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UPDATING ANTIBIOTIC USE  
FOR ACNE MANAGEMENT IN 2023

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## Vehicles Matter!



Leon H. Kircik MD

**C***utibacterium acnes* (*C. acnes*, formerly *Propionibacterium acnes*), the bacterium that lends its name to one of the most common dermatologic conditions, has been studied for decades. Yet science continues to uncover discoveries about this ubiquitous, commensal organism and the pathogenesis of acne vulgaris.

A Gram-positive lipophilic bacterium that is dominant in sebaceous glands, *C. acnes* has been classified into three phylotypes.<sup>1</sup> Although *C. acnes* is not infectious, proliferation of the bacterium in the anaerobic milieu of the sebum-rich, blocked follicle helps to promote the development of acne vulgaris by driving pro-inflammatory processes.<sup>2</sup> Treatment targeted at reducing *C. acnes* populations and their associated local inflammation is foundational to acne management. Antibiotic treatment for acne using tetracycline class antibiotics or clindamycin, which targets the bacterium, is rational and well-established. However, the risk of developing antibiotic resistance requires a cautious approach to the use of both topical and oral antibiotics.

Relatively recently, sarecycline, a next-generation oral tetracycline, has come to market for the treatment of acne. It has been shown to bind simultaneously to two different subunits of *C. acnes*, which accounts for its narrow-spectrum activity.<sup>3</sup> While the risk for antibiotic resistance associated with sarecycline may be reduced relative to other antibiotics used to treat acne, prescribers, and patients are nonetheless cautioned to use the agent responsibly and to continue to employ strategies to mitigate resistance risk. That means that patients require concomitant topical treatment with benzoyl peroxide, an antimicrobial agent that is effective against gram-positive bacteria but not associated with promoting antibiotic resistance.<sup>4</sup> Benzoyl peroxide works via oxidation, which renders it effective against certain microorganisms but also potentially incompatible with other topical drugs.

A combination topical formulation currently under investigation for the treatment of acne is a novel first-in-class fixed-dose triple combination topical gel that contains clindamycin phosphate 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% in a polymeric mesh gel. This formulation is yet another example that “vehicles matter.” The polymeric mesh allows for benzoyl peroxide and adapalene microparticles to be homogeneously dispersed in the gel, thus overcoming the issue of adapalene and benzoyl peroxide being unstable together in the same topical formulation.

In a 12-week phase 2 double-blind, randomized, vehicle-controlled clinical trial including subjects aged 9 years or older with moderate-to-severe acne, once daily topical application of triple combo achieved treatment success in more than 50% of participants over the vehicle at week 12. Reductions in inflammatory and noninflammatory lesions were greater than 70%.<sup>5</sup>

These impressive trial results suggest that a triple combination may be a versatile treatment option for a significant proportion of patients with acne. The three-agent formulation may be a suitable treatment for patients with mild to moderate acne vulgaris, allowing for the concomitant use of three different drugs in a single application.

Trial data suggest that the triple-combination topical formulation may exhibit synergistic efficacy by simultaneously affecting multiple pathophysiologic factors associated with acne vulgaris, including targeting *C. acnes* to reduce its proliferation and inflammation.

Once again, “VEHICLES MATTER” !!!

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### DISCLOSURE

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# Antibiotic Stewardship in Acne: 2023 Update

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## ABSTRACT

Antibiotics, topical and oral, are a cornerstone in the treatment of *acnes vulgaris* specifically by targeting the skin bacterium *Cutibacterium acnes*. Billions of individuals have received antibiotics as part of their treatment resulting in a worldwide pandemic of antibiotic resistance not only for *C. acnes* but also many other pathogens. With the increasing prevalence of acne and exponentially increasing utilization of antibiotics, prescribers must urgently embrace the notion of antibiotic stewardship to maintain the efficacy of acne treatments while attenuating the rise of resistance. This paper serves as an update on *C. acnes* resistance to antibiotics commonly employed in the treatment of acne and the necessity of implementing benzoyl peroxide in the treatment regimen as monotherapy or combination antibiotic therapies for overcoming and preventing resistance.

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## INTRODUCTION

Acne is a common cutaneous inflammatory condition affecting both adolescents and adults worldwide. Acne manifests itself as comedones, papules, pustules, and cysts or nodules on the face, shoulders, chest, and back. Regardless of lesion type or severity of the disease, acne can result in pigmentary alterations and scars.<sup>1</sup> Over 60% of post-acne scars did not resolve within 6 months according to a prospective split-face study in 32 patients with moderate facial acne.<sup>1</sup> Furthermore, in an international prospective study of 324 patients with acne in Asia and Australia, 32% reported post-inflammatory hyperpigmentation to be more bothersome than acne.<sup>2</sup> As such, active disease, as well as the sequelae of acne (post-inflammatory hyperpigmentation and scarring), results in a significant psychosocial burden.<sup>3</sup> In this context, early treatment intervention is critical as the incidence of acne scarring increases with increased duration of time before adequate treatment.<sup>4</sup>

Antibiotics have been a fixture in acne treatment for decades. Their benefit is derived from their anti-inflammatory and antimicrobial properties against *Cutibacterium acnes* (formerly *Propionibacterium acnes*), the key pathogenic player in the development of acne.<sup>5</sup> With years of antibiotic usage, there is a global unmet need to address the current and future state of antibiotic resistance.<sup>6</sup> This review serves to elucidate the pathophysiology of acne focusing on the role of *C. acnes*, review mechanisms of antibiotic action and resistance,

highlight global patterns of *C. acnes* antibiotic resistance, and discuss the critical utility of implementing benzoyl peroxide (BPO) into a daily acne treatment regimen for overcoming and preventing resistance.

### Pathophysiology of Acne Vulgaris and the Role of *C. Acnes*

Acne arises due to inflammatory dysregulation and dysbiosis of the epidermis and pilosebaceous subunits.<sup>7</sup> The 4 pillars of acne pathogenesis are: (1) excess sebum production, (2) follicular epidermal hyperproliferation with plugging, (3) proliferation of *C. acnes*, and (4) inflammation.<sup>8</sup> Follicular plugging further promotes the growth and activity of *C. acnes* due to the increased anaerobic environment of the pilosebaceous unit. All act in concert with interdependence, with no one component necessarily igniting the disease.

Colonization of *C. acnes*, a gram-positive lipophilic bacterium that is dominant in sebaceous, lipid-rich areas of skin, is considered a crucial component in the pathogenesis of acne.<sup>9,10</sup> *C. acnes* affects numerous components of skin and inflammatory homeostasis through the following: (1) increasing sebum production, (2) promoting abnormal differentiation and proliferation of keratinocytes, and (3) activating the innate immune system via stimulating pro-inflammatory proteins to be expressed on keratinocyte cell surfaces (eg, Toll-like receptors, TLRs; protease-activated receptors, PARs) and to be secreted into the surrounding environment (eg, matrix metalloproteinases, MMPs).<sup>11,12</sup>

**FIGURE 1. Practical approach to acne management.** Adapted from Thiboutot et al<sup>21</sup>

| Mild   |  | Moderate  |  | Severe  |  |  |  |
|--|--|---|--|---|--|--|--|
| Comedonal  |  | Papular/Pustular  |  | Papular/Pustular  |  | Cysts/Nodules  |  |
| Topical Retinoid OR<br>Fixed combination with<br>retinoid ><br>BPO or Azelaic Acid<br>> Salicylic Acid |  | Fixed Combination OR<br>BPO OR<br>Topical Retinoid OR<br>Azelaic Acid |  | Fixed Combination<br>Preferred<br><br>+/-<br><br>Hormonal therapy and/or<br>Oral Antibiotic |  | Fixed Combination + Oral<br>Antibiotic Preferred<br>OR<br>+ Oral Isotretinoin<br>OR<br>+ Oral Hormonal Therapy |  |

*C. acnes* is classified into 3 phylotypes (I, II, and III) based on gene sequences or biological characteristics (ie, lipase activity).<sup>13</sup> These phylotypes are further subdivided into subspecies to delineate their distinct phylogenetic, genomic, and phenotypic characteristics. While there are no quantitative differences in *C. acnes* of the skin between acne patients and controls, different phylogenetic groups display distinct characteristics that may induce the formation of biofilms and immune responses leading to acne.<sup>14</sup> For example, a case-controlled study of 24 patients with severe acne of the face and back found a decrease in *C. acnes* phylotype diversity with a predominance of phylotype 1A1.<sup>15</sup> *C. acnes* biofilms, which are microbial aggregates embedded in extracellular cellular matrix milieu that allow for inter-microbial communication and protection from host surveillance mechanisms, are also thought to act as an adhesive within sebum thereby increasing the cohesiveness of keratinocytes in the pilosebaceous unit leading to the formation of microcomedones.<sup>16</sup> Jahns et al corroborate this notion in their case-control study, which demonstrated that more frequent biofilm formation in sebaceous follicles was found in facial biopsy samples of acne patients compared to control samples.<sup>17</sup> In addition to comedone formation, *C. acnes* is considered etiological to inflammatory acne lesions due to the interaction of *C. acnes* with numerous biological targets as previously noted.<sup>18</sup> Interestingly, acne-associated *C. acnes* phylotypes induce higher concentrations of interferon-gamma (IFN- $\gamma$ ) and interleukin (IL)-17 suggesting activation of both Th1 and Th17 pathways possibly due to expression of different antigenic components compared to phylotypes associated with normal skin, which are associated with induction of higher levels of IL-10.<sup>13,19</sup>

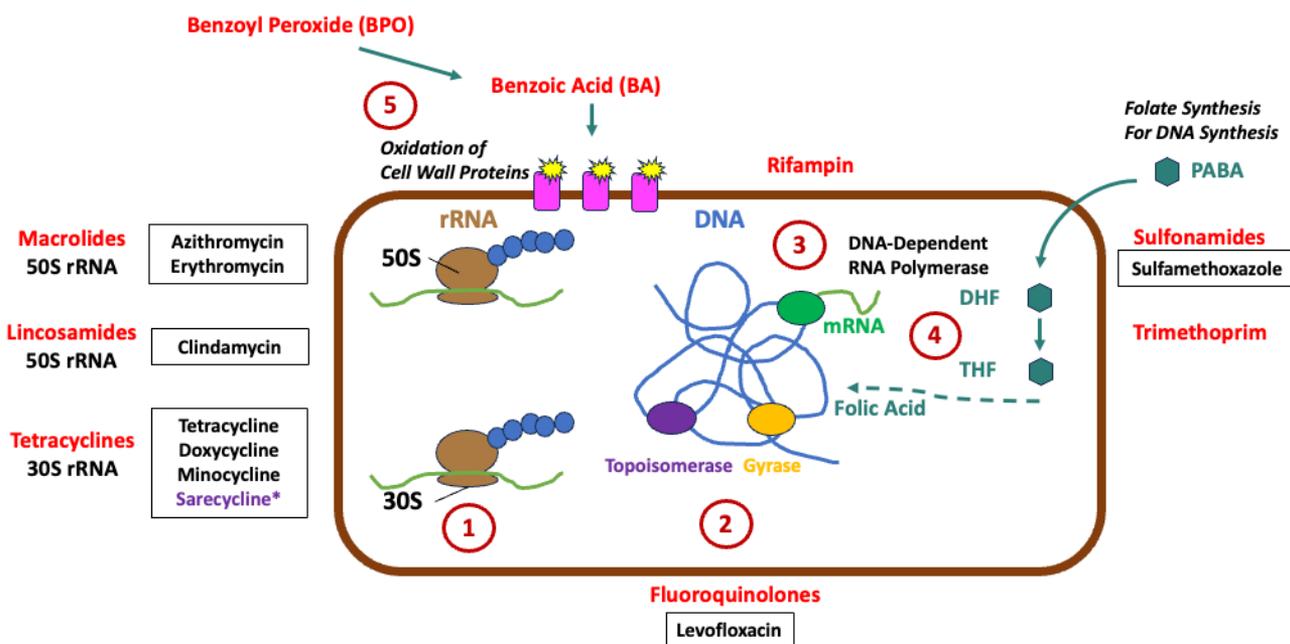
To date, there is no case of acne without *C. acnes*, and therapeutically induced reduction of *C. acnes* population directly or indirectly via antibiotics or retinoids (through suppression of sebum production), respectively, reduces inflammation.<sup>9</sup> Thus, targeting *C. acnes* is a mainstay in acne treatment for all patients regardless of skin type, disease severity, and lesion type.

### Current Paradigm in Acne Treatment

Current treatments focus on simultaneously targeting multiple aspects of acne pathophysiology: reducing sebum production, normalizing keratinization, killing *C. acnes*, and reducing inflammation.<sup>20</sup> According to a 2018 Delphi international consensus as well as guidelines from the European Dermatology Forum and American Academy of Dermatology, topical retinoids are the first line in mild or moderate disease as they affect all components and may be used as monotherapy or in combination with other therapeutics (Figure 1).<sup>21-23</sup> Addition of topical antibiotics to target *C. acnes* is also advised in combination with a retinoid but not as monotherapy given the worldwide problem of antibiotic resistance.<sup>24-27</sup> Among antimicrobials, BPO is the preferred topical agent given its mechanism of action as a strong oxidative agent with potent bactericidal activity while preventing the development of antibiotic resistance.<sup>23</sup> For patients with severe and moderately severe acne recalcitrant or intolerant to topical combination therapy with topical retinoid and BPO, the addition of oral antibiotic, oral isotretinoin, or hormonal therapy is recommended by the guidelines (Figure 1). While the AAD guidelines recommend oral antibiotic use for 3 to 4 months, recent studies found that approximately 20% of patients continuously used them for  $\geq 6$  months.<sup>28,29</sup>

The utilization of antibiotics in dermatology, particularly for the treatment of acne, has come under intense scrutiny. According to the Scientific Panel on Antibiotic Use in Dermatology (SPAUD), which operates under the purview of the American Acne and Rosacea Society, dermatologists prescribe ~8.2 million oral antibiotic prescriptions annually.<sup>30</sup> Given the high prevalence of acne worldwide, the use of antibiotics must be judicious as there is a massive selective pressure of these treatments on both pathogenic and nonpathogenic microbes that lead to alterations in the microbiome and selection of antibiotic-resistant organisms. Not only do antibiotic prescribing patterns affect resistance patterns of *C. acnes* relevant for acne treatment but also that of numerous other organisms and their sites of colonization, which have far-reaching implications for infectious diseases of both the skin and viscera.<sup>30</sup> For example,

**FIGURE 2. Mechanisms of action of antibiotics utilized for the treatment of *C. acnes*.** (1) Macrolides, lincosamides, and tetracyclines, which are the most common antibiotic classes utilized for acne treatment, exhibit bactericidal activity via binding and inhibiting different rRNA subunits. Inhibition of rRNA halts the machinery that translates mRNA to proteins required for bacterial replication and virulence. Sarecycline is a unique narrow-spectrum tetracycline that occupies binding sites on both 30S and 50S rRNA subunits. (2) Fluoroquinolones inhibit DNA topoisomerase and gyrase – proteins that are involved in the unwinding and stability of DNA that prepares it for transcription by DNA polymerase to generate mRNA transcripts. (3) Rifampin blocks DNA-dependent RNA polymerase, which is required to transcribe DNA into mRNA. (4) Trimethoprim/sulfamethoxazole blocks enzymes involved in the folate synthesis pathway, which is essential for the formation of one-carbon metabolites utilized in the synthesis of bacterial DNA. (5) BPO is converted in the stratum corneum into the active metabolite BA, which is bactericidal via oxidation of proteins leading to reduced integrity of the bacterial cell wall.



Abbreviations: rRNA, ribosomal RNA; mRNA, messenger RNA; BPO, benzoyl peroxide; BA, benzoic acid

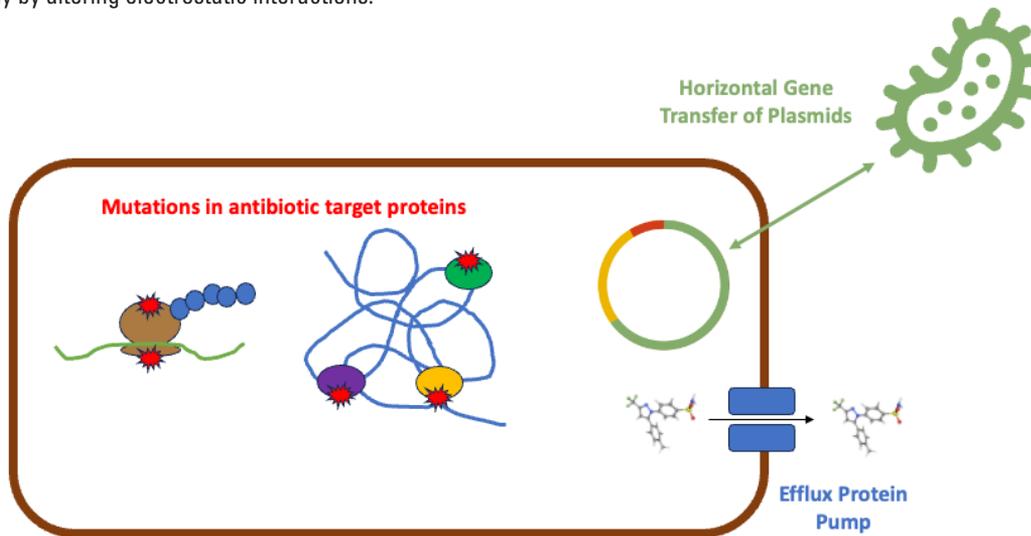
a 3-fold greater incidence of oropharyngeal colonization with *Streptococcus pyogenes* (with 85% exhibiting resistance to at least one tetracycline antibiotic) was found in patients using oral and/or topical antibiotics for at least 3 months compared to control patients without antibiotics for at least 6 months.<sup>31</sup> A large retrospective cohort analysis of over 118,000 patients found a 2.15-fold greater risk of developing an upper respiratory tract infection in those treated with oral and/or topical antibiotics.<sup>32</sup> In addition, facial application of erythromycin 2% gel for 12 weeks resulted in a greater amount of *S. aureus* nasal carriage as well as erythromycin-resistant coagulase-negative staphylococci on the face and at remote sites such as the back and anterior nares.<sup>33</sup> These erythromycin-resistant bacteria persisted over at least 4 weeks despite discontinuation of antibiotic treatment.

The implications of antibiotic use in a global context cannot be understated. With respect to acne, understanding antibiotic resistance patterns of *C. acnes* is critical as appropriate antibiotic usage is a lynchpin in the acne treatment algorithm.

### Current Antibiotics Utilized in the Treatment of Acne

Numerous antibiotics of different classes have been utilized to target *C. acnes* (Figure 2). The most commonly prescribed oral antibiotics in the United States from 1993 to 2016 according to a National Ambulatory Medical Care Survey (NAMCS) are minocycline, doxycycline, and clindamycin.<sup>34</sup> The major classes of antibiotics employed for treating acne include the following: (1) tetracyclines, (2) lincosamides, and (3) macrolides. All 3 classes target ribosomal RNA (rRNA) – the machinery by which bacterial proteins are translated from messenger RNA (mRNA) into amino acids and arranged into functioning peptides. They, however, target different components of this machinery; macrolides and lincosamides bind and inhibit the 50S larger ribosomal subunit albeit at different positions, whereas tetracyclines inhibit the 30S smaller ribosomal subunit (Figure 2). Given their established safety and efficacy, tetracyclines are the preferred first-line treatment option for acne.<sup>35</sup> Commonly used oral antibiotics in the tetracycline class include tetracycline, doxycycline, minocycline, and,

**FIGURE 3.** Bacterial mechanisms of antibiotic resistance. Antibiotic resistance mechanisms are generally due to: (1) mutations in antibiotic target proteins (ie, rRNA, topoisomerase, gyrase, DNA polymerase), (2) presence of efflux protein pumps that extrude antibiotics from the cellular interior, or (3) acquisition of antibiotic resistance genes via horizontal gene transfer of plasmids from other bacterial species. These plasmids may contain genes that encode for multi-drug efflux proteins as well as genes encoding for proteins that are involved in post-translational modifications of rRNA (eg, methylation), which may indirectly alter the binding sites of antibiotics through direct interference by that modification unit or indirectly by altering electrostatic interactions.



Abbreviations: rRNA, ribosomal RNA

more recently, sarecycline.<sup>36</sup> Sarecycline unexpectedly binds simultaneously to both the 30S and 50S subunits in *C. acnes*, which lends to its narrow-spectrum activity.<sup>37</sup> In addition to the tetracyclines, clindamycin is the canonical lincosamide utilized in acne treatment.<sup>38</sup> From the macrolide group, azithromycin and erythromycin are the most utilized.<sup>35</sup>

Although not considered a typical antibiotic, BPO exhibits a unique mechanism of action whereby it is converted to benzoic acid (BA) in the stratum corneum, which then non-specifically oxidizes bacterial cell wall proteins, thus exerting bactericidal activity.<sup>39</sup> The importance of BPO and this mechanism of action is discussed in detail in a later section.

Other antibiotics also used for acne treatment but at much lower rates include fluoroquinolones and sulfonamides (Figure 2). Fluoroquinolones, such as levofloxacin, inhibit DNA topoisomerase and gyrase, which are involved in bacterial DNA unwinding and stability in preparation for transcription of DNA into mRNA.<sup>40,41</sup> Sulfonamides, such as sulfamethoxazole, block the formation of dihydrofolate in the folate synthesis pathway, which is a critical metabolite in microbial DNA synthesis. A combination of sulfamethoxazole with trimethoprim is often employed as trimethoprim also inhibits the formation of tetrahydrofolate in the folate synthesis pathway.<sup>42</sup> Rifampin, an antimycobacterial, binds to DNA-dependent RNA polymerase

to inhibit the transcription of bacterial DNA. While it is not yet used for acne vulgaris, it has utility against *C. acnes* biofilm in a foreign body infection model.<sup>43</sup> It, therefore, may theoretically be effective for the treatment of acne.

### ***C. Acnes* Mechanisms of Acquiring Antibiotic Resistance**

Targeting *C. acnes* is central to acne treatment success. As antibiotic agents have been utilized for billions of patients worldwide for many decades, antibiotic-resistant *C. acnes* strains have invariably emerged and now pose challenges for current and future acne patients. Before the turn of the 21<sup>st</sup> century, *C. acnes* resistance rose over 40% from 20% in 1978 to 62% in 1996.<sup>44</sup> Furthermore, there are also instances of antibiotic-resistant *C. acnes* in patients who have never undergone antibiotic treatment.<sup>45</sup> Thus, it is important to understand the mechanisms behind how *C. acnes* acquires resistance (Figure 3).

Mutations in genes encoding ribosomal RNA are frequently found in *C. acnes* strains isolated from acne patients exhibiting macrolide resistance.<sup>46</sup> 23S rRNA, found within the 50S subunit, is the microbial target of macrolides (ie, clindamycin), and mutations at the binding site of these antibiotics result in their inability to bind and inhibit its function. This resistance is thought to be caused by long-term, low-concentration exposure of macrolides thereby providing a low-level selection

pressure.<sup>47</sup> Similarly, mutations in 16S rRNA (found within the 30S subunit), as well as DNA gyrase and topoisomerase genes (*gyrA* and *parC*, respectively), explain resistance to tetracycline and fluoroquinolones, respectively.<sup>48,49</sup>

Efflux protein pumps are another mechanism of resistance where bacteria pump out antibiotics from the cellular interior to the exterior.<sup>50,51</sup> Notably, efflux pumps can selectively extrude a distinct class of antibiotics or can pump out several classes leading to multi-drug resistant bacteria.<sup>52</sup> Genes encoding efflux protein pumps could be intrinsic to the bacteria or acquired through horizontal gene transfer from other bacteria.<sup>53</sup>

*C. acnes* antibiotic resistance may also be due to acquisition of exogenous resistance genes, which are transmitted between bacteria, also known as horizontal gene transfer.<sup>54,55</sup> These genes include *erm(x)* and *erm(50)*, which are found on plasmids that are independent from the *C. acnes* genome, and function to methylate 23S rRNA.<sup>56</sup> Multi-drug resistant strains more commonly harbor plasmids containing these genes, which are transmitted not only between *Cutibacterium* strains but also between *C. acnes* and other species, including the major skin commensal bacterium *Staphylococcus epidermidis*.<sup>57</sup> This phenomenon of plasmid transfer explains why previously antibiotic-naïve patients with acne harbor resistant *C. acnes* strains.

#### Antibiotic Resistance Patterns – A Global Outlook

Antibiotic resistance patterns of *C. acnes* vary among different world regions due to prescribing patterns.<sup>14</sup> In the United States, resistance rates ordered from greatest to least are for erythromycin followed by clindamycin and tetracycline.<sup>30</sup> Rates of resistance to any antibiotic ranged from 50.8% to 93.6% across numerous countries, including the UK, Spain, Italy, Greece, Sweden, and Hungary.<sup>58</sup> In Japan, resistance rates were documented to be 2.5 times higher in 2020 than in 2013.<sup>45</sup> Overall, many countries have reported that antibiotic resistance is present in over 50% of *C. acnes* strains.<sup>59</sup>

The antibiotics with the greatest overall resistance rates were the macrolides and lincosamides. In France and Spain, approximately 70% and 91% of strains exhibited resistance to clindamycin and erythromycin.<sup>60</sup> Japan exhibited resistance rates of approximately 19% and 23% to clindamycin and erythromycin, respectively; while Bangkok, Thailand, had resistance rates of over 70% for both.<sup>61,62</sup> In Hong Kong, China, resistance rates were 53.5% and 20.9% for clindamycin and erythromycin, respectively.<sup>63</sup> Azithromycin resistance, however, has been scarcely studied. Nonetheless, a study in Mexico reported 82% resistance and a study in India reported 100% resistance.<sup>64,65</sup> High resistance rates to azithromycin were also found in China.<sup>66</sup>

The tetracycline class also experienced significant resistance rates albeit less than the macrolides and lincosamides. Resistance rates to tetracycline in France and Spain ranged from 0% to 26.4%.<sup>58</sup> Hong Kong similarly had 16.3% resistance to tetracyclines.<sup>63</sup> For doxycycline and minocycline, resistance rates in Japan were 4.3% and 0%, respectively.<sup>61</sup> In Thailand, resistance rates were 51.7% and 51.1% for tetracycline and doxycycline, respectively.<sup>62</sup>

With respect to trimethoprim/sulfamethoxazole, studies in Jordan, Thailand, and Mexico reported resistance rates of *C. acnes* isolates to be 31%, 100%, and 68%, respectively.<sup>62,64,67</sup> For fluoroquinolones, resistance rates were 15% for levofloxacin in Jordan and 6.3% for moxifloxacin in China.<sup>67,68</sup> While considering the aforementioned reported rates of resistance, it is important to note that there is significant variation in sampling (eg, superficial swabs, biopsies) and total number of patients per country.

#### Utilization of BPO for Antibiotic Stewardship in Acne

BPO is available in numerous over-the-counter and prescription formulations such as washes, lotions, and gels. It is converted to BA once it penetrates the stratum corneum after topical application.<sup>69</sup> During this conversion, highly reactive oxygen species are generated, which oxidize bacterial proteins thereby damaging cell walls.<sup>39,70</sup> As such, BPO is effective against gram-positive bacteria and fungi but less so against gram-negative bacteria due to the presence of outer membranes.<sup>39</sup> In addition to its antimicrobial effects, BPO also increases the rate of epithelial cell turnover and desquamation thereby exhibiting keratolytic and comedolytic effects.<sup>70</sup>

The mechanism of BPO bactericidal activity is unique among antibiotics in that it is not targeted toward particular bacterial machinery such as rRNA but is rather a generalized approach aimed at dismantling the bacterial cell wall. BPO can therefore be used against a wide variety of bacteria despite their resistance patterns while also minimizing the risk of selecting resistant bacteria.<sup>71</sup> No resistance has been reported with BPO when used in acne treatment to date.<sup>23</sup> As such, BPO is considered first-line as topical monotherapy or in combination with oral antibiotics in the AAD guidelines to reduce the risk of resistance development.<sup>21</sup> This is exemplified by a study that demonstrated that daily application of the topical combination drug 2.5% BPO/0.1% adapalene for 4 weeks resulted in a 97% reduction of antibiotic-susceptible and antibiotic-resistant *C. acnes* strains with some resistant strains being eliminated in some patients.<sup>72</sup>

#### Combination Topical Drugs Incorporating BPO for Acne Treatment

While BPO has been incorporated in various combination

regiments, there have been some limitations. These have generally included tolerability and oxidation.<sup>73,74</sup> Traditional BPO formulations and higher concentrations of BPO tend to cause skin irritation such as dryness, peeling, erythema, and stinging/burning. This has been addressed with the development of novel vehicles and colloidal delivery systems.<sup>75-77</sup> BPO is also highly oxidative, which leads to potential bleaching of clothing and hair. This oxidative property also causes degradation of tretinoin, thereby reducing treatment efficacy and classically precluding their combined application.<sup>78</sup> Microencapsulation and micronization technologies now allow for the combination of BPO and tretinoin while reducing oxidation.<sup>79</sup>

Notwithstanding these limitations, BPO has been incorporated with retinoids and antibiotics resulting in a plethora of dyad combination topical products that are synergistically effective in treating acne while minimizing antibiotic resistance. Topical antibiotic combination treatments include BPO with either clindamycin or erythromycin at varying concentrations.<sup>80</sup> BPO 5%/clindamycin phosphate 1% gel,<sup>81</sup> BPO 3.75%/clindamycin phosphate 1.2% gel,<sup>82</sup> and BPO 2.5% / clindamycin phosphate 1.2% gel<sup>83</sup> are the currently approved BPO/clindamycin combinations for patients 12 years and older. Microencapsulated tretinoin 0.1%/BPO 0.3% cream was recently approved in 2021 for the treatment of acne in patients  $\geq 9$  years of age.<sup>84</sup> BPO 2.5% gel in combination with different concentrations of adapalene (0.1% and 0.3%) has also been approved for acne patients aged  $\geq 9$  and 12 years, respectively.<sup>85</sup>

A novel first-in-class, fixed-dose, triple combination topical gel (IDP-126) containing clindamycin phosphate 1.2%, BPO 3.1% and adapalene 0.15% in a polymeric mesh gel with micronized particles of BPO and adapalene was recently studied in a 12-week phase 2 double-blind, parallel-group, randomized and vehicle-controlled clinical trial in patients aged  $\geq 9$  years with moderate-to-severe acne.<sup>86</sup> Once-daily topical application of IDP-126 achieved treatment success ( $>50\%$  of participants) over vehicle at week 12 with over 70% reductions in inflammatory and noninflammatory lesions.<sup>86</sup> Furthermore, treatment success rates appeared to be greater (synergistic) than the expected additive effect of each component as the rates were 1.7-1.8 times greater than with the component dyads. Similar treatment success was demonstrated in 2 identically designed, 12-week phase 3 pivotal trials.<sup>87</sup> Furthermore, a head-to-head study comparing the efficacy of IDP-126 to Epiduo<sup>®</sup> Forte (BPO 2.5%/ adapalene 0.3% gel) is currently underway (NCT04892706).<sup>88</sup> Given these results and the polymeric mesh technology that now allows for BPO to be combined with previously incompatible actives such as tretinoin due to oxidation, triple combination IDP-126 offers a potential new once-daily tolerable "monotherapy" that may exhibit synergistic efficacy by simultaneously affecting multiple pathophysiologic factors

giving rise to acne while also minimizing the development of *C. acnes* antibiotic resistance strains.

## CONCLUSION

Targeting *C. acnes* is a critical component in all international guidelines for the treatment of acne.<sup>21</sup> While this is done with the use of topical and oral antibiotics, it has been found that antibiotic treatment is being prescribed well over the recommended limit of 3 months, thereby leading to a selection pressure for antibiotic resistance.<sup>28</sup> The rise in *C. acnes* antibiotic resistance is a global phenomenon given the ubiquitous use of antibiotics in billions of patients with acne. Antibiotic stewardship is now more important than ever, not only because the effectiveness of current antibiotic regimens for acne will decline but also because other pathologies due to virulent *C. acnes*, such as prosthetic joint infections, may become more prevalent and difficult to treat.<sup>9</sup> Vaccines against *C. acnes* are also being studied in an effort to circumvent the use of antibiotics.<sup>89-91</sup>

BPO, an age-old topical medication with a unique antimicrobial mechanism of action where its metabolite BA oxidizes bacterial proteins thereby destroying cell walls, emerges as a necessary agent to combat antibiotic resistance. This seemingly non-targeted yet elegant mechanism has proven effective in treating both non-resistant and antibiotic resistant *C. acnes* strains.<sup>71</sup> Furthermore, use of BPO in acne treatment has resulted in preventing *C. acnes* resistance.<sup>23</sup> Advances in vehicle and encapsulation technologies have also allowed BPO to be elegantly formulated with other antibiotics and retinoids such as tretinoin despite its oxidative capacity. This is evident with numerous topical BPO dyads already approved for the treatment of acne and now with the emergence of IDP-126, the first-in-class topical triple-combination gel containing clindamycin phosphate 1.2%, BPO 3.1%, and adapalene 0.15%. Taking together the data highlighting the efficacy of BPO on all strains of *C. acnes* while minimizing the development of resistance, implementation of BPO should be considered in every patient with acne in our era of antibiotic overuse.

## DISCLOSURES

Leon Kircik MD has served as either an investigator, consultant, speaker or advisory board member for Allergan, Allmirall, Biofrontera, Galderma, L'Oreal, Mayne Pharma, Ortho Dermatologics, and SUN Pharma. Naiem T. Issa has received funding from the following entities either as a speaker, consultant, advisor, or investigator from Bristol Myers Squibb, Castle Biosciences, Dermavant Sciences, DermTech, Galderma, LEO Pharma, Lilly, National Eczema Association, Ortho Dermatologics, Pfizer, RBC Consultants, Verrica Pharmaceuticals, and WebMD.

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