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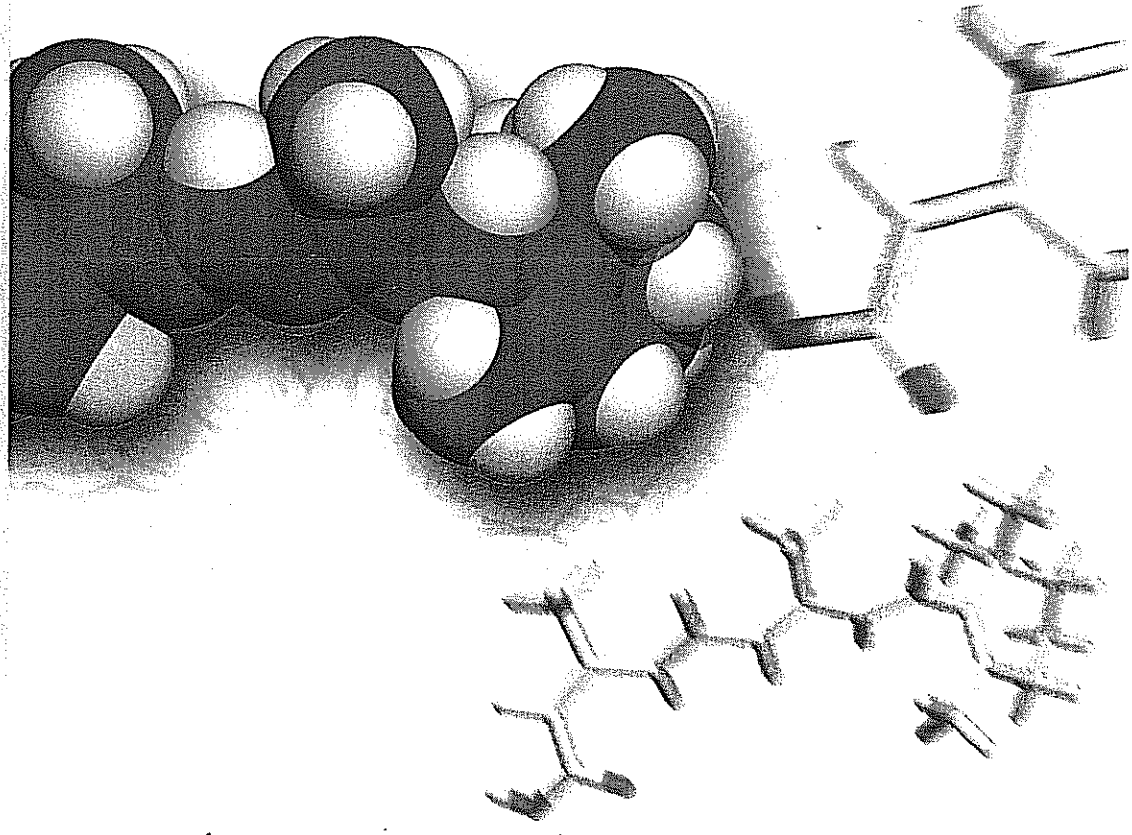
Antibiotic Resistance and the Role of Combination Acne Therapy



Introduction

Emil Tanghetti, MD

The era of bacterial resistance to antibiotics began almost as early as the antibiotic era itself. Within 10 years of the introduction of penicillin, most hospital strains of *Staphylococcus aureus* produced β-lactamase.[1] By 1959, a strain of *Shigella dysenteriae* isolated in Japan was resistant to 4 antibiotics and was able to transfer this resistance to other bacteria by means of plasmids. Appropriate and questionable uses of these drugs, including overuse, suboptimal dosing, and inappropriate prescribing, as well as their use in animal feeds, led to increasing resistance worldwide.[2] The United Kingdom acted early on to preserve antibiotics by decreasing their use. Between 1995 and 2000, antibiotic use had dropped by 23% in the United Kingdom.[3,4] In the second half of the 1990s, there was a 33% decline in antibiotic prescriptions for acne in the United Kingdom, including a 12% decrease in the use of topical antibiotics.[3]

Propionibacterium acnes, although initially susceptible to a wide range of antibiotics, also has undergone selection pressures as a result of antibiotic use. Decreasingly sensitive strains have been noted worldwide since the 1980s.[5] However, dermatologists have taken the threat of antibiotic resistance seriously, and numerous recommendations have been issued regarding the management of acne in such a way as to preserve the utility of these drugs. These management methods include the avoidance of antibiotic monotherapy and the use of combination therapy with benzoyl peroxide (BPO).

In this supplement, Tanghetti[6] discusses the science and clinical manifestations of bacterial resistance in acne therapy as well as recommendations for using antibiotic therapy effectively and conservatively. Clindamycin 1%–BPO 5% topical gel is approved by the US Food and Drug Administration for the treatment of inflammatory acne vulgaris. Both components have antibacterial and anti-inflammatory activity.[7,8] Acne management guidelines recommend adding BPO to long-term antibiotic regimens in acne to help suppress resistant *P acnes* variants.[9] In addition, reducing *P acnes* colonization minimizes inflammation. Topical retinoids possess anticomedolytic and anti-inflammatory properties and thus have been recommended as first-line therapies for most patients with acne. Therefore, topical antibiotics, BPO, and retinoids are considered primary therapies for most patients with acne. Kircik[10] discusses the findings from a community-based trial of clindamycin 1%–BPO 5% topical gel and 2 different commonly prescribed retinoids.

Postinflammatory hyperpigmentation (PIH) is a distressing accompaniment to acne for many patients of color. Frequently, the PIH lesions are even more distressing to these patients than their acne, and the lesions may require several months to resolve. Because more deeply pigmented skin is more prone to develop PIH when irritated, an important consideration in any acne regimen for a patient of color is to prevent irritation and PIH.[11] Taylor[12] presents the findings from the community-based trial regarding the effect of the different therapeutic regimens on PIH in a subset of subjects of color.

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The Impact and Importance of Resistance

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Bacterial resistance to antibiotics began to emerge soon after their introduction. Beginning in the 1970s, Propionibacterium acnes *also began to show decreased sensitivity to the antibiotics typically used in acne management. Clinically, this trend has translated to decreased efficacy and even nonresponse to therapy. A variety of recommendations regarding optimum use of antibiotics in acne management have been developed to preserve the utility of these drugs. Most important is the use of combination therapy with benzoyl peroxide (BPO) to help minimize the development of resistance. Retinoids also are recommended in acne therapeutic regimens because these agents are active against most acne pathogenetic mechanisms, but they have no apparent activity preventing antibiotic resistance when used in combination with a topical antibiotic.*

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Bacterial resistance to antibiotics was noted as early as 1942. However, although systemic and topical antibiotics were used frequently and effectively in the management of inflammatory acne, its causative pathogen, *Propionibacterium acnes*, initially was highly susceptible to a broad range of antibiotics. Figure 1 depicts the rise in antibiotic-resistant *P acnes* during this period.[1-6]

The goal of antibiotic therapy in acne treatment is to decrease *P acnes* populations and inhibit the production of *P acnes*–associated inflammatory mediators.[7] The prescribing of antibiotics for acne has led to selection pressures whereby susceptible bacterial populations are killed and resistant variants are selected and multiply. It is important to note, however, that bacterial resistance to specific antibiotics potentially can be reversed if the selective pressure exerted by the antibiotic is withdrawn.[8]

Bacterial Resistance in Acne and Soft Tissue Infections

Initially, there was no reported evidence of *P acnes* resistance in patients who were not responding to systemic antibiotic therapy, and it was concluded that *P acnes* resistance was uncommon and not clinically relevant. However, in 1983, Leyden and colleagues[2] found that the mean minimum inhibitory concentrations (MICs) for tetracycline were 4- to 5-times greater in patients with acne who received long-term systemic antibiotics than in antibiotic-free controls. The average MIC for erythromycin was 100-times greater in antibiotic-treated patients, and there was evidence of cross-resistance between erythromycin and clindamycin. The definition and clinical significance of decreasing antibiotic susceptibility of *P acnes* remain to be clarified. MICs are determined in an aqueous-based system, and the relationship between increasing MICs and decreased antibiotic susceptibility in the lipid-rich follicular environment is unclear.[8] For example, benzoyl peroxide (BPO), while extremely efficacious against *P acnes*, has a high MIC value of 150 μg/mL.[9] However, it has been demonstrated that patients with acne carrying resistant strains of *P acnes* have higher bacterial counts and poorer treatment response than those patients with sensitive strains.[2,10] In addition to nonresponse to antibiotic therapy, another pattern seen in patients with erythromycin-resistant *P acnes* is that of an initial good therapeutic response followed by a gradual worsening, probably concomitantly with the emergence of resistant organisms and the ascension of these resistant variants to predominance.[10,11] Other effects on bacterial ecology may occur in this setting where bacteria are exposed to long-term antibiotics, though the clinical significance of the effects are unknown. For example, one study found an increased rate of upper respiratory tract infections in subjects receiving topical or oral antibiotics for acne.[12]

The most serious resistance issue currently facing clinical dermatologists is the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is now the most common identifiable cause

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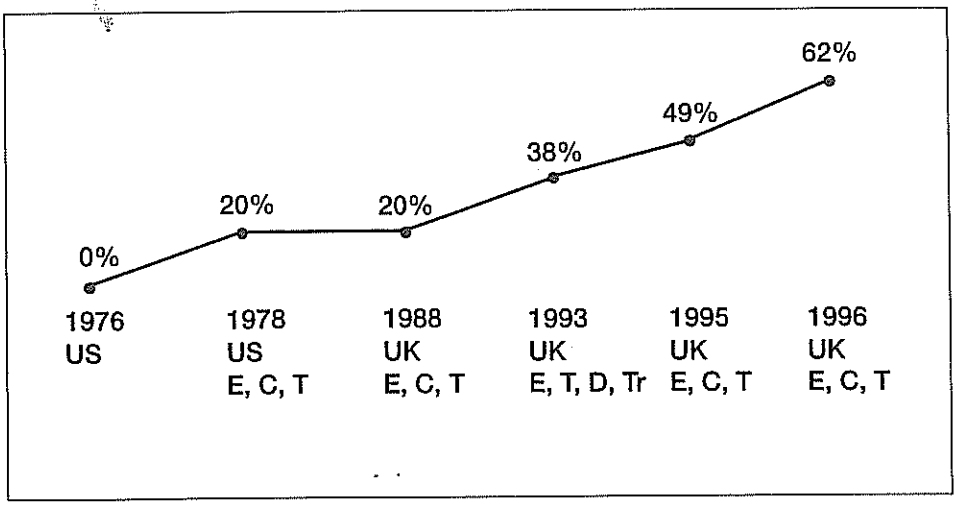

Figure 1. Increasing resistance of *Propionibacterium acnes* to antibiotics. The years reported indicate when the studies were conducted. US indicates United States; E, erythromycin; C, clindamycin; T, tetracyclines; UK, United Kingdom; D, doxycycline; Tr, trimethoprim.[1-6]

of skin and soft tissue infections in many US cities as well as the most common pathogen isolated from emergency department patients. In a study undertaken in 11 university-affiliated emergency departments, *S aureus* was isolated from 320 of 422 patients (76%) with skin and soft tissue infections.[13] Of these isolates, 78% (249/320) were MRSA. The overall prevalence of MRSA in the study population was 59%. Large proportions of MRSA isolates were antibiotic susceptible, with a sensitivity of 100% for trimethoprim/sulfamethoxazole (217/217) and rifampin (186/186) and 95% (215/226) for clindamycin but only 6% (13/226) for erythromycin. This finding is important, and erythromycin resistance may be a marker for inducible clindamycin resistance. MRSA susceptibility was 92% (207/226) for tetracycline and 60% (106/176) for fluoroquinolones.[13] As MRSA infections become more common, consideration should be given to preserving the effectiveness of antibiotics useful in this setting.

Mechanisms of Resistance

Bacterial mechanisms that lead to antibiotic resistance include inactivation of the antibiotic via enzymes such as β-lactamase, production of an efflux pump to extrude the drug and maintain subtherapeutic drug levels, and camouflage of bacterial targets by means of RNA changes in the ribosome where the antibiotic acts.[14] Resistance via mutations in genes encoding 23S and 16S ribosomal RNA was first demonstrated in *P acnes* isolates in the United Kingdom and now constitute the principal mechanism of *P acnes* resistance to erythromycin and tetracycline worldwide.[15] Ross et al[15] also found resistant *P acnes* strains where mutations could not be identified, suggesting that uncharacterized resistance mechanisms have evolved.

Strategies to Prevent Bacterial Resistance in Acne Therapy

The problem of bacterial resistance to antibiotics extends to every area of medicine where antibiotics are used. To preserve these medical resources, the Centers for Disease Control and Prevention has issued broad recommendations to help reduce resistance through correct use of drugs.[16] Recommendations for the control of resistance in acne management are more specific. These strategies are based on the need to avoid long exposures to systemic antibiotics and the demonstrated utility of combination therapy in addressing multiple pathogenetic mechanisms in acne (Table).[17-20] One recommendation is to avoid prescribing antibiotics if BPO or topical retinoids may be equally effective,[20] and another recommendation is to add BPO to a regimen if long-term topical or oral antibiotic therapy is required.[17-20] BPO is a powerful broad-spectrum bactericidal agent with some anti-inflammatory activity.[21] Its lipophilic nature facilitates entry into the sebaceous follicles in acne.[22] So far, *P acnes* remains sensitive to BPO.[23] In addition, physicians should stress good compliance.[18,20]

It has been demonstrated in numerous studies that the combination of BPO and a topical antibiotic offers superior efficacy to monotherapy with either agent.[11,24,25] Importantly, this combination has been shown to prevent the development of antibiotic resistance in patients with acne and to bring substantial clinical improvement to patients already carrying antibiotic-resistant *P acnes*.[26] In a 16-week, double-blind, randomized comparison of the antimicrobial and antipropionibacterial efficacy and tolerability of clindamycin 1%–BPO 5% topical gel versus clindamycin gel 1% monotherapy, clindamycin–BPO topical gel reduced total mean baseline *P acnes* counts by 99% at week 4 and maintained this result throughout the

Strategies to Prevent the Development of Resistance in Acne Therapy*

Withdraw antibiotics as soon as inflammation is controlled[17]

Use topical retinoids with BPO and antibiotics to speed improvement and target microcomedones[17,18]

Avoid monotherapy with topical antibiotics for patients who require more than 12 weeks of therapy; combine with BPO[18,19]

Minimize antibiotic use if BPO or topical retinoids may be equally effective[20]

Use BPO and/or retinoids for maintenance therapy[17]

Stress the importance of good compliance[18,20]

Use isotretinoin for resistant cases[17]

*BPO indicates benzoyl peroxide.

study.[24] In the clindamycin monotherapy treatment group, the total mean bacterial count reduced by 85.3% at week 4, 96.5% at week 8, 92.1% at week 12, and 87.9% at week 16. The clindamycin-resistant *P acnes* counts remained at or below baseline values with the combination gel throughout the treatment, while the counts increased to greater than 1600% of baseline by week 16 with clindamycin monotherapy (P=.018 vs combination gel)(Figure 2). In addition, drug-resistant coagulase-negative staphylococci increased to greater than 3500% of baseline by week 16 with clindamycin monotherapy (P<.001).[24]

Combinations of retinoids and topical antibiotics also have proven to be effective against both inflammatory and noninflammatory acne lesions. In a 12-week, multicenter, randomized, investigator-blinded, parallel-group study of 150 subjects, the subjects applied either tazarotene cream 0.1% plus clindamycin gel 1% or tretinoin gel 0.025% plus clindamycin gel 1%.[27] Tazarotene cream appeared to offer a substantial advantage in reducing both overall disease severity and open and closed comedone counts. The median change from baseline in inflammatory lesions was greater in the tazarotene cream

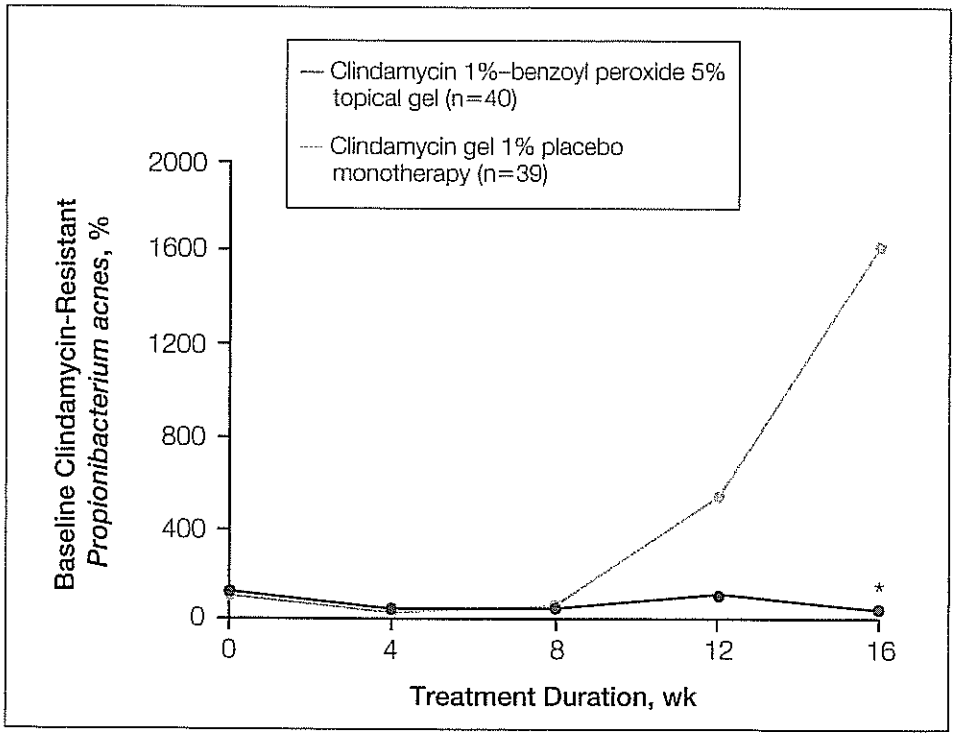

Figure 2. Baseline clindamycin-resistant *Propionibacterium acnes* in the treatment of acne with clindamycin 1%–benzoyl peroxide 5% topical gel vs clindamycin gel 1% monotherapy. Asterisk indicates P=.018 vs combination gel. Adapted from Cunliffe et al,[24] Copyright 2002, with permission from Excerpta Medica, Inc.

treatment group ($P=.53$). At week 12, 88% of the tazarotene cream plus clindamycin gel treatment group showed a 50% or greater global improvement compared with 75% of the tretinoin gel plus clindamycin gel treatment group; 66% and 52%, respectively, showed a 75% or greater improvement.[27]

Recently, a topical gel containing clindamycin phosphate 1.2% and tretinoin 0.025% was approved for the treatment of acne vulgaris in patients 12 years and older. In a study comparing its use versus clindamycin phosphate gel 1.2% monotherapy in 2010 subjects, the antibiotic-retinoid combination offered greater efficacy.[28] At week 12, inflammatory lesions decreased 61% from baseline in the combination gel treatment group and 55% in the clindamycin monotherapy treatment group. The decrease from baseline in noninflammatory lesions was 50% and 41%, respectively.[28]

Even though the combination of this topical retinoid and topical clindamycin in the treatment of acne is effective, there are concerns regarding this combination without the addition of BPO. As the Cunliffe et al[24] study showed, the use of clindamycin without BPO does have the potential for resistance to rapidly develop. Physicians may have important reservations about the use of retinoid-clindamycin combinations without the concomitant use of BPO for patients with acne who require more than 12 weeks of therapy.

Conclusion

Bacterial resistance to antibiotics is increasingly important worldwide. Serious consideration must be given to conserving the efficacy of these essential drug resources, such as reducing their use when feasible and using them carefully when deemed necessary. In the management of acne, the use of topical BPO is an important concomitant drug in long-term antibiotic therapy. Systemic and topical monotherapy should be avoided, but combination therapy with clindamycin and BPO has been shown in numerous studies to offer improved efficacy and tolerability versus monotherapy of either drug.

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