Antibiotic Resistance and Acne: Where We Stand and What the Future Holds

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ABSTRACT

Antibiotic resistance is described as "a global public health challenge" and a "major health security challenge of the 21st century" by global health authorities,[1] and there is a growing need for dermatologists to counteract it in their treatments of acne.[3,4] Antibiotic limiting regimens, such as a combination of topical retinoids and benzoyl peroxide, have shown effectiveness in the treatment of acne; and topical probiotics could also play a needed role.

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INTRODUCTION

Antibiotic resistance has become a global priority, and the science ministers of the G8 countries have deemed it to be a "major health security challenge of the 21st century."[1] The World Health Organization has also identified antibiotic resistance as a "rapidly evolving health issue extending far beyond the human health sector," emphasizing the urgent need for a cross-sectoral approach.[2]

Although dermatologists account for approximately 1% of the physicians in the United States, they prescribe 4.9% of the antibiotics (Figure 1).[3] Dermatologists regularly prescribe antibiotics for acne vulgaris (AV) and other long-term inflammatory dermatoses; but antibiotic resistance has led to a decreased sensitivity of certain bacterial organisms, such as *Propionibacterium acnes*, to antibiotics.[4]

For example, Ross et al collected phenotypes and genotypes of 73 antibiotic-resistant strains of *P. acnes* that were acquired from the skin of acne patients in the United Kingdom, United States, France, Germany, Australia, and Japan, and found that most erythromycin-resistant isolates were cross-resistant to clindamycin.[5] Tetracycline-resistant isolates had differing degrees of cross-resistance to doxycycline and minocycline, and isolates from the United States had higher cross-resistance to minocycline than isolates from other countries.[5] The investigators also found resistant strains in which mutations could not be identified, which suggests that uncharacterized resistance mechanisms have evolved.[5]

DISCUSSION

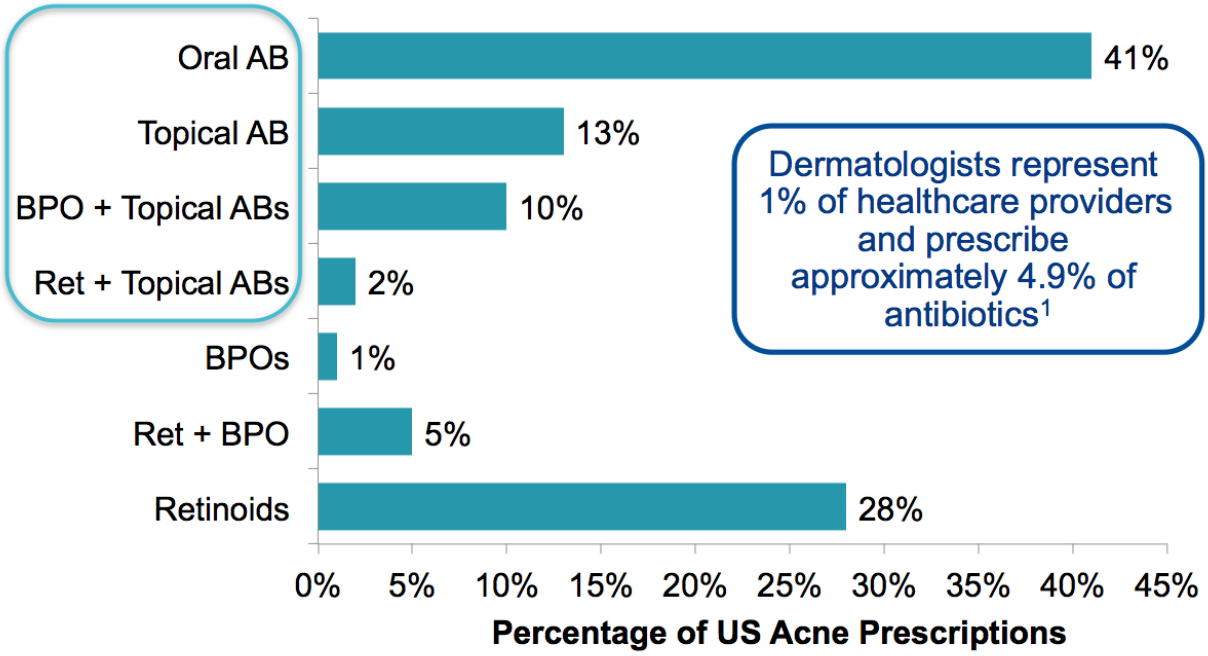
As the sensitivity of *P. acnes* to several oral and topical antibiotics has decreased, the efficacy of oral tetracyclines and erythromycin has also noticeably decreased, which has led to an escalation in the prescribing of doxycycline, minocycline, and other antibiotics for *P. acnes*.[6] Additionally, changing patterns of antibiotic sensitivity and the escalation of more virulent pathogens, such as community-acquired methicillin-resistant *Staphylococcus aureus,* macrolide-resistant *staphylococci* and *streptococci,* and mupirocin-resistant *S. aureus,* have led to major changes in clinicians prescribing patterns of antibiotics.[7]

Although most of the time clinicians are responding to these new resistance patterns in an appropriate fashion, it is important to note that both correct and incorrect use of antibiotics can promote antimicrobial resistance. Oral and topical antibiotics account for 54% of all prescriptions written for acne in the field of dermatology, and approximately 66% of antibiotic use in dermatology is for acne.[7] Even when dermatologists use antibiotics responsibly, we are contributing to resistance. However, when used inappropriately, resistance rates grow at an even more rapid rate. Antibiotic monotherapy, long-term administration of antibiotics, and dosing below the recommended levels especially promote the development of bacterial resistance.[8] Not only do these practices result in *P. acnes* resistance and acne treatment failures, but they have also resulted in the spread of resistance to other organisms colonizing the skin.[8] Long-term use of antibiotics has even yielded systemic consequences, including an increased risk of upper respiratory tract infections.[8]

Studies have demonstrated that antibiotic limiting regimens, such as a combination of topical retinoids and benzoyl peroxide (BPO), can be highly effective for the treatment of acne.[8,9,10] The ACCESS I and ACCESS II trials have shown that topical retinoids with BPO are effective for both the primary and maintenance treatment of *P. acnes* (Figure 2).

ACCESS I was a randomized, vehicle-controlled, multicenter, double-blind study that assessed the efficacy and safety of combination therapy using doxycycline and an adapalene 0.1% and BPO 2.5% combination gel (Epiduo®) for the treatment of

FIGURE 1. Acne prescription profiles in dermatology.[1]



[1]Symphony Health PHAST Monthly Prescription

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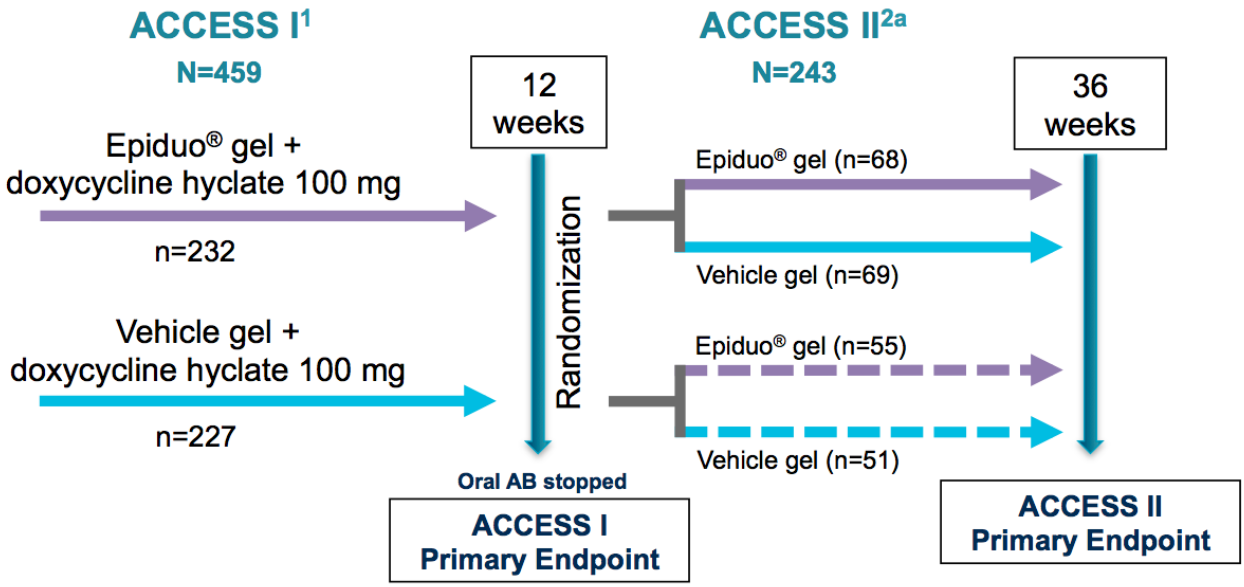
AB, antibiotic; BPO, benzoyl peroxide; Ret, retinoids.

FIGURE 2. Adapalene/benzoyl peroxide in patients with severe acne: the ACCESS study.



[a]First 280 patients who completed the previous study, ACCESS I, and had obtained at least a "Good" improvement, defined as about 50% improvement from baseline or better (grade 0, 1, 2, or 3) were eligible for ACCESS II enrollment.
AB, antibiotic.

[1]Stein Gold L et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis.* 2010;85(2):94-104.

[2]Poulin Y, Sanchez NP, Bucko A, et al. A 6-month maintenance therapy with adapalene-benzoyl peroxide gel prevents relapse and continuously improves efficacy among patients with severe acne vulgaris: results of a randomized controlled trial. *Br J Dermatol.* 2011;164(6):1376-1382.

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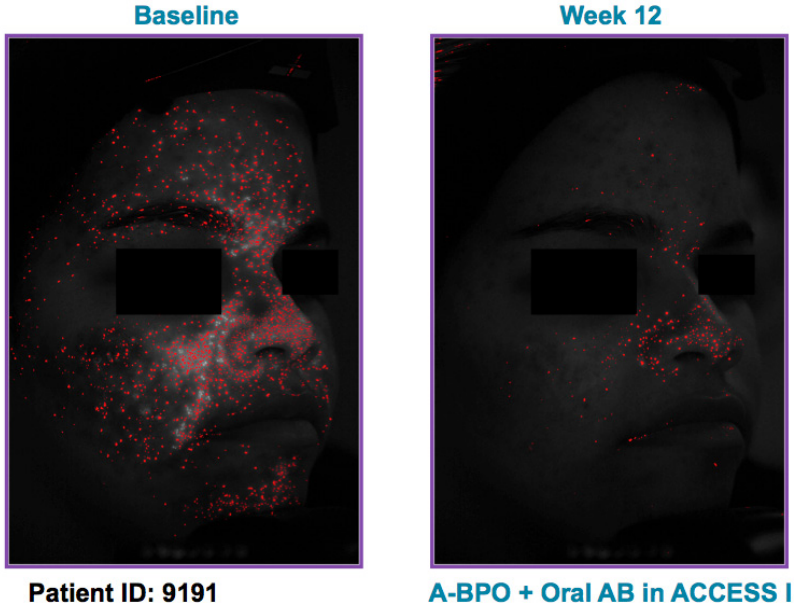
FIGURE 3. UV fluorescence of Propionibacterium acnes through ACCESS I.



UV digital fluorescence photographs from a phase 4, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study of adapalene 0.1%/benzoyl peroxide 2.5% fixed-dose combination with oral doxycycline vs. vehicle gel with oral doxycycline for 12 weeks, followed by adapalene 0.1%/benzoyl peroxide 2.5% or vehicle gel for an additional 24 weeks, in patients with severe acne vulgaris (N=243).

A, adapalene; AB, antibiotic; BPO, benzoyl peroxide.
Data on file, Galderma Laboratories, L.P.

severe AV.[9] A total of 459 subjects were randomized in a 1:1 ratio to receive for 12 weeks oral doxycycline once daily or either Epiduo or a vehicle gel once daily. The efficacy of doxycycline and Epiduo was demonstrated by week 2 compared with the vehicle arm for total inflammatory and noninflammatory lesions.[9] By week 12, the doxycycline and Epiduo group was superior to vehicle in reducing total inflammatory and noninflammatory lesion counts and for global success and overall participant satisfaction.[9] Digital UV fluorescence photography also showed an expeditious and efficacious reduction to *P. acnes* in the doxycycline and Epiduo group (Figure 3).[9]

Whereas ACCESS I focused on the primary treatment of acne with Epiduo, ACCESS II evaluated the safety and efficacy of Epiduo for maintenance therapy or relapse prevention.[10] ACCESS II was a 24-week, multicenter, double-blind, randomized extension of ACCESS I that compared Epiduo with vehicle in 243 subjects. After the randomized subjects were treated for 12 weeks in ACCESS I, and had experienced at least a 50% global improvement in their AV, they were randomized to receive Epiduo gel or its vehicle once daily for 24 weeks.[10] By week 24, when Epiduo was compared with vehicle, it yielded a significantly higher lesion maintenance success rate for all lesions; and a significantly greater number of subjects who had been administered Epiduo had an equivalent or superior Investigator's Global Assessment score at week 24 than at baseline.[10] In ACCESS II, Epiduo resulted in further decrease of lesion counts, and 45.7% of subjects were "clear" or "almost clear" at week 24 (Figure 4).[10,11]

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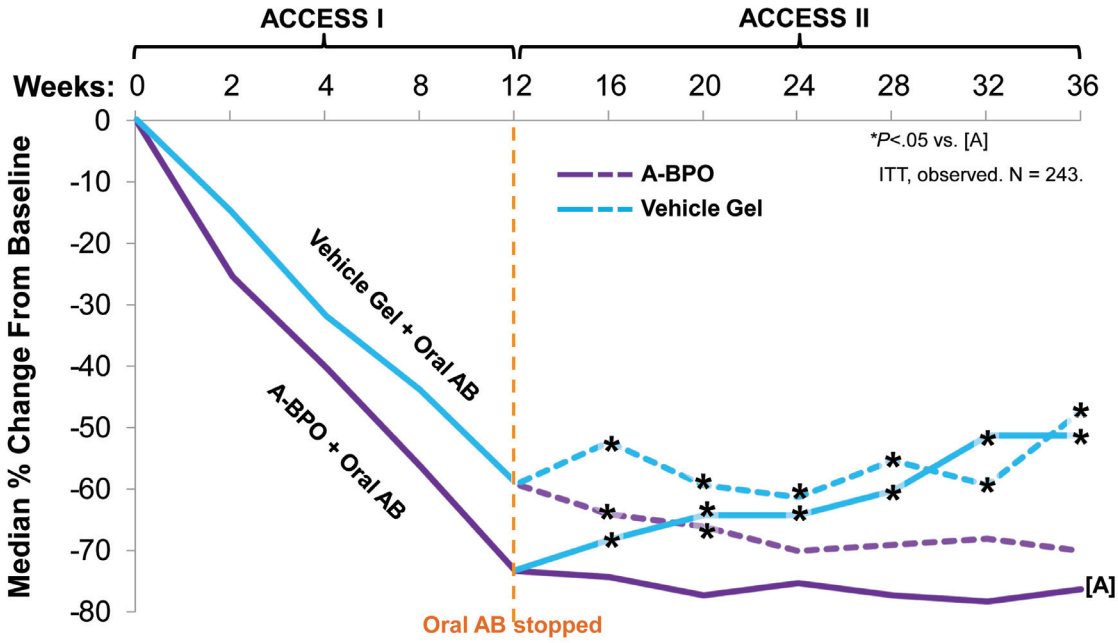
Leyden et al evaluated the effectiveness of adapalene and BPO combination gel in the reduction of antibiotic-sensitive and resistant strains of *P. acnes* on the facial skin. This 4-week, open-label, single-center study included 30 healthy adults with high facial *P. acnes* populations that were resistant to one or more of the following antibiotics: erythromycin, tetracycline, clindamycin, minocycline, and doxycycline.[12] Although all of the subjects had *P. acnes* strains resistant to one or more of the 5 antibiotics at baseline, the total *P. acnes* counts decreased by 1.1 logs after 2 weeks of treatment and by 1.6 logs after 4 weeks.[12] In addition to reducing population densities of *P. acnes*, adapalene and BPO combination gel completely eradicated antibiotic resistant strains in some subjects.[12]

FIGURE 4. Total lesion reduction in ACCESS II.



Tan J, Stein Gold L, Schlessinger J, et al. Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. *J Drugs Dermatol.* 2012;11(2):174-180.

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AB, antibiotic; A-BPO, adapalene/benzoyl peroxide.

The Global Alliance to Improve Outcomes in Acne has recommended several strategies for the prevention of *P. acnes* antibiotic resistance that limit antibiotics and use a topical retinoid and BPO. Antibiotics should be limited to the shortest duration possible and never be used as a monotherapy.[13] The number of patients still filling prescriptions for antibiotics in the absence of a BPO topical treatment is astounding. Whether or not these patients are being advised to use the two concurrently, or they stop using the BPO independently despite counseling to the contrary, remains unclear. But it is our responsibility to our patients to emphasize the importance of using BPO every time an oral or topical antibiotic is prescribed or refilled. Moreover, dermatologists should discontinue antibiotics when there is no further improvement or the improvement is only slight.[13] Oral antibiotics should ideally be used for 3 months, but 6 to 8 weeks into treatment might be an appropriate time point at which to assess the response to antibiotics. Lastly, the concurrent use of oral and topical antibiotics, particularly if chemically different, should be discontinued.[13]

Antibiotics should also be avoided for maintenance therapy. In lieu of antibiotics, maintenance therapy should include the use of a topical retinoid and BPO to limit antibiotic resistance. Benzoyl peroxide reduces the likelihood of antibiotic-resistant *P. acnes* emerging, and rapidly reduces the number of sensitive and resistant strains of *P. acnes* at the site of application. Benzoyl peroxide should be used either concomitantly or pulsed as an anti-resistance agent, and it may be helpful to use BPO for a minimum of 5 to 7 days between antibiotic courses. As studies continue to further validate the efficacy of BPO, and validate its essential role in the fight against antibiotic resistance, it will continue to assume a larger role in the practice of dermatology.

Topical Probiotics

While thought leaders in the fields of public health, infectious disease, and dermatology continue to explore ways to maintain the efficacy of our antibiotic armamentarium and prevent further resistance from developing, other researchers are searching for novel therapeutic options. Topical probiotics have the potential to be a treatment of interest for acne. While studies are still very preliminary, they do show some promising results.[14]

Probiotics are healthy strains of bacteria that potentially improve the health of their host, and there are 3 means by which probiotics can benefit a patient via topical administration. First, if a live culture is actually capable of surviving on the skin's surface, that strain could potentially provide a protective shield on the patient's skin, blocking colonization by possibly harmful organisms.[14] Second, some probiotics are capable of producing and secreting antimicrobial substances into their environment; so one can envision an antimicrobial alternative to antibiotics that works via a unique mechanism.[14]

Third, when certain probiotic strains are placed in contact with epithelial cells, they are capable of inhibiting inflammatory pathways and thus the production of inflammatory cytokines.[14] As chronic inflammation plays a major role in acne, a natural immunomodulator could play a needed role.

CONCLUSION

Antibiotics have played a leading role in the treatment of acne for decades. However, recent issues surrounding resistance force us to question how much longer we can count on these drugs, and whether or not they will maintain their front-line role as safe, effective treatments. It is our responsibility to take whatever measures we can to limit the development of further antibiotic resistance, and those measures are reviewed here. While we fight to maintain the clinical value of antibiotics, we must also continue to search for novel approaches to the treatment of acne. An ongoing search for unique treatments that can be used in concert with or as alternatives to antibiotics will allow us to best prepare ourselves for what the future has in store.

DISCLOSURES

Whitney P. Bowe MD has served as a consultant for Johnson & Johnson Consumer Companies Inc, on an advisory panel for Galderma Labs, and as a consultant for Procter and Gamble.

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