be helpful in reducing the severity of inflammatory acne by a variety of mechanisms. First, zinc has been shown to inhibit the migration of neutrophils to sites of inflammation, and thus prevent or reduce acute inflammatory processes [53]. The growth of the acne-causative bacterium *P. acnes* has been shown to be hindered by zinc [53]. Additionally, recent studies have shown that zinc reduces the expression of TLR2 on the surface of keratinocytes [54]. Limiting its expression subsequently inhibits the activation of the immune response. Other anti-inflammatory mechanisms of action include decreasing the release of both TNF-α and IL-6, which are cytokines involved in inflammation [55].

Oral zinc salt preparations have historically been shown to be effective in reducing the severity of mild and moderate inflammatory acne vulgaris when either used alone or in combination with another acne treatment [56,57]. A recent study compared the effectiveness of oral zinc gluconate to the antibiotic minocycline, and although the latter decreased the amount of inflammatory acne lesions by a larger percentage, zinc was still viewed as a viable alternative [58]. The major side effects of systemic zinc treatment include nausea and vomiting, but these are dose-dependent and usually transient.

In one study, topical erythromycin preparations combined with zinc and applied twice daily reduced the acne severity grade and papule count in comparison to using placebo, and was just as effective as using oral tetracycline twice a day [59]. These results could be explained by a later study, which found that adding zinc salts to *in vitro P. acnes* cultures reduced the resistance of the bacterium to erythromycin [60]. This suggests that zinc should definitely be considered when treating acne with erythromycin, especially given the increase in erythromycin-resistant *P. acnes*.

6.2.2 *Systemic antibiotics*

6.2.2.1 *Lymecycline*

Lymecycline is a broad spectrum antibiotic of the tetracycline class. It is more water-soluble than tetracycline at physiological pH values, and is, therefore, absorbed more quickly and delivered faster to tissues [61]. Because of its better absorption capabilities, lymecycline is used at lower doses than tetracycline. Specifically, 408 mg of lymecycline is equivalent in its action to 500 mg of tetracycline hydrochloride [62]. Other benefits of lymecycline include: a lower potential to form ulcers than doxycycline and oxytetracycline [63] and a higher tolerability with regard to photosensitivity when compared to doxycycline [64].

When compared with minocycline, lymecycline was shown to be just as effective in reducing the amount of both

inflammatory and non-inflammatory lesions over 12 weeks of therapy in patients with mild to moderate acne vulgaris [65]. The two drugs also shared similar side effect profiles; one study suggests that lymecycline is associated with slightly fewer adverse gastrointestinal and dermatological effects. However, the most notable finding of the study was lymecycline being four times more cost-effective [65]. The total treatment cost for lymecycline for 12 weeks was £ 17.88, whereas the cost of minocycline during this same time period was £ 70.46, a considerable difference of £ 52.58. Additionally, some studies have noted certain rare, life-threatening hypersensitivity reactions with minocycline use, including serum sickness-like disease and eosinophilic pneumonitis [66] and autoimmune reactions, such as drug-induced lupus and autoimmune hepatitis [67,68]. These syndromes have not been reported with lymecycline use [69].

The addition of adapalene gel to lymecycline may result in a shorter treatment duration that may, in turn, reduce the risk of the development of antibiotic resistance. One study explored the use of 0.1% adapalene gel combined with oral lymecycline 300 mg/day versus the use of oral lymecycline and a placebo gel for 12 weeks [70]. The results showed not only a significantly higher reduction of the mean number of total, inflammatory and non-inflammatory groups in the combination group, but also showed a significant difference in treatment beginning at week 8.

6.3 Synergistic benzoyl peroxide treatment combinations

Recent research suggests that the benzoyl peroxide free radicals are more highly active in the presence of a chemical compound that possesses a tertiary amine within its structure, including the antibiotics clindamycin and erythromycin [71]. Additionally, benzoyl peroxide penetrates comedones and microcomedones, which exposes the bacteria to higher concentrations of both more benzoyl peroxide and the antibiotic. The antibiotic then has both antibacterial and anti-inflammatory properties; for example, clindamycin inhibits leukocyte chemotaxis and is bacteriostatic [72]. Other studies have shown that the chemical with the tertiary amine does not even need to be an antibiotic, as other substances have been used to activate benzoyl peroxide in the treatment of other skin diseases [73]. Nevertheless, studies have suggested that the use of benzoyl peroxide in combination with the aforementioned antibiotics may prevent the development of antibiotic resistance as well as improve the clinical manifestations of acne vulgaris in those who have already developed antibiotic resistance [74,75]. The development of resistance to acne treatment can be explained, in part, by the formation of biofilm by *P. acnes*. Enhanced free radical activity should help break this barrier and result in the clinical improvement of symptoms. A recent randomized, single-blind comparison of topical clindamycin plus benzoyl peroxide versus adapalene for mild to moderate acne showed that although both were effective treatments for acne, the combination therapy had a faster onset of action, resulted in a greater decrease in inflammatory and total lesions, and was better tolerated overall [76]. The authors suggested that the earlier onset of action and relatively mild side effect profile will improve compliance, as many adolescents are easily discouraged by slow onset of actions (and thus, delayed visible results) and intolerable side effects.

6.4 Solubilized benzoyl peroxide formulations

There have been studies that have noted the increased efficacy of solubilized benzoyl peroxide preparations, as benzoyl peroxide is a poorly soluble chemical compound. It is thought that by making a benzoyl peroxide solution more soluble, it would increase bioavailability and enhance follicular penetration [77]. Preliminary studies show that solubilizing benzoyl peroxide in toluene improves antibacterial activity against aerobes and anaerobes *in vitro* [78]. Unfortunately, toluene cannot be used *in vivo*, as it is carcinogenic and toxic to humans. Another 4-week study consisting of 23 patients with moderate inflammatory acne tested solubilized benzoyl peroxide treatment versus a combination of benzoyl peroxide and clindamycin [79]. The results showed that solubilized benzoyl peroxide treatment showed a greater decrease in non-inflammatory lesions by the first week and inflammatory lesions by the fourth week than the combination therapy. Both therapies had a comparable patient satisfaction and side effect profiles. The implications of these findings suggest that solubilizing benzoyl peroxide is at least as, if not more, effective as the synergistic combination of clindamycin and benzoyl peroxide. This antibiotic-sparing therapy is important because it would prevent the progression of antibiotic resistance. However, larger, randomized studies are still needed to verify and better define these findings.

6.5 Photodynamic therapy

Research has shown that *P. acnes* naturally produces porphyrins, mainly protoporphyrin and coproporphyrin. These compounds are photosensitizers with the ability to absorb light and subsequently undergo excitation, which allows them to form reactive free radicals [41]. These free radicals, such as the type produced by benzoyl peroxide, are very reactive and are capable of destroying bacteria. Photodyanamic therapy (PDT) takes advantage of these naturally produced porphyrins and uses an exogenous light source to excite these porphyrins to produce the free radicals. Certain compounds are able to act as topical photosensitizing agents and augment the absorption of light by porphyrins and subsequent production of free radicals. These include aminolaevulinic acid (ALA) and two esterified derivatives of ALA, methylaminolaevulinate hydrochloride (MAL) and hexyl aminolaevulinate hydrochloride (HAL) [80]. When applied onto the affected area, topical ALA or its derivatives are taken up by the pilosebaceous units. ALA is converted to protoporphyrin IX (PpIX) by intracellular enzymes involved in the heme cycle [81]. Both MAL and HAL are hydrolyzed to ALA first, but they have a higher potential for penetration into the cells given

their lipophilic nature, and they subsequently cause a greater accumulation of photoactive porphyrins [80]. PpIX accumulates within the pilosebaceous unit, increasing the amount of porphyrins that are able to absorb light and form free radicals. PDT entails applying a topical photosensitizing cream to the skin, and then illuminating the area with a specific light source of a specific wavelength for a certain period of time [41]. The peak light absorption of PpIX is at a wavelength of 415 nm (blue light) and 630 nm (red light), and these are two commonly used light sources during PDT [82].

The efficacy of ALA-PDT has been demonstrated by multiple studies. One study found that topical ALA-PDT plus red light inhibits two pathogenic steps of acne: it causes prolonged cessation of sebaceous gland function, and thus inhibiting sebum production, and decreases the amount of follicular bacteria [83]. And although there was a clinical and statistically significant clearance of inflammatory acne by this therapy, it was found to be associated with significant side effects, such as transient hyperpigmentation, superficial exfoliation and crusting, all without scarring, however.

Various studies have shown that both ALA- and MLT-PDT are effective at treating acne vulgaris. There is one recent study that compared the efficacy of those two photosensitizers. Fifteen patients with at least 12 inflammatory acne lesions received one split-face treatment with ALA and one with MLT, and they were subsequently followed up at 6 and 12 weeks [84]. At 12 weeks, there was a 59% median reduction in the inflammatory acne lesions on both treated sides of the face and thus, no differences in efficacy between the two treatments. However, the authors did note a slight increase in the median amount of non-inflammatory lesions on both sides of the face at the 12 week mark. The one difference that they did find was that ALA-PDT was associated with more severe and prolonged side effects, including swelling and erythema of the skin.

6.6 Vaccine for Propionibacterium acnes

Although the inflammatory immune response to *P. acnes* definitely plays a role in the pathogenesis of acne, the organism's ability to form a biofilm and its direct cytotoxic effects have made further research in vaccines worth pursuing. In a recent study by Nakatsuji *et al.*, an acne vaccine was created that targeted a cell wall-anchored sialidase of *P. acnes* [85]. Sialidases are thought to be used by *P. acnes* in order to catabolize sialoglycoconjugates to obtain sialic acids that ultimately act as substrates for energy production [39]. However, authors of the study also note that sialidase may also facilitate the adhesion of *P. acnes* to sebocytes. The results of the study show that mice immunized with anti-*P. acnes* sialidase antibody produced detectable antibody levels, effectively neutralized the cytotoxicity of *P. acnes in vitro* and suppressed *P. acnes*-induced IL-8 production in human sebocytes. Additionally, mice that received the sialidase vaccine had decreased swelling and erythema of ears that were injected with live *P. acnes* 3 weeks after receiving the vaccine when compared to control mice. Another study by the same group showed that mice that were exposed to intranasal immunization with inactivated *P. acnes* generated *in vivo* protective immunity against *P. acnes*, facilitated the resolution of ear inflammation in mice, neutralized the cytotoxicity of *P. acnes* and attenuated the production of pro-inflammatory cytokine IL-8 in human sebocytes [86].

These results certainly are promising because these two vaccines do, in fact, suppress inflammation after inoculation of vaccinated mice with *P. acnes*. However, the question is whether or not results from the mouse model will translate well to the human model. One would also need to assess if these antibodies have the potential to crossreact with other cells and tissue of the vaccine recipient. Given that the genome of *P. acnes* has been mapped, more virulence factors will certainly be discovered with time, which will help discover more potential vaccine targets. As a caveat, however, there have been studies that have shown a positive correlation between *P. acnes* antibody titers and disease severity [87-89], thus, not all vaccines may be beneficial [90].

7. Conclusion

Emerging treatments of acne vulgaris consist of various topical and systemic agents. Topical picolinic acid and systemic zinc salts show promise in acne therapy. The topical antibiotic dapsone is an effective therapy for acne, especially for inflammatory lesions. Lymecycline is an oral antibiotic that is just as effective as minocycline, but with slightly less side effects and much better cost effectiveness. New formulations that better solubilized benzoyl peroxide increase the delivery of the active free radical to the pilosebaceous unit, and, thus, increase its effectiveness, especially against the biofilm of *P. acnes*. Benzoyl peroxide allows a higher concentration of antibiotic to penetrate into the pilosebaceous unit when both are used in combination; certain antibiotics also better activate benzoyl peroxide to form free radicals. Therefore, this synergistic relationship enhances activity against the *P. acnes* biofilm and also helps prevent the development of antibiotic resistance. Photodynamic therapy with topical photosensitizers may also be an effective option, especially when other treatments are contraindicated. Nevertheless, more treatments will continue to appear as our knowledge of the pathogenic mechanism of acne improves and provide a wider array of therapeutic targets.

8. Expert opinion

Acne therapy will evolve as our understanding of acne pathogenesis improves. Due to their convenience and efficacy, combination therapies that address multiple mechanisms in acne pathogenesis will become standard first-line agents. However, the components of these regimens will continue to evolve as more agents become available. Zinc, for example, is one new agent that has been combined with multiple antibiotics with promising results. Lymecycline is also a new antibiotic that may replace other tetracyclines as an equally effective, but

less expensive alternative. Other agents, including topical dapsone, picolinic acid and PDT, have also not established their role in acne therapy, but they will probably be positioned as one component of a multi-drug regimen as well.

Further study into the central role of biofilms in acne pathogenesis will produce new targets and strategies in acne therapy. Biological, chemical and physical means should be investigated for their effect on the biofilm. For example, agents that reduce the attachment of *P. acnes* to the follicular lining, inhibit the ability of *P. acnes* to synthesize extracellular matrix or disrupt the already formed chemical bonds within the biofilm may be advantageous. Research and progress may parallel research in cystic fibrosis, periodontal disease, otitis media, device related infection and dental caries where extensive investigation in preventing and treating biofilms has already been performed. RNAIII-inhibiting peptide, for example, has been shown to inhibit biofilm formation on implanted devices [91]. Researchers have also utilized surfactants to dissolve biofilms and high pressure water jets to physically disrupt biofilms in chronic rhinosinusitis and dental care, respectively [92]. Although it is in its nascent stage, the study of biofilms will probably lead to multiple new and effective strategies in acne therapy.

Declaration of interest

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Affiliation

Kirk A James[1], Craig N Burkhart[†2] & Dean S Morrell[2]
[†]Author for correspondence
[1]UNC School of Medicine, Chapel Hill, North Carolina, USA
[2]UNC School of Medicine - Dermatology, 410 Market Street, Suite 200 Chapel Hill, NC 27516, USA
Tel: +1 919 966 2485; Fax: +1 919 966 6460; E-mail: craig_unc@yahoo.com