The problem of antibiotic resistance

Current guidelines on the treatment of acne discourage the use of antibiotics for long periods,1 and still, 5 million prescriptions are for oral antibiotics are written annually to treat the condition. The bacteria that is involved in the pathogenesis of acne vulgaris is Propionibacterium acnes (P. acnes) with four main pathogenic features including excess production of sebum, bacterial colonization, inflammation, and abnormal keratinization.¹ Ideally, practitioners should target as many of those features as possible, and may look to combinations of topical and systemic therapies to do so. Antibiotics have an antimicrobial impact by reducing the presence of P. acnes as well as an anti-inflammatory effect by hindering production of inflammatory mediators associated with P. acnes.² Medical professionals have been very dependent on antibiotics to manage acne: for more than 50 years, both topical and oral antibiotics have been the foundation of acne treatment.
The development of antibiotic resistance can be traced over time. A study dating back to 1976 saw no evidence of antibiotic-resistant propionibacteria on the skin of more than 1,000 acne patients. The first sign of resistance to topical erythromycin and clindamycin was reported in 1979, followed by reports of resistance to tetracycline in the 1980s. The figure has soared since, with the incidence of antibiotic resistance in acne being 20% in 1978 and 72.5% in 1995. Commonly-prescribed antibiotics erythromycin and clindamycin, in particular, have been identified as the cause of the growing increase in resistance over time. It does not take long for strains of bacteria that are insensitive to antibiotics to emerge: one study showed such strains to appear after eight weeks of topical antibiotic monotherapy. Several studies have found a link between resistance and higher counts of *P. acnes* as well as failure of response to therapy.

One could argue that worries about the continuing development

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**Strategies for Limiting Antibiotic Resistance in Acne**

1. Avoid topical or oral antibiotics as monotherapy or maintenance therapy
2. Limit duration of antibiotic use
3. Use benzoyl peroxide (BPO) in conjunction with antibiotics (leave-on or wash)
4. Avoid simultaneous use of oral and topical antibiotics without benzoyl peroxide (BPO)
5. Use topical retinoid with or without benzoyl peroxide instead of antibiotics
of bacteria that are insensitive to therapeutic acne medications does not need to give us pause, for serious acute propionibacterial infections that are life-threatening, for instance in the post-surgical setting, are not treated with acne medications. Moreover, acne that is resistant to antibiotics does not pose risks to patients nor the community in terms of the threat of resistant propionibacterial infections.

**The transfer of resistance**

When regimens that involve either topical or oral antibiotics to treat acne are extended, it has led to selection pressure or the transfer of resistant genes to bacteria that has the potential to be pathogenic, for example, some strains of staphylococci or streptococci. When regimens that involve either topical or oral antibiotics to treat acne are extended, it has led to selection pressure or the transfer of resistant genes to bacteria that has the potential to be pathogenic, for example, some strains of staphylococci or streptococci.2,3 These resistant organisms could present a treatment challenge. The organisms can have an impact on flora not only on the skin but at other sites, such as the nose and the throat.7 A study found patients treated with any antibiotic exhibited a three-fold elevated risk of group A streptococcus colonization by *Streptococcus pyogenes* (*S. pyogenes*) compared to patients who are not using antibiotic therapy. Cultures from patients exposed to antibiotics were resistant to at least one tetracycline antibiotic, compared to 20% from those not using antibiotics. Furthermore, a subgroup analysis found topical antibiotics were not innocuous where resistance is concerned, with topicals having an effect on distant flora and patterns of resistance via direct inoculation or systemic absorption. Topical antibiotics can also change the microbial equilibrium by elimination of certain bacteria. As a result, species like *S. pyogenes*, which would typically be under control in number, have the opportunity to thrive.7

Topical erythromycin use has resulted in, on both local and distant sites, in rising numbers of resistant coagulase-negative staphylococci (CNS).8-10 Aerobic flora that is rich in *Staphylococcus epidermis* (*S. epidermis*) has demonstrated that it is resistant not only to treatment with erythromycin but has partial resistance to other antibiotic therapies like clindamycin and tetracyline after just three months of therapy.8

The gravity of *S. epidermis* should not be minimized. The bacteria has been identified as pathogenic, particularly in surgical patients, those with indwelling catheters, and premature infants. Even more worrisome is that CNS has displayed its ability to transfer resistance to *S. aureus*, a more pathogenic organism that tends to flourish and spread more widely with the use of topical antibiotic treatment.

The development of resistance to antibiotics that are in the arsenal to treat acne does not seem to be a
distressing matter since physicians are not likely to look to most acne therapies to treat \textit{S. epidermis} or group A \textit{streptococcus}. Exceptionally, acne therapies minocycline and trimethoprim-sulfamethoxazole are regarded as first-line systemic agents to treat community-acquired methicillin-resistant \textit{S. aureus} (MRSA). To date, minocycline resistance is uncommon, but that is not true for trimethoprim.\textsuperscript{11}

Alas, treatment choices become fewer as more and more multi-drug-resistant organisms surface.

**Clinical Relevance of Antibiotic Resistance:**

1. Transfer of resistance to more pathogenic organisms
2. Reduced clinical response to antibiotic therapy
3. Potential increase in pathogenicity of \textit{P. acnes}

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**Steps to Limit Antibiotic Resistance in Acne**

Clinicians can stem the tide of antibacterial resistance by altering their prescribing habits. Indeed, prescribing practices affect the rates of \textit{P. acnes} resistance. As well, selection pressure can influence more pathogenic bacteria than \textit{P. acnes}, it stands to reason that clinical practice guidelines can be an instrument to control antibiotic resistance.\textsuperscript{1} An organization known as the Global Alliance to Improve Outcomes in Acne recommends the combination of a topical retinoid in addition to an antimicrobial agent as first-line therapy for the majority of acne patients.\textsuperscript{1}

The same group suggests strategies to keep a reign on resistance including limiting the prescription of oral antibiotics in moderate and moderately severe acne cases. They also suggest adding on benzoyl peroxide (BPO) and a topical retinoid when topical antibiotics are used for patients with mild-to-moderate acne.

BPO, either used alone or in conjunction with a topical retinoid, is an effective treatment for patients with resistant \textit{P. acnes}. It also helps contain the problem of antibiotic resistance. BPO has been used extensively, with no bacterial resistance reported with its use. Topical retinoids are a good therapeutic choice, for they decrease both inflammatory and non-inflammatory lesions.\textsuperscript{12,13}

BPO is available in leave-on formulations or simple washes. Both formulations have been described as conferring protection against the development of antibiotic resistance. A study found the leave-on formulation suppresses existing insensitive strains, as well as decreasing the emergence of bacterial strains resistance to antibiotics like erythromycin.
and clindamycin.\textsuperscript{5,14,15-20} A wash containing BPO decreases \textit{P. acnes} colonization\textsuperscript{21,22}.

Another approach to eliminating resistant strains of \textit{P. acnes} is the use of adapalene combined with BPO. The therapeutic combination of the two, delivered as a gel, resulted in a significant decrease in resistant strains of bacteria by week four.\textsuperscript{12} In some patients, the combination was highly effective, completely eliminating resistant strains.

**Conclusion**

Antibiotics continue to play a vital role in treating acne, but the rise in \textit{P. acnes} resistance should raise red flags for prescribers and give them pause to examine their prescribing patterns and treatment decisions. A lack of response or sub-optimal response to treatment is associated with resistant strains. In addition, \textit{P. acnes} have become increasingly pathogenic. Furthermore, extended regimens of antibiotic treatment have fuelled the transfer of resistance to non-targeted pathogenic bacteria. Clearly, fewer numbers of antibiotic prescriptions coupled with shorter courses of antibiotic treatment, as well as the liberal use of the topical antimicrobial agent BPO, will contain the ongoing challenge of antibiotic resistance. These strategies will effectively decrease inflammatory and non-inflammatory lesion counts and not compromise patient satisfaction with treatment.

**References**

3. Crawford WW, Crawford IP, Stoughton RB, et al. Laboratory induction and clinical occurrence of


