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