A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Decoding Acne: Genetic Markers, Molecules, and *Propionibacterium Acnes*

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ISSN: 1545 9616

June 2013 • Volume 12 • Issue 6 (Supplement)

JO0613

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DECODING ACNE: GENETIC MARKERS, MOLECULES, AND *PROPIONIBACTERIUM ACNES*

Original Release Date: June 1, 2013
Most Recent Review Date: May 1, 2013
Termination Date: May 31, 2014
Estimated Time to Complete Activity: 1 hour
Medium or Combination of Media Used: Written supplement
Method of Physical Participation: Journal article, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection

Statement of Need

Most dermatology residency programs provide little instruction on "the art of acne therapy." Topical therapy is considered the standard of care in acne treatment and includes retinoids, benzoyl peroxide, and antibiotics. Many residency programs teach a monotherapy, stepwise approach to acne therapy and focus on combining additional drugs with existing treatment. Adding a topical retinoid to an existing treatment is one of the most common topical treatment combinations. The stepwise approach can be effective; however, this suggests that the clinician cannot predict how the acne will respond to the therapy. Studies show that initiating treatment with a fixed-dose combination product including a retinoid and a non-antibiotic, antimicrobial agent targets multiple pathogenic factors and provides advantages over the stepwise approach. The lack of education in residency programs indicates a need to increase dermatology clinician knowledge of available acne products in order to provide optimal care and minimize antibiotic resistance in the management of acne.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of aesthetic practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of aesthetic medicine.

Upon completion of this activity, participants should be able to:

- Identify the pathogenesis of acne vulgaris and how it is an inflammatory disease.
- Evaluate the role of diet and environment in the management of acne vulgaris.
- Explain how to suppress the emergence of resistant Propionibacterium acnes.
- Develop a treatment strategy for topical acne treatments including benzoyl peroxide, retinoids, and fixed-dose combinations.

Target Audience

This activity is intended for dermatologists, residents in dermatology, and physician assistants who treat patients with acne vulgaris.

Accreditation Statement

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Faculty Credentials

Linda Stein Gold MD (Henry Ford Hospital, Detroit, MI), Jonathan S. Weiss MD (Gwinnett Dermatology, Snellville, GA), Leon H. Kircik MD (Physicians Skin Care, PLLC, Louisville, KY).

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The faculty/authors have the following disclosed conflicts of interest: Dr. Weiss has accepted grants for research from Galderma, Allergan, Stiefel (including Barrier Therapeutics and Connetics), and Valeant (including Dermik, Coria, and Ortho). He has accepted honoraria for consulting from Galderma, Stiefel, and Valeant. Dr. Stein Gold has served as consultant, speaker, and teacher for Galderma, as well as teacher and speaker for Warner Chilcott and LEO, and consultant for Stiefel and Ferndale. Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Galderma, Allergan, Bayer, LeoPharma, Promius Pharma, Quinnova, Stiefel/GSK, Taro, Valeant, and Warner Chilcott.

The peer reviewers have no relevant conflicts of interest to disclose.

The planning committee of this activity, Nick Gillespie (Assistant Publisher JDD), Lucy James (Editorial Project Manager JDD), Melissa Kerr (Marketing Associate JDD), Luciana Halliday (Director of Sales JDD), and James Creg (University of Louisville), have no relevant conflicts of interest to disclose.

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Acne: Evolving Concepts of Pathogenesis Need to Guide Therapeutic Developments

Jonathan S. Weiss MD

For decades, acne has been and remains one of the most common diseases diagnosed and treated by dermatologists. Despite this prominence in our field, a full understanding of the pathogenesis of acne remains uncertain. We are continually unfolding the complex nature of this prevalent condition, but the more we learn, the more we question our preconceived notions. This supplement reviews 3 presentations at a recent symposium that focused on newer issues in acne pathogenesis and treatment.

Two articles in this supplement discuss the evolving concepts in acne pathogenesis. For years we have pointed to the 4 basic components of acne pathogenesis: hyperkeratinization, excess sebum production, bacterial proliferation, and inflammation. While these factors remain central to our current thinking, their relative importance may not be what we believed as recently as 5 years ago. The notion that hyperkeratinization leading to microcomedone formation is the initiating event in the development of acne appears, at best, to be debatable. In her article, Linda F. Stein Gold MD eloquently points to the presence of inflammation throughout the course of acne lesions, even predating the formation of the microcomedone and lasting through what was previously thought to be the postinflammatory phase of scarring. Her article also points out the intertwining of hormonal influences and dietary factors with the other pathogenic factors.

Another important issue in the current arena of acne therapy is bacterial resistance. Leon H. Kircik MD writes extensively on the importance of this resistance in our current therapeutic choices. Specifically, he points out the key role of benzoyl peroxide (BP) in combating not only the development of resistant *Propionibacterium acnes*, but also its importance in reducing the use of antibiotics as we fight against community-acquired methicillin-resistant *Staphylococcus aureus*.

The implications for acne therapy of the studies reviewed in this supplement are enormous. As pointed out in my article, new concepts of pathogenesis require a different focus as we develop new therapeutic entities. Clearly, a focus on better, more pure anti-inflammatory molecules will be essential moving forward, especially those that are not antibiotics. Research on the role of diet may also augment current pharmacologic therapies. Finally, the development of more therapeutic molecules to which *P acnes* cannot or will not develop resistance will be extremely important. Retinoids and BPs appear to be mainstays of acne therapy, to which we need to add new classes of effective therapeutic molecules.

Jonathan S. Weiss MD
Gwinnett Dermatology, Snellville, GA

What's New in Acne and Inflammation?

Linda F. Stein Gold MD
Henry Ford Hospital, Detroit, MI

ABSTRACT

Acne is a disease that leaves physiological as well as physical scars. As we attempt to understand this complicated disease, new research challenges our traditional understanding that the microcomedone is the initial step in the development of the acne lesion. Recent evidence suggests that subclinical inflammation is the primary event in lesion development and that inflammation persists throughout the lesion life-cycle. Therefore, all types of acne should be considered "inflammatory" acne.

J Drugs Dermatol. 2013;12(suppl 6):s67-s69.

INTRODUCTION

As dermatologists, acne is the bread and butter of our practice, yet the disease harbors many mysteries as to the sequence of events leading to the development of its lesions. Acne is a disease that leaves lasting physiological and physical scars. Many of our patients feel exceptionally self-conscious about their skin with even a mild breakout. Teenagers will plead to stay home from school, and our adult patients may choose to work from home. Are our patients paranoid, or is society judging them negatively purely because of the fact that they have acne? A study was conducted asking both adults and teenagers to assign attributes to a young woman shown in a photograph. The same woman was depicted in one photograph with a clear complexion and in another with a mild acne eruption. Both adults and teenagers were more likely to assign positive attributes (intelligent, happy, healthy, trustworthy) to the clear-skinned woman,[1] whereas the young woman depicted with mild acne was perceived as shy, stressed, and boring. This study highlighted the importance of proper and aggressive treatment for our acne patients.

As we attempt to develop a better understanding of this complicated disease, basic tenets of the pathophysiology of acne have been reexamined. The traditional view of acne lesion progression is that the microcomedone is the initiating event in the development of all acne lesions. This subclinical lesion forms from abnormal keratin desquamation and excess sebum production, along with proliferation of *Propionibacterium acnes*. Both noninflammatory and inflammatory lesions develop from this primary lesion. If *P acnes* proliferates and generates inflammatory mediators, inflamed papules and pustules develop. In addition, inflammatory lesions may develop from noninflammatory lesions.[2,3]

Recent studies suggest that subclinical inflammation may precede the development of the microcomedone. Jeremy et al conducted an immunohistochemical study to determine whether inflammatory events occur pre- or posthyperproliferation of the follicular epithelium.[4] They examined biopsies from patients with acne in both involved (n=12) and uninvolved (n=20) areas of the back. As a control, they looked at back-skin in patients without acne (n=10). Inflammatory markers such as T cells, neutrophils, macrophages, α6-integrin, and interleukin (IL)-1 were examined and compared. Significant inflammatory factors were identified around clinically normal follicles of uninvolved skin from acne patients before epithelial hyperkeratinization. These findings included large numbers of $CD4^+$ T cells over and above the constitutive level of surveillance T cells in normal skin, accompanied by a large macrophage presence equivalent to that seen in clinically apparent early (<6 hours) inflamed lesions. In addition, levels of IL-1 were upregulated around hair follicles in uninvolved skin, and aberrant integrin expression was observed in the epidermis around these uninvolved follicles as well as inflamed lesions. Thus, this study provides evidence for the involvement of inflammatory events in the very earliest stages of acne lesion development.

Recent evidence suggests not only that inflammation may be a primary event in acne, but that it may persist throughout the lesion life cycle. Seventy-seven percent of biopsy specimens of atrophic scars demonstrate inflammatory cell infiltrates.[5] In addition, the residual dyschromias reveal inflammation in persistent inflammatory erythema and persistent inflammatory hyperpigmentation.[6] Moreover, *P acnes* promotes inflammation not only as a viable microorganism, but also because even its nonviable state is proinflammatory and is slowly degraded.[7]

Propionibacterium acnes plays a central role in the pathogenesis of acne. It is controversial as to whether *P acnes* colonization is a primary event or a secondary event in lesion initiation.[8]

Propionibacterium acnes does play a role in initiating the host's innate and adaptive immune responses. Viable organisms, as well as fragments, can activate Toll-like receptors and the inflammatory pathway. Defensins, cytokines, and chemokines are then produced by the recruited inflammatory calls. The cytokines stimulate their receptors within the epidermis, infundibulum, and sebaceous cells. The host's adaptive immune response is also involved, with an intense perifollicular population of memory and effector T cells in normal-appearing skin responding to an antigen that is likely *P acnes*.[8]

Androgens are key to the development of acne. Men who lack androgens or who have androgen insensitivity do not develop acne and produce reduced amounts of sebum or no sebum.[9-11] Dihydrotestosterone and dehydroepiandrosterone sulfate are the most commonly implicated androgens in acne development.[12] Androgens come from multiple sources, including endocrine organs, local cutaneous synthesis, and exogenous sources from diet. With the onset of puberty and the increase in circulating and local androgens, androgen receptors on keratinocytes and sebocytes mediate hyperkeratinization and sebaceous gland development. Under the influence of androgens, the quantity and quality of sebum changes. The surface lipid is made up of cholesterol and cholesterol esters in the prepubertal child. Adult sebum contains shorter-chain fatty acids, squalene, triglycerides, and fatty alcohols.[13-15] Cholesterol is likely consumed at the onset of puberty for the production of androgens and other hormones. Greater *P acnes* densities are seen in adult sebum.[16]

The role played by diet in the development of acne has been controversial over the years, but we now understand that inflammatory acne is influenced by diet and environment. Two non-Westernized populations in which the adolescents and adults do not develop acne have been studied: the Kitavan Islanders of Papua New Guinea and the Aché hunter-gatherers of Paraguay.[17] Their diet differs significantly from the Westernized diet in that it is rich in low glycemic index (GI) foods. The Kitavan dietary staples are sweet potatoes, fruit, coconut, and fish, and Kitavans consume no dairy, alcohol, coffee, or tea. Westernized societies, by contrast, eat a diet rich in high GI foods, including sugar, pasta, bread, and flour; and this diet causes chronic hyperinsulinemia, which stimulates the insulin-like growth factor (IGF)-1 receptor.[18] Free IGF-1 is also increased and IGF-binding protein 3 is reduced, with the consequence that IGF-1 independently augments sebogenesis and results in proinflammatory cytokine release.[19-20] It has been shown that changing to a low GI diet can decrease sebum output, reduce acne lesion counts, and increase monounsaturated fats.[20] Unsaturated fats have been associated with epidermal hyperkeratosis.[21]

Specific foods, including skim milk and chocolate, have been recognized as contributing to the development of acne. The risk grows with increased milk consumption, with an odds ratio of 1.78 (95% confidence interval [CI], 1.22-2.59) in those consuming more than 3 portions per week, and with skim milk showing a stronger association than whole milk. Conversely, consumption of fish was associated with a protective effect, with an odds ratio of 0.68 (95% CI, 0.47-0.99).[22] Chocolate has long been suspected as a cause of acne. A recent study showed a significant increase in total lesions and a dose-dependent relationship between the amount of pure chocolate consumed and the number of lesions on days 4 and 7.[23]

With new scientific data, we have reevaluated our understanding of the initial stages in the development of an acne lesion. Subclinical inflammation now appears to precede the microcomedone. With this theory, anti-inflammatory treatments should be effective in treating not only the papules and pustules, but also the open and closed comedones, given that all lesions arise from an inflammatory environment. A study by Skidmore et al examined the long-term use of subantimicrobial-dose doxycycline (SDD) for the treatment of moderate acne.[24] In this study, 40 adults with moderate facial acne were given SDD (20 mg) twice daily for 6 months. Subantimicrobial-dose doxycycline vs placebo not only significantly reduced inflammatory lesions ($P<.01$), but also the number of comedones ($P<.01$).

Perhaps one reason why topical retinoids work well in the treatment of both noninflammatory and inflammatory acne is that they are not just "comedone busters," but also have potent anti-inflammatory properties. Topical adapalene is the best studied. Adapalene has anti-inflammatory actions through the inhibition of at least 3 pathways: Toll like receptor 2, leukocyte migration, and the activator protein 1 pathway. As a result, adapalene blocks the release of inflammatory cytokines and inhibits cellular inflammation.[25]

"In summary, the evolving view of acne pathogenesis suggests that acne is an inflammatory disease, and thus all acne should be regarded as inflammatory acne."

CONCLUSION

In summary, the evolving view of acne pathogenesis suggests that acne is an inflammatory disease, and thus all acne should be regarded as inflammatory acne. It would be more appropriate to refer to open and closed comedones as "comedonal" lesions as opposed to "noninflammatory" lesions. Continued investigation and understanding of the pathogenesis of acne can lead to better treatments and targeted therapies.

DISCLOSURES

Dr. Stein Gold has served as consultant, speaker, and teacher for Galderma, as well as teacher and speaker for Warner Chilcott and LEO, and consultant for Stiefel and Ferndale.

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AUTHOR CORRESPONDENCE

Linda F. Stein Gold MD

E-mail:.....lstein1@hfhs.org

Messages From Molecules: Deciphering the Code

Jonathan S. Weiss MD
Gwinnett Dermatology, Snellville, GA

ABSTRACT

Acne therapy should be based on pathogenesis. Current mainstays of therapy include topical retinoids, antibiotics, and benzoyl peroxide. Newer research has shown that inflammation may precede comedo formation. Gene array analysis of acne lesions has elucidated newer inflammatory mediators that may become future targets for therapeutic development.

J Drugs Dermatol. 2013;12(suppl 6):s70-s72.

INTRODUCTION

Acne, like any other disease, demands that the practitioner understand its pathogenesis to implement treatment in a logical, medically sound manner. Gone are the days of the mid-20th century when dermatologists had limited products that were felt to be effective in the treatment of acne, and about which little was known of their exact mechanism of action, let alone how little was known about the underlying biochemical and pathologic basis of the disease. Combination therapy is the gold standard for acne therapy, as dermatologists employ topical agents, systemic agents, or both in any individual patient. The challenge that we face is to use acne medications in the most rational manner possible to treat the condition effectively. Further, as we research the next generation of acne therapies, a thorough understanding of the biochemical and molecular basis of the pathogenesis of acne will allow researchers and clinicians to more effectively develop and implement therapies.

Pathogenesis

The main pathogenic factors in acne remain (1) hyperkeratinization, (2) inflammation, (3) bacterial proliferation (*Propionibacterium acnes*), and (4) overproduction of sebum under hormonal influences. Concepts on the relative importance of each of these factors in the pathogenesis of acne are evolving. Throughout much of the past 50 years, it was accepted that the microcomedo was the basis of all subsequent acne lesions (Figure 1). A clinically undetectable, microscopic keratinous plug occludes the hair follicle, leading to follicular dilation, which ultimately results in the clinical lesion recognized as the comedo. If the orifice of the comedo is open, the keratinous plug turns black, resulting in a blackhead, or open comedo. If the orifice remains closed, the earliest clinical lesion is a closed comedo, or whitehead. Behind the keratinous plug, bacteria can proliferate, leading to recruitment of neutrophils and resulting in inflammation that is recognized clinically as acneiform papules and pustules.

More current research has led to the discovery that inflammation precedes comedo formation,[1] so it is possible that the comedo is actually an inflammatory lesion, at least in some (if not all) patients (Figure 2). Jeremy et al demonstrated in an immunohistochemical study that inflammatory markers preceded the formation of microcomedones in acne patients.[1] Furthermore, some studies of oral antibiotics used as single agents to treat acne demonstrated a reduction in the number of comedones, suggesting that anti-inflammatory activity itself can help reduce these lesions.

Propionibacterium acnes, the bacterium that drives acne, remains a viable target for acne therapy.[2] However, *P acnes* has begun to develop resistance to many of the antimicrobial agents that were formerly effective in treating acne. Furthermore, many of the antibiotics used to treat acne, namely doxycycline and trimethoprim/sulfamethoxazole, are important in the fight against methicillin-resistant *Staphylococcus aureus*; so reducing their use in the treatment of acne garners importance. As we move forward, finding and using agents other than antibiotics to reduce and/or ameliorate the proinflammatory effects of *P acnes* should become a focus of research.

While hormonal factors that influence sebum production play a role in driving acne pathogenesis, they appear to affect some patients more than others, especially women. Therapeutic agents that address hormonal contributions to acne include spironolactone and oral contraceptives. Many women respond well to these agents when used as adjuvant therapy. Hormonal targets will not be further discussed in this paper.

Therapeutic Targets: Molecules Matter

In considering therapeutic targets, 3 categories of molecules are central to the importance of current and future acne therapy: (1) inflammatory mediators, (2) cellular targets, and (3) pharmacologic compounds.

With the revelation that inflammation may precede hyperkeratinization and comedo formation, targeting inflammatory mediators should become a major focus of acne therapy research. Trivedi et al performed gene array analysis of acne lesions and found upregulation of multiple genes associated with inflammation and tissue remodeling.[3] Upregulated genes included matrix metalloproteinases (MMPs) 1 and 3, interleukins (ILs) 8 and 1, β-defensin 4, serine proteases, L-selectin (lymphocyte adhesion molecule 1), chemokine receptor 1, tenascin C, and CD163 antigen.[3] The degree of upregulation and the roles of these molecules in inflammation and/or tissue remodeling are noted in Table 1.[3] In reviewing the molecules that are upregulated in acne lesions, it becomes apparent that therapies that target these molecules may help to reduce both inflammation and processes that lead to scarring, an issue that is poorly addressed by today's therapeutics.

Cellular targets for the reduction of inflammation in acne include leukocyte migration, toll-like receptor 2 on neutrophils,

FIGURE 1. Classic concepts on the pathogenesis of acne. *P acnes, Propionibacterium acnes.*

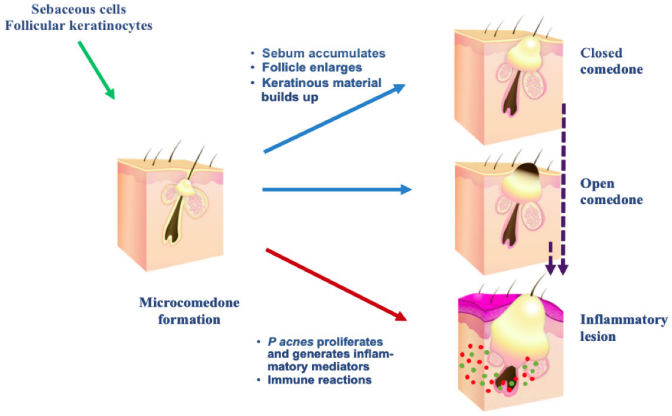
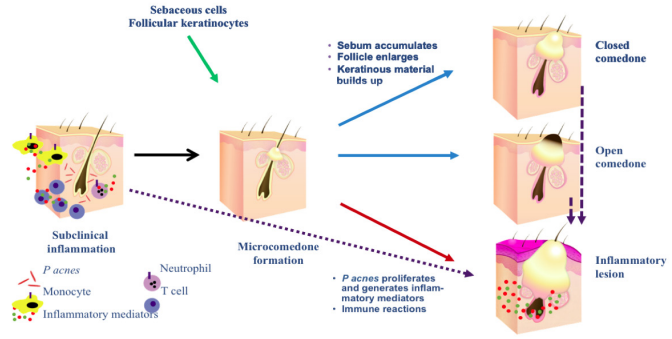


FIGURE 2. Newer concepts on the pathogenesis of acne. *P acnes, Propionibacterium acnes.*

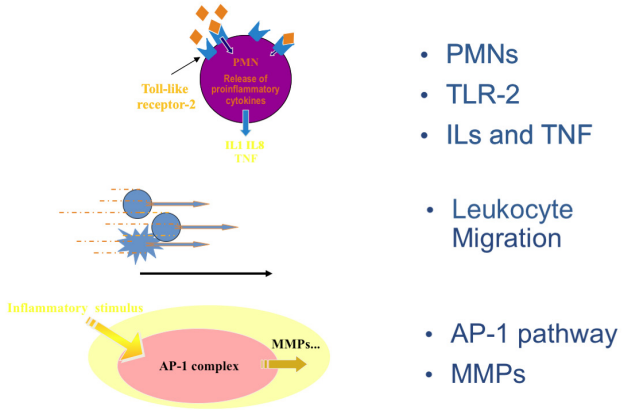


inflammatory mediators released by polymorphonuclear leukocytes (PMNs) such as IL-8, IL-1, and tumor necrosis factor (TNF), and the activator protein 1 pathway, which leads to the production of MMPs by dermal cellular elements (Figure 3).[4] Current medications that target all these factors include retinoids. As discussed below, not all topical retinoids have the same degree of anti-inflammatory activity in vitro.

Pharmacologic agents consist of molecular structures that interact with cellular and extracellular molecules via multiple mechanisms to exert their effects. The differing molecular structures of these pharmacologic agents confer differing properties to the medications, despite the fact that 2 different medications may be of the same class. Hence, 2 topical retinoids, while both having chemical structures that interact with retinoid receptors, may have quite different effects based on their structures and the specific receptors with which they bind. Current pharmacologic molecules that exhibit anti-inflammatory properties include benzoyl peroxides (BPs), retinoids, and antibiotics.

Benzoyl peroxide reduces inflammation through its bactericidal effects and by inhibiting the release of reactive oxygen species.[5] BP tends to be antineutrophilic and has some marginal effects on protein kinase C. The anti-inflammatory effects of BP are enhanced in combination therapy with both antibiotics and with topical retinoids.[6] When used alone, the reduction in inflammatory

FIGURE 3. Acne: cellular inflammatory targets. AP-1, activator protein 1; IL, interleukin; MMP, matrix metalloproteinase; PMN, polymorphonuclear leukocyte; TLR-2, Toll-like receptor 2; TNF, tumor necrosis factor.



lesions with BP is not felt to be concentration dependent. There was no statistical difference in inflammatory lesion reduction when BP 2.5% was tested separately against BP 5% and BP 10%.[5] Other benefits of BPs include their bactericidal activity, with no known development of resistance by bacteria to their effects, and the protection against the development of antibiotic resistance by antibiotics that are administered concomitantly with BPs. The BP molecule also has weak anticomedonal effects.

Retinoids have long been appreciated for their comedolytic properties, but as a class of drugs they also have significant anti-inflammatory effects.[7] Inhibition of peritoneal macrophage lipoxygenase and inhibition of arachidonic acid–induced ear inflammation in mice have both been exhibited by retinoids. While this is a class effect, the later-generation retinoid adapalene has been shown to have more potent anti-inflammatory effects than the first-generation retinoid tretinoin (Figure 4).[7] As demonstrated in Figure 4, the anti-inflammatory effects of adapalene in vitro are comparable to indomethacin and greater than betamethasone valerate. Further differences in retinoids that favor later-generation compounds include variance in chemical structure, receptor specificity, chemical stability, and compatibility with other topical medications.[8] While no comparative studies exist between tazarotene, tretinoin, and adapalene with regard to inflammatory properties, they do have differences in receptor specificity and pregnancy category.

> "Current therapeutic modalities for mild to moderate acne do fine, but they do not prevent a large number of patients from deteriorating."

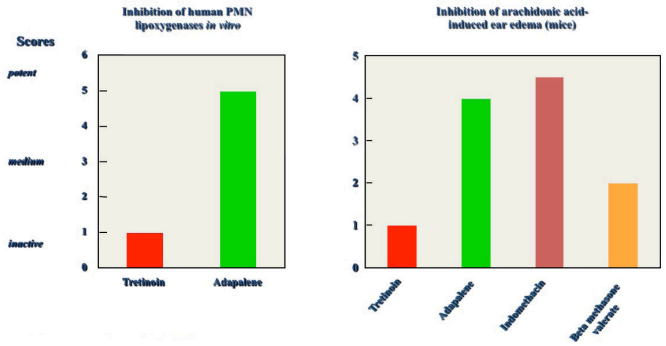
In addition to their antibacterial effects, antibiotics have several anti-inflammatory properties. Tetracyclines have been shown to downregulate cytokines such as TNF-α and IL-1β, inhibit angiogenesis and PMN chemotaxis, inhibit phospholipase A_2, leading to reduced production of reactive oxygen species by PMN ara-

TABLE 1.

Top 10 Inflammatory Genes Upregulated in Acne Lesions Relative to Normal Skin[3]

Gene Title	Gene Symbol	Fold Change	Function of Protein[10]
matrix metalloproteinase 1	*MMP1*	92.166	Degradation of extracellular matrix during tissue remodeling
matrix metalloproteinase 3	*MMP3*	64.020	
interleukin-8	*IL-8*	52.521	Mediator of inflammatory response
ß-defensin 4	*DEFB4*	33.300	Antimicrobial activity; locally regulated by inflammation
serine proteinase inhibitor, clade A	*SERPINA1*	8.649	Serine protease inhibitor
selectin L (lymphocyte adhesion molecule 1)	*SELL*	6.796	Facilitation of leukocyte migration to sites of inflammation
chemokine (C-C motif) receptor 1	*CCR1*	4.057	Critical for recruitment of effector immune cells to sites of inflammation
interleukin-1 family, member 9	*IL-1F9*	3.343	Cytokine expressed in keratinocytes
tenascin C	*TNC*	3.022	Guidance of migrating neurons and axons
CD163 antigen	*CD163*	2.979	Induction of local inflammation

FIGURE 4. Retinoids: anti-inflammatory activity.[7] PMN, polymorphonuclear leukocyte.



chidonic acid metabolites, inhibit nitric oxide activity, and inhibit multiple leucocyte-derived MMPs, including collagenases and elastases.[9] While their use may be limited because of concerns about antibiotic resistance, tetracycline antibiotics remain a mainstay of acne therapy. Given that low-dose, subantimicrobial versions of doxycycline are available for the treatment of rosacea, it may be possible that similar therapies will be developed and proven effective for the treatment of acne.[2]

CONCLUSION

Concepts on the pathogenesis of acne are evolving. While hyperkeratinization, bacterial colonization and proliferation of *P acnes*, and inflammation are still central to the pathogenic process, their relative importance may be different to what was previously thought. Given recent research showing inflammation as the potential initiating event in acne pathogenesis, research into newer therapies may need to focus on the mediators that drive that inflammation. Current therapeutic modalities for mild to moderate acne do fine, but they do not prevent a large number of patients from deteriorating. Combination therapy with systemic antibiotics, topical retinoids, and BP remains a mainstay of the current therapeutic armamentarium. Hopefully, gene array analysis and/or other studies that elucidate pathogenic factors and molecules previously underappreciated and unaddressed in acne therapy will provide the basis for acne therapies of the future.

DISCLOSURES

Dr. Weiss has accepted grants for research from Galderma, Allergan, Stiefel (including Barrier Therapeutics and Connetics), and Valeant (including Dermik, Coria, and Ortho). He has accepted honoraria for consulting from Galderma, Stiefel, and Valeant.

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AUTHOR CORRESPONDENCE

Jonathan S. Weiss MD
E-mail: jsweiss@bellsouth.net

The Role of Benzoyl Peroxide in the New Treatment Paradigm for Acne

Leon H. Kircik MD
Mount Sinai Medical Center, New York, NY
Indiana University School of Medicine, Indianapolis, IN
Physicians Skin Care, PLLC, Louisville, KY

ABSTRACT

Bacterial resistance became a true clinical concern for dermatologists in the 1980s, when the first reports emerged of the resistance of *Propionibacterium acnes* to oral antibiotics. Subsequent studies have documented acne treatment failure associated with resistance to topical antibiotics. Beyond dermatology practice, antibiotic resistance has now become recognized as a worldwide health concern. In contrast to antibiotics commonly used in the treatment of acne, benzoyl peroxide (BP)'s mechanism of action is different. Benzoyl peroxide is a bactericidal agent. Combining BP with a topical antibiotic in a stable formulation has been proven in clinical trials to reduce total *P acnes* count by 99.7% after 1 week of therapy, eliminating both susceptible and resistant strains of *P acnes*. However, we have recently noticed BP's benefits as monotherapy in the treatment of acne. Benzoyl peroxide works rapidly on *P acnes* without causing antibiotic resistance. Hence, we may have to reconsider the role of topical antibiotics such as clindamycin in the treatment paradigm of acne vulgaris.

J Drugs Dermatol. 2013;12(suppl 6):s73-s76.

INTRODUCTION

Theoretical concern about the development of antibiotic resistance emerged almost immediately upon the discovery of penicillin. In fact, Alexander Fleming reportedly said of his discovery, "The bacteria will not take this sitting down." Just as Fleming and others predicted, bacterial resistance became a true clinical concern for dermatologists in the 1980s, when the first reports emerged of the resistance of *Propionibacterium acnes* to oral antibiotics.[1] Subsequent studies have documented acne treatment failure associated with resistance to topical antibiotics.[2]

Beyond dermatology practice, antibiotic resistance has now become recognized as a worldwide health concern. The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as perhaps the most notable sign of the consequences of resistance and is probably the most widely recognized resistance concern in the general public. As public health officials, health care professionals, and even international governmental organizations continue to suggest strategies to combat resistance, as dermatology providers we may have to be more conscious of our use of antibiotics, especially for the treatment of acne. One of the well-established acne treatments, benzoyl peroxide (BP), has reemerged as an important tool in treating acne while minimizing resistance. New findings suggest that BP may not only help to reduce antibiotic resistance when used in combination with antibiotics, but may also be sufficient to reduce *P acnes* when used alone as monotherapy without an antibiotic.

The Problem of Resistance

Initial reports of the resistance of *P acnes* to oral and topical antibiotics raised alarm in the dermatology community. Importantly, *P acnes* resistance rates have been estimated to be as high as 60% in some patient populations.[3] Across the health care field, concern about long-term antibiotic use and subsequent resistance risk has grown alongside the number of reports of community-acquired MRSA skin and soft tissue infections.[4,5] One report suggested that in the 10-year period from 1988 to 1998, rates of MRSA at select dermatology outpatient clinics increased by nearly 10-fold, accounting for 11.9% of all *S aureus* strains in 1998—up from 1.5% in 1988.[4] Concern about MRSA in both the medical and lay communities was amplified by the recent emergence of the multidrug-resistant MRSA USA300 clone in San Francisco and Boston.[5]

Clinicians have largely associated the greatest risk for resistance with the use of oral antibiotics; however, recent research confirms that resistance to topical antibiotics is prevalent among *S aureus* isolates.[6] Globally, resistance to erythromycin is most common. In North America, 57.8% of resistant *S aureus* strains were resistant to erythromycin. MRSA is the second most common form of resistance globally as well as in North America, accounting for about one-third of global resistance and for 36.9% of resistance in North America. Clindamycin resistance is the third most common, with rates of 21.5% globally and 22.5% in North America (Table 1).[6]

Understanding Resistance

Scientists have elucidated the processes by which bacterial resistance emerges. Bacteria are adept at developing and transferring resistance, and they can do so rapidly. The phenomenon of "survival of the fittest" applies to antibiotic therapy and bacterial resistance. Those bacteria that demonstrate resistance to an

TABLE 1.

Rates of *S Aureus* Resistance[6]

S Aureus Isolates Resistant to:	Percentage of Resistance, by Region			
	Global (N=1,975)	North America (n=1,182)	Europe (n=587)	International (n=206)
Methicillin	32.9	36.9	29.8	18.4
Mupirocin	9.8	9.1	7.3	20.9
Fusidic acid	6.8	4.2	12.6	4.9
Erythromycin	48.4	57.8	37.5	25.7
Clindamycin	21.5	22.5	24.0	8.7
Gentamicin	7.0	3.9	10.4	15.5
Tetracycline	17.2	13.7	18.2	34.0

antibiotic agent persist and generally can pass on their resistant genes to other bacteria as well as to subsequent generations.

Plasmid transfer appears to be the major process by which multiple-antibiotic–resistant organisms proliferate, and it facilitates the transfer of resistance among both Gram-negative and Gram-positive bacteria.[7] The plasmid is comprised of double-stranded DNA that is separate from the chromosomal DNA. The plasmid DNA can transfer genetic material horizontally through a process called conjugation; once integrated into the host DNA, the genetic material is present in replicated cells. New genetic material can be shared with incredible speed. Within heterogeneous bacterial populations with appropriate donors, millions of bacteria have been shown to acquire a plasmid within just a few days.[8]

The alternative mode of resistance transfer is via transposons, which facilitate horizontal DNA transfer, also known as horizontal gene transfer, or viral transfer of resistance.[9]

A single bacterium can also develop resistance to a given antibiotic upon exposure. For example, via the efflux pump, a bacterium can flush out antibiotics before they exert an effect.[10]

Resistance transfer is of concern not only for the organisms that treatment is targeting, but extends to the possibility of resistance spreading between organisms; susceptible pathogens can theoretically acquire antimicrobial resistance from other microorganisms. Put another way, we in dermatology need to worry about not only the difficulty of treating resistant *P acnes*, but also the risk of spreading antibiotic resistance in the treatment of other infectious diseases.

Resistance in Acne Management

The problem of resistance has been especially well documented in the management of acne vulgaris and has been linked to resultant acne treatment failure.[2] However, resistance among acne patients is not limited to *P acnes*; researchers have also identified resistant strains of *Staphylococcus epidermidis* among acne patients treated with oral erythromycin.[11-13] Another study of acne patients showed that systemic antibiotic therapy was associated with *Streptococcus pyogenes* colonization and resistance in the oropharynx. While only 20% of *S pyogenes* cultures from control subjects not treated with antibiotics were resistant to at least one tetracycline, 85% of cultures from antibiotic-treated patients demonstrated resistance.[13]

Against the backdrop of growing antibacterial resistance, guidelines for acne management were published in 2003 that emphasize the use of topical antimicrobials and retinoids as well as shortened courses of systemic antibiotics.[14] A 2009 update of the recommendations further underscores concerns about the risk of resistance, calling for the use of oral or topical antibiotics in combination with BP.[15] They also emphasize the critical role of topical retinoids in long-term acne treatment. The guidelines may be influencing practice. Overall, prescribing for topical antibiotic monotherapy for acne actually decreased slightly from 2001 to 2005.[16] The use of topical clindamycin/BP combination formulations increased.[16]

While the use of combination clindamycin/BP formulations is consistent with current guidelines, this approach to acne management does not fully reflect current knowledge about the prevalence of resistance, the mechanisms of resistance, or our understanding of the pathogenesis of acne vulgaris.

Although the *P acnes* bacterium is generally considered pathogenic in acne vulgaris, acne is not an infectious process.[17] Rather, the findings of recent research and the current treatment guidelines concur that acne is primarily an inflammatory rather than infectious process. *Propionibacterium acnes* has been thought to contribute directly to the inflammation of acne vulgaris by instigating inflammatory cytokine responses via activation of Toll-like receptor 2,[18] though even this is now controversial.[17] There is clear evidence that acne and associated scarring are associated with a marked increase in inflammatory cytokine gene transcripts in active acne lesions, including tumor necrosis factor α and interleukin-1β.[14] These proinflammatory cytokines amplify nuclear factor κB signaling pathways.[18]

Presently, the primary oral antibiotics used for acne are the second-generation tetracyclines, minocycline and doxycycline.[19,20] Less commonly used alternatives include erythromycin, trimethoprim/sulfamethoxazole, and azithromycin.[20] These lipophilic oral antibiotics have all been shown in vivo to reduce *P acnes* colonization after 6 weeks of therapy. In an experimental model, the log reduction in *P acnes* colonization was greatest with minocycline.[21]

Although few randomized controlled trials have studied the clinical efficacy of oral antibiotics in acne, tetracycline and erythromycin have been shown to reduce inflammatory lesions by 64% and 67%, respectively.[2] Other comparative studies have typically shown few or no important differences in clinical efficacy between the oral antibiotics. A recent Cochrane meta-analysis concluded that minocycline is effective for moderate acne, but data are insufficient to compare its efficacy to that of other acne therapies.[22]

Tetracyclines, macrolides, and trimethoprim-sulfamethoxazole can be used to treat moderate to severe acne.[14,19] Whereas long-term therapy is commonly used, short courses may be effective and may reduce the risk for development of antibiotic resistance.[15]

Alternatively, topical BP is a relatively inexpensive agent that is proven bactericidal against *P acnes* with no known risk of resistance.

The Reemergence of Benzoyl Peroxide

Lincosamide antibiotics such as clindamycin and macrolide antibiotics such as erythromycin have a similar method of action, inhibiting the protein synthesis of *P acnes* by attaching to the 50S subunit of the bacterial ribosome.[23] In contrast, BP's mechanism of action does not involve bacterial ribosomal synthesis. Benzoyl peroxide is a potent oxidizing agent. By generating reactive oxygen species that physically interact with constituents of the bacteria, it exerts a bactericidal effect.

Combining BP with a topical antibiotic in a stable formulation has been proven in clinical trials to reduce total *P acnes* count by 99.7% after 1 week of therapy, eliminating both susceptible and resistant strains of *P acnes*.[24] Clinically, combination therapy with BP and a topical antibiotic has been proven to prevent the emergence of resistant strains of *P acnes*. For this reason, the current clinical recommendation is to include BP in topical anti-acne regimens to preclude the development of antibiotic resistance.[15]

Benzoyl peroxide's efficacy as a monotherapy was traditionally considered to be limited; however, the agent is readily used in fixed-dose combinations with antibiotics or topical retinoids, providing documented benefit.[25-27] For example, the fixed-dose combination of adapalene 0.1%/BP 2.5% was associated with early improvement in quality of life and high levels of treatment satisfaction among treated patients compared with control subjects.[26] In clinical trials, adapalene/BP combination gel showed a significantly higher success rate (P<.006 or P=.006) and a greater percentage reduction in all acne lesion counts (P<.017 or P=.017) compared with adapalene or BP monotherapy.[27]

We are also now noticing BP's benefits as monotherapy in the treatment of acne. The effect of BP on *P acnes* is rapid. After just 2 days of treatment with BP 5%, an almost 2-$\log_{10}$ decrease in *P acnes* counts was observed. No further decrease was observed at subsequent times.[28]

Lee et al found that *P acnes* synthesizes coproporphyrin III, producing the well-known orange-red follicular fluorescence under 385-nm to 415-nm light.[29] Benzoyl peroxide's activity against *P acnes* was demonstrated in an elegant study using 385-nm to 415-nm light fluorescence.[30] When subjects with acne were treated with BP 10%, *P acnes* counts were significantly lower compared with untreated controls both at day 3 (P=.007) and at day 7 (P=.0001). Researchers also cultured *P acnes* from subjects and showed that a decrease in cultured *P acnes* density in the treated group paralleled the dramatic decrease in porphyrin fluorescence. Of note, documented recolonization of *P acnes* 10 days after stopping BP was matched by a corresponding reappearance of porphyrins.[30] Because the intensity of fluorescence is proportional to the density of *P acnes* and decreases with BP treatment, digital fluorescence photography was selected as a reliable, noninvasive method to estimate the suppressive effects of BP 10% on *P acnes*.[30]

Thirty healthy adults with high facial *P acnes* counts (>10 colony-forming units/cm^2 from the forehead) were recruited for a 4-week, single-center, open-label study.[31] The study sought to assess the presence of *P acnes* subpopulations resistant to erythromycin, tetracycline, and clindamycin before and throughout the course of treatment with the BP 2.5% and adapalene 0.1% fixed-dose combination. Subjects were instructed to apply adapalene 0.1%/BP 2.5% gel to the forehead once daily for 4 weeks. Cultures were taken at screening, baseline, week 2, and week 4. *P acnes* counts were high at baseline but reduced significantly by week 4 (Table 2.) Total *P acnes* were reduced by a mean 80% at week 2 and 93% at week 4. Erythromycin-resistant strains were reduced by 89% and 97%, clindamycin-resistant strains by 82% and 92%, tetracycline-resistant strains by 79% and 92%, minocycline-resistant strains by 85% and 97%, and doxycycline-resistant strains by 67% and 88%, respectively at week 2 and week 4. The authors acknowledge that their study was limited in scope; however, results demonstrate that the fixed-dose combination gel containing adapalene 0.1% and BP 2.5% effectively inhibited both antibiotic-susceptible and antibiotic-resistant *P acnes*.[31]

TABLE 2.

Reduction in *Propionibacterium Acnes* With Adapalene 0.1%/BP 2.5% Combination Gel[31]

	Percent Mean Reduction (SD) at Week 2	Percent Mean Reduction (SD) at Week 4
Total *P acnes*	-80% (21.6)	-93% (8.1)
Erythromycin-resistant *P acnes*	-89% (20.4)	-97% (8.9)
Clindamycin-resistant *P acnes*	-82% (32.1)	-92% (19.7)
Tetracycline-resistant *P acnes*	-79% (25.7)	-92% (15.6)
Minocycline-resistant *P acnes*	-85% (22.6)	-97% (3.7)
Doxycycline-resistant *P acnes*	-67% (28.0)	-88% (14.5)

SD, standard deviation.

CONCLUSION

As concerns about antibiotic resistance have continued to evolve, so has the management of various diseases, including acne vulgaris. The use of BP, especially in combination with topical antibacterials such as clindamycin, has emerged as an important strategy for reducing the risk of developing bacterial resistance. However, data suggest that the potent bactericidal effects of BP can quickly diminish *P acnes* colonization without the need for the use of additional topical antibiotic. Using BP in conjunction with a topical retinoid such as adapalene rather than in combination with an antibiotic may be a reasonable treatment strategy. The once-daily fixed combination formulation of adapalene 0.1% and BP 2.5% is a proven effective, convenient option for acne management that targets multiple aspects of the pathogenesis of acne. Therefore, we may have to reconsider the role of topical antibiotics such as clindamycin in the new treatment paradigm of acne.

"The once-daily fixed combination formulation of adapalene 0.1% and benzoyl peroxide 2.5% is a proven effective, convenient option for acne management that targets multiple aspects of the pathogenesis of acne."

DISCLOSURES

Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Galderma, Allergan, Bayer, LeoPharma, Promius Pharma, Quinnova, Stiefel/GSK, Taro, Valeant, and Warner Chilcott.

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AUTHOR CORRESPONDENCE

Leon H. Kircik MD
E-mail:.....wedoderm@yahoo.com

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1. Which type of milk has been associated with acne?
   a. Whole milk
   b. 2% milk
   c. Skim milk
   d. Almond milk

2. Which diet is associated with lack of acne?
   a. Low glycemic index
   b. High glycemic index
   c. Gluten free
   d. None of the above

3. Sources of androgens include:
   a. Endocrine organs
   b. Local cutaneous synthesis
   c. Exogenous sources from diet
   d. All of the above

4. What is currently felt to be the initiating pathophysiologic event in the formation of acne lesions?
   a. Follicular plugging (microcomedo formation)
   b. Inflammation
   c. Overproduction of sebum
   d. Infection with *Propionibacterium acnes*
   e. a and/or b

5. Which of the following topical retinoids has been shown to have anti-inflammatory activity in vitro similar to indomethacin?
   a. Tretinoin
   b. Adapalene
   c. Tazarotene
   d. Bexarotene
   e. All of the above

6. Which concentration of benzoyl peroxide is likely to reduce inflammatory acne lesions by the greatest percentage in any given acne patient?
   a. 2.5%
   b. 5%
   c. 10%
   d. They will all likely be equally effective
   e. They will all likely be ineffective

7. Which one of the following has a different mechanism of action on bacteria?
   a. Erythromycin
   b. Clindamycin
   c. Tetracycline
   d. Benzoyl peroxide

8. Which one of the following has the most resistance to *Propionibacterium acnes*?
   a. Erythromycin
   b. Tetracycline
   c. Doxycycline
   d. Minocycline

9. Which one of the following is a mechanism of action for benzoyl peroxide in the treatment of acne?
   a. Antibacterial
   b. Antiviral
   c. Antifungal
   d. Antineoplastic

Evaluation Form

Decoding Acne: Genetic Markers, Molecules, and *Propionibacterium Acnes*

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