

Avoiding the Danger of Rising Resistance in *Cutibacterium acnes*: Criticality of Benzoyl Peroxide and Antibiotic Fixed Combinations

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SYNOPSIS AND OBJECTIVE

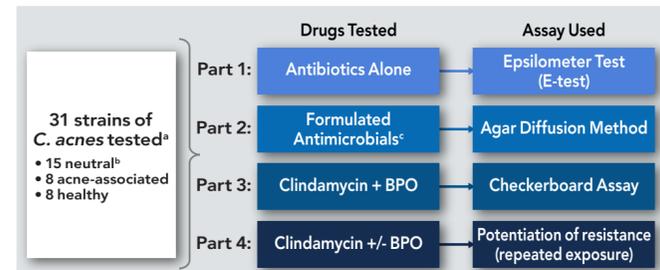
- Topical antibiotics such as clindamycin are often used to treat acne; accordingly, dermatologists prescribe almost 5% of all antibiotics, though they account for <1% of the US physician population¹
- Resistance to topical antibiotics in *Cutibacterium acnes* (*C. acnes*)—the bacteria involved in acne pathogenesis—was first reported in the US in the 1970s²
- Since then, several countries have reported >50% of *C. acnes* strains as resistant to certain antibiotics^{3,4}
- This emergence of resistant strains can lead to increased therapeutic failure⁵
- Combination formulations containing an antibiotic and the antimicrobial benzoyl peroxide (BPO) may reduce the risk of resistance, especially with prolonged use^{6,7}
- This four-part study tested susceptibility of *C. acnes* strains and the development of resistance to antibiotics alone or in combination with BPO

METHODS AND RESULTS

Study Overview

- The study comprised 4 parts, with 31 individual strains of *C. acnes* evaluated (Figure 1)

FIGURE 1. Study design



^aClassification based on Fitz-Gibbon S, et al. *J Invest Dermatol.* 2013;133(9):2152-60. "Neutral" are reported to cause acne but also colonize normal skin, "acne-associated" colonize skin with acne, and "healthy" colonize healthy skin. ^bOne strain sometimes classified as acne-associated. ^cComprising 6 branded products or products in development: CLIN 1.2%/adapalene 0.15%/BPO 3.1% (Ortho Dermatologics), CLIN 1% gel (Ortho Dermatologics), CLIN 1.2%/BPO 3.75% gel (Ortho Dermatologics), Minocycline 4% foam (Journey Medical Corporation), CLIN 1.2%/BPO 5% gel (Stiefel Laboratories), erythromycin 3%/BPO 5% gel (Ortho Dermatologics), CLIN, clindamycin phosphate; BPO, benzoyl peroxide.

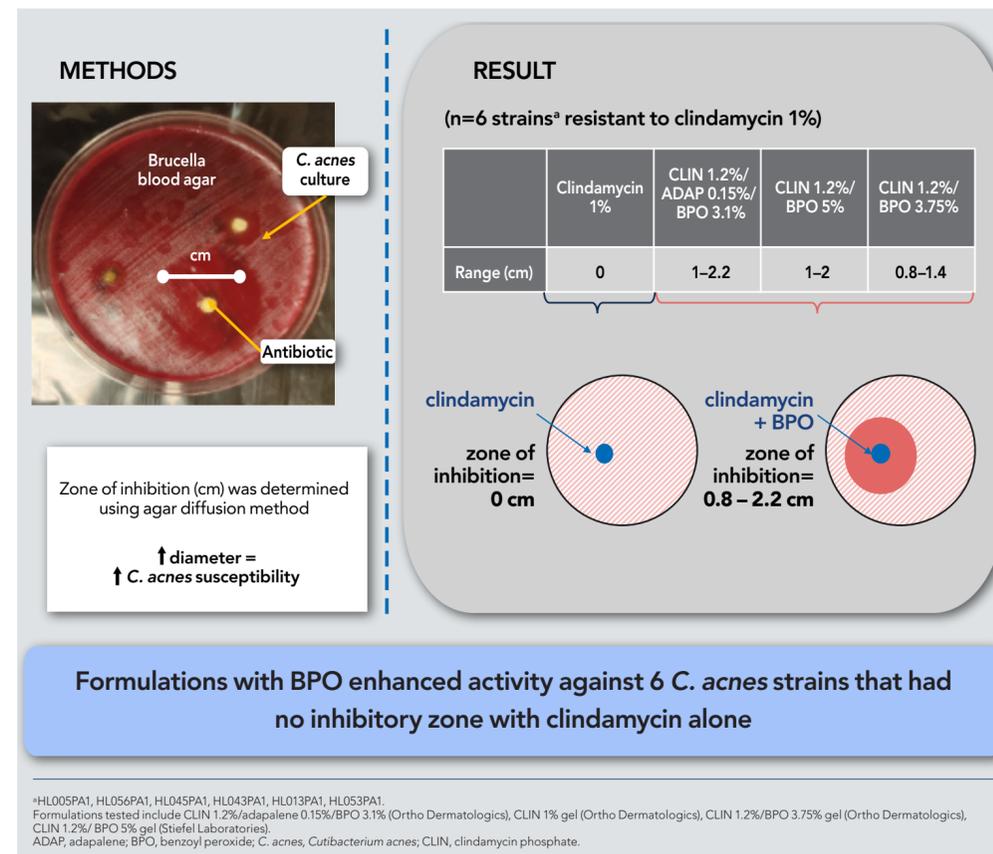
Part 1: *C. acnes* Sensitivity to Antibiotics

- C. acnes* susceptibility to antibiotics was assessed via minimum inhibitory concentration (MIC) values obtained from epsilometer tests
 - MIC is the lowest concentration of an antibiotic needed to inhibit bacterial growth
 - Lower MIC indicates higher antibiotic susceptibility
- All antibiotics tested (erythromycin, clindamycin, doxycycline, and minocycline) had similar MIC ranges, indicating similar activity against most *C. acnes* strains tested
 - Erythromycin had higher (worse) MIC₉₀, the lowest concentration required to inhibit 90% of strains tested, compared to other antibiotics
- Five *C. acnes* strains had elevated MIC to multiple antibiotics tested, an indication of resistance

Part 2: *C. acnes* Sensitivity to Antibiotic Formulations +/- BPO

- C. acnes* susceptibility to antibiotics alone or in a fixed-dose combination with BPO was determined by measuring zone of inhibition using agar diffusion method, with larger diameter indicating increased bacterial inhibition (Figure 2, left)
- All antimicrobial formulations produced similar ranges of zones of inhibition, indicating similar activity against the *C. acnes* strains
- Six *C. acnes* strains had no inhibitory zone (0 cm), all with clindamycin 1%; fixed-dose formulations of clindamycin with BPO had enhanced activity against the same 6 isolates compared to clindamycin alone (range: 0.8-2.2 cm; Figure 2, right)

FIGURE 2. *C. acnes* Sensitivity to Clindamycin Compared to Clindamycin+BPO



Part 3: Effect of Clindamycin + BPO on *C. acnes* Inhibition

- The effect (synergistic, additive, antagonistic, or neutral) of combining clindamycin with BPO on *C. acnes* inhibition was evaluated using a checkerboard assay, wherein two test compounds are combined in varying concentrations
- The combination of clindamycin and BPO resulted in an additive effect for 4 of 7 acne-associated strains tested and neutral effect for 3 strains
- Microscopic images from a separate in vitro experiment confirmed this finding (Figure 3)

Part 4: Preventing Antibiotic Resistance With BPO

- Development of resistance was assessed using serial passage of bacterial cultures in increasing concentrations of clindamycin alone or in combination with BPO (Figure 4, left)
- Bacterial cultures repeatedly exposed to clindamycin + BPO did not develop resistance to *C. acnes*, which occurred with exposure to clindamycin alone (Figure 4, right)

FIGURE 3. Scanning Electron Microscopy of Clindamycin + BPO

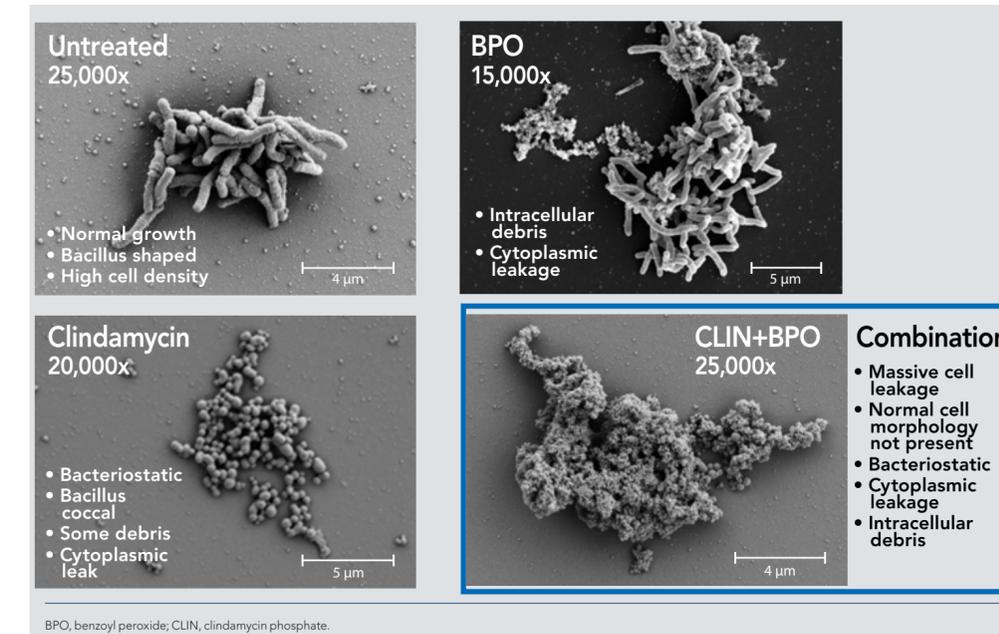
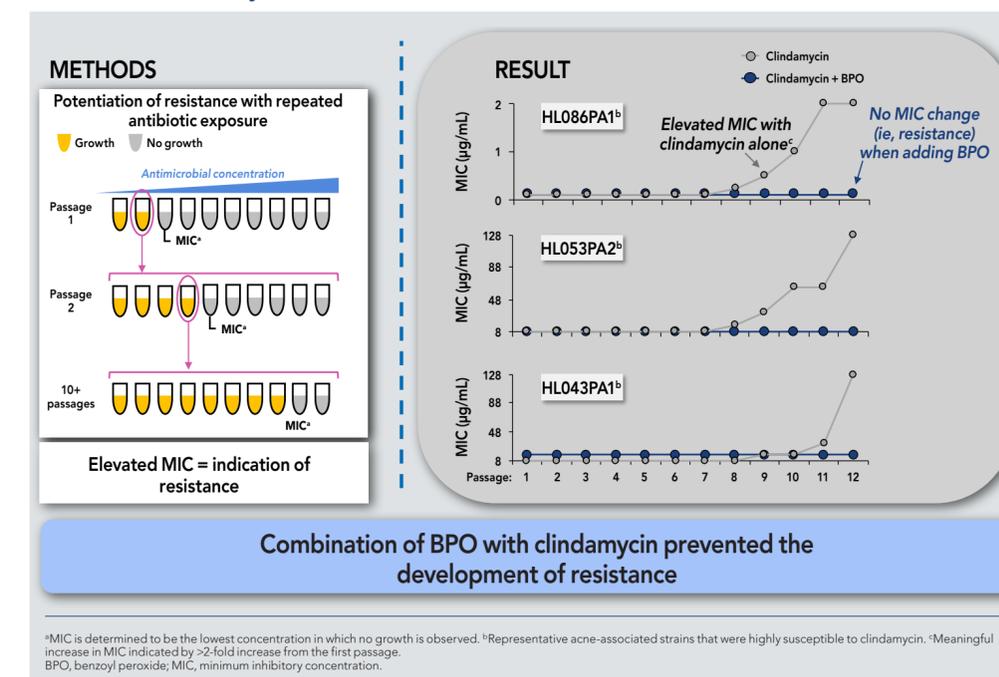


FIGURE 4. Development of Antibiotic Resistance to Clindamycin Compared With Clindamycin+BPO



CONCLUSIONS

- Tested antimicrobial compounds possessed similar activity against most *C. acnes* strains, with formulations containing BPO having enhanced activity against strains less susceptible to clindamycin
- Combination of clindamycin and BPO resulted in an additive effect for over half of acne-associated strains tested
- Overall, adding BPO to an antibiotic can improve antimicrobial activity against *C. acnes*, and may protect against the development of resistance

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AUTHOR DISCLOSURES

Mahmoud Ghannoum has acted as a consultant or received contracts from Scynexis, Inc, Bausch & Lomb, Pfizer, and Mycovia. James Q. Del Rosso has served as a consultant, investigator, and/or speaker for Ortho Dermatologics, Abbvie, Amgen, Arcutis, Dermavant, EPI Health, Galderma, Incyte, LEO Pharma, Lilly, MC2 Therapeutics, Pfizer, Sun Pharma, and UCB. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharma, UCB, Arcutis, and Lilly. Leon Kircik has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Julie Harper has received honoraria from Aclaris, Almirall, BioPharmX, Cassiopea, Cutanea, Dermira, Foamix, Galderma, LaRoche-Posay, Ortho Dermatologics, and Sun Pharma. Other authors have nothing to disclose.