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Propionibacterium acnes Resistance: A Worldwide Problem

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Propionibacterium acnes · Antibiotic resistance · *P. acnes* mutations · Worldwide problem

Abstract
Antibiotic therapy directed against *Propionibacterium acnes* has been a mainstay of treatment for more than 40 years. Despite years of widespread use of systemic tetracyclines and erythromycin, change in *P. acnes* sensitivity to antibiotics was not seen until the early 1980s. The first clinically relevant changes in *P. acnes* antibiotic sensitivity were found in the USA shortly after the introduction of topical formulations of erythromycin and clindamycin. By the late 1980s, *P. acnes* strains with very high MIC levels for erythromycin and elevated MICs for tetracycline were increasingly found in the UK and the USA. Mutations in the genes encoding the 23S and 16S subunits of ribosomal RNA were first identified in the UK and also seen in a recent survey from clinics in Europe, Japan, Australia and the USA. In addition, strains were found in which these known mutations could not be identified, indicating that as yet unidentified resistance mechanisms have evolved. These findings indicate the need to develop strategies to minimize the use of antibiotics in acne therapy.

The link between proliferation of *Propionibacterium acnes* in the environment of the microcomedo and the development of the inflammatory phase of acne has been well established. Over the past 25 years, antimicrobial therapy has been the major area of new drug development by the pharmaceutical industry. *P. acnes* is highly sensitive to a wide range of antibiotic classes (table 1) including the tetracycline and macrolide families. The challenge for antimicrobial therapy has been delivery into the lipid-rich environment of the microcomedo where *P. acnes* is proliferating in a cocoon of abnormally desquamated follicular corneocytes.

Widespread use of tetracyclines and erythromycin occurred for more than 25 years before less-sensitive strains and clinically relevant or 'resistant' strains were identified. In the late 1970s, a few strains of *P. acnes* that were relatively insensitive to erythromycin and clindamycin were first reported and were not viewed to be clinically significant [1]. In the early 1980s, shortly after the introduction of topical formulations of erythromycin and clindamycin, clinically relevant, less-sensitive strains were reported from a small group of patients in the USA [2]. Some of these strains were highly resistant to erythromycin. Subsequently, in the late 1980s and early 1990s in extensive studies at Leeds, more clinically significant antibiotic resistance and strains with multiple drug resistance were identified [3–5]. For example, continuous monitoring for nearly a decade in Leeds showed a steady increase in resistance with a prevalence of 65% seen in a specialized referral center by 1997 [5]. In addition, resistant *P. acnes* strains were identified in other countries [6–9].

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Table 1. *P. acnes* sensitivity to antibiotic classes

Very sensitive	Resistant
Tetracyclines, especially minocycline and doxycycline	Aminoglycoside
Erythromycin and other macrolides	Mupirocin
Clindamycin	Metronidazole
Penicillin and cephalosporins	
Quinolones	
Sulfonamides	

Table 2. *P.acnes* antibiotic resistance

Erythromycin	Mutations in the genes encoding 23S ribosomal RNA
Group I	A→G transition at *E. coli* equivalent base 2058
	Highly resistant to erythromycin
	Variable for other macrolides and clindamycin
Group III	G→A transition at *E. coli* equivalent base 2057
	Low level erythromycin resistance
Group IV	A→G transition at *E. coli* equivalent base 2059
	Highly resistant to erythromycin and all macrolides
	Elevated but variable resistance to clindamycin
Tetracycline	Mutation in the gene encoding 16S ribosomal RNA
	G→C transition at *E.coli* equivalent base 1058
	Variable resistance to tetracycline, doxycycline and minocycline

Table 3. *P. acnes* resistance: worldwide study

	73 strains
	35 resistant to erythromycin only
	15 resistant to tetracycline only
	23 resistant to both
Erythromycin	Group I phenotype – 14 strains
	Group III phenotype – 3 strains
	Group IV phenotype – 22 strains
	Unidentified – 9 strains
Tetracycline	16S RNA mutations at base 1058 – 34 strains
	Unidentified – 4 strains

Table 4. Future strategies

Minimize antibiotic use
Withdraw antibiotics once inflammation is controlled
Use combination topical retinoids/antibiotic therapy
Maintenance therapy
Topical retinoids
Benzoyl peroxide or benzoyl peroxide-antibiotic therapy
Isotretinoin systemically for resistant cases

Molecular Basis for *P. acnes* Resistance

In general, bacteria develop antibiotic resistance by acquiring mobile genetic elements such as plasmids, which can be transferred between strains of a species and even between species in some instances. With tetracyclines and erythromycin, mobile plasmids and transposons encode for pump proteins that efflux antibiotics away from ribosomes, and less commonly resistance is due to enzymatic inactivation [10–12]. In the case of clinically relevant strains of resistant *P. acnes*, mobile elements have not been found. Rather, point mutations in the genes encoding the 23S rRNA (erythromycin) and the 16S rRNA (tetracycline) have been identified [13–16].

Three phenotypes for erythromycin-resistant *P. acnes* have been classified (table 2). Group I is associated with an A→G transition at *Escherichia coli* equivalent nucleotide base 2058 and confers resistance to erythromycin and all macrolide, lincosamide and streptogramin B (MLS) antibiotics with the MIC varying with both drug and strain. Phenotype III is associated with a G→A transition at base 2057 and confers low level resistance to erythromycin only. Group IV has an A→G mutation at base 2059 and confers high level resistance to all 14, 15 and 16 membered ring macrolides. In the case of tetracycline, resistance is associated with a mutation (G→C transition) in the 16S rRNA of the small ribosomal subunit at *E. coli* equivalent base 1058.

Worldwide Survey

In a recent survey, resistant strains isolated in France, Germany, Japan, Australia and the USA were compared with UK strains (table 3): a total of 73 strains of which 35 were resistant to erythromycin alone, 15 to tetracycline alone and 23 resistant to both were studied [17]. Interestingly, strains from Germany and Japan were resistant to only erythromycin and those from Australia were predominately resistant to tetracycline.

Phenotype I erythromycin resistance was found in 24 strains, type III in 3 and type IV in 22 strains and 9 strains with unidentified mutations. In the case of tetracycline, 34 of 38 strains showed the previously described mutation at base 1058. Nine erythromycin-resistant isolates

from Germany did not have base mutations for 23S rRNA but did show the resistance pattern found with phenotype I.

P. acnes was more sensitive to tetracycline than to macrolides with lowest MIC_{90} seen with the more lipophilic tetracyclines such as doxycycline and minocycline. The highest levels of minocycline resistance was seen in strains from the USA. These strains of *P. acnes* were highly sensitive to penicillin, trimethoprium and madifloxacin (a recently approved quinolone).

Clinical Significance of 'Resistant Strains'

Classically, the clinical significance of less-sensitive strains is established by comparing the MIC or the minimum bactericidal concentration with the achievable concentration of the antibiotics in the body site in which the organism is proliferating. Unfortunately, no data exist for antibiotic levels in individual sebaceous follicles. Despite technological advances in microanalytical techniques, antibiotic levels in individual follicles have not yet been quantified. This means that no clinically relevant 'break point' has been established. Rather, we have had to resort to a much more difficult type of analysis, i.e. comparing clinical outcomes in those treated with antibiotics to which *P. acnes* is insensitive [4]. Despite the difficulties of such studies, there are enough data to indicate that clinical outcomes are poor in those with 'resistant strains'. In clinical practice, one cannot obtain *P. acnes* antibiotic sensitivities on a routine basis. Rather, one must use clinical sense in the setting of a patient who is no longer responding to an antibiotic which was previously effective.

Implication and Strategies for the Future

It is now clear that antibiotic resistant strains of *P. acnes* are found worldwide. The level of resistance is greatest to erythromycin but tetracycline resistance including minocycline is also occurring, as is reduced sensitivity to clindamycin. The evidence points to an evolving problem. The common practice of long-term use of antibiotics, years in many instances, is now hard to defend unless one prescribes some form of benzoyl peroxide which suppresses emergence of resistant strains [18]. In this regard, the potential usefulness of benzoyl peroxide washes, which deposit benzoyl peroxide which resists rinsing off, are particularly interesting. Another strategy is the use of topical retinoids to maintain clearing once antibiotic therapy has suppressed the inflammatory phase of acne and possibly to consider systemic isotretinoin as an option for those in whom inflammation cannot be controlled without prolonged antibiotic use (table 4).

References

1 Crawford WW, Crawford IP, Stoughton RB, Cornell RC: Laboratory induction and clinical occurrence of combined clindamycin and erythromycin resistance in *Corynebacterium acnes*. J Invest Dermatol 1979;72:187–190.
2 Leyden JJ, McGinley KJ, Cavalieri S, et al: *Propionibacterium acnes* resistance to antibiotics in acne patients. J Am Acad Dermatol 1983; 8:41–45.
3 Eady EA, Jones CE, Gardner KJ, et al: Tetracycline-resistant propionibacteria from acne patients are cross-resistant to doxycycline, but sensitive to minocycline. Br J Dermatol 1993; 128:556–560.
4 Eady EA, Cove JH, Holland KT, Cunliffe WJ: Erythromycin resistant propionibacteria in antibiotic-treated acne patients: Association with therapeutic failure. Br J Dermatol 1989;121: 51–57.
5 Eady EA: Bacterial resistance in acne. Dermatology 1998;196:59–66.
6 Kurokawa I, Nishijima S, Kawabata S: Antimicrobial susceptibility of *Propionibacterium acnes* isolated from acne vulgaris. Eur J Dermatol 1999;9:25–28.
7 Fluhr JW, Gloor M, Dietz P Hiffler U: In vitro acitvity of 6 antimicrobials against *Propionibacteria* isolates from untreated acne papulopustulosa. Zentbl Bakteriol 1999;289:53–61.
8 Cooper AJ: Systemic review of *Propionibacterium acnes* resistance to systemic antibiotics. Med J Aust 1998;169:259–261.
9 Dreno B, Legallou F, de Saint Marie I, Richet H: Prevalence of erythromycin-resistant propionibacteria and *Staphylococcus epidermidis* in acne patients in France (abstract). J Invest Dermatol 1997;108:379.
10 Leclercq R, Courvalin P: Intrinsic and unusual resistance to macrolide, lincosamide and streptogramin antibiotics in bacteria. Antimicrob Agents Chemother 1991;35:1273–1276.
11 Weisblum B: Erythromycin resistance by ribosomal modification. Antimicrob Agents Chemother 1995;39:577–585.
12 Schnappinger D, Hillen W: Tetracyclines: antibiotic action, uptake, and resistance mechanisms. Arch Microbiol 1996;165:359–369.
13 Ross JI, Eady EA, Cove JH, et al: Clinical resistance to erythromycin and clindamycin in cutaneous propionibacteria isolated from acne patients is associated with mutations in 23S rRNA. Antimicrob Agents Chemother 1997; 41:1162–1165.
14 Eady EA, Ross JI, Cove JH, et al: Macrolide-lincosamide-streptogramin B (MLS) resistance in cutaneous propionibacteria: Definition of phenotypes. J Antimicrob Chemother 1989;23: 493–502.
15 Ross JI, Eady EA, Cove JH, Cunliffe WJ: 16S rRNA mutation associated with tetracycline resistance in a gram-positive bacterium. Antimicrob Agents Chemother 1998;42:1702–1705.
16 Eady EA, Ross JI, Cove JH: Multiple mechanisms of erythromycin resistance. J Antimicrob Chemother 1990;26:461–471.
17 Ross JI, Snelling AM, Eady EA, et al: Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. Br J Dermatol 2001;144:339–346.
18 Bojar RA, Cunliffe WJ, Holland KT: The short-term treatment of acne vulgaris with benzoyl peroxide: Effects on the surface and follicular cutaneous microflora. Br J Dermatol 1995; 132:204–208.