Systematic review of antibiotic resistance in acne: an increasing topical and oral threat

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Topical and oral antibiotics are routinely used to treat acne. However, antibiotic resistance is increasing, with many countries reporting that more than 50% of *Propionibacterium acnes* strains are resistant to topical macrolides, making them less effective. We reviewed the current scientific literature to enable proposal of recommendations for antibiotic use in acne treatment. References were identified through PubMed searches for articles published from January, 1954, to March 7, 2015, using four multiword searches. Ideally, benzoyl peroxide in combination with a topical retinoid should be used instead of a topical antibiotic to minimise the impact of resistance. Oral antibiotics still have a role in the treatment of moderate-to-severe acne, but only with a topical retinoid, benzoyl peroxide, or their combination, and ideally for no longer than 3 months. To limit resistance, it is recommended that benzoyl peroxide should always be added when long-term oral antibiotic use is deemed necessary. The benefit-to-risk ratio of long-term antibiotic use should be carefully considered and, in particular, use alone avoided where possible. There is a need to treat acne with effective alternatives to antibiotics to reduce the likelihood of resistance.

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Introduction

Topical and oral antibiotics are routinely used to treat acne. However, antibiotic resistance is increasing, with many countries reporting that over 50% of *Propionibacterium acnes* strains are resistant to topical macrolides, making them less effective. Collateral damage to the steady-state microbiome is a major concern, particularly for *Staphylococcus aureus* and meticillin-resistant *S aureus* (MRSA), and antibiotic resistance in non-target bacteria promotes the growth of opportunistic pathogens. The Global Alliance to Improve Outcomes in Acne recommends that topical and oral antibiotics are not used as monotherapy or concurrently, and that combination of a topical retinoid and antimicrobial agent (eg, benzoyl peroxide [BPO]) is preferred as first-line therapy for almost all people with acne. To limit antibiotic resistance, BPO should always be added when long-term antibiotic use is deemed necessary. Comprehensive and detailed antibiotic resistance studies and joint recommendations from both dermatologists and microbiologists are long overdue. Here, we discuss the scientific literature and propose recommendations for international implementation and further clinical microbiological studies.

Search strategy and selection criteria

References were identified through searches of PubMed for articles published from January, 1954, to March 7, 2015, using several search terms. 465 publications were identified using the search terms acne (all fields) AND resistance (all fields) NOT insulin, 323 of which were published after 2000. A search using the terms acne (all fields) AND resistance (all fields) AND macrolide (all fields) led to the identification of 83 publications, 45 of which were published after 2000. 77 publications were identified using terms acne (all fields) AND resistance (title) NOT insulin, 44 of which were published after 2000. 24 of 77 publications were review articles, but four were excluded because they were not relevant to this Review. One 2010 review[1] included a search via MEDLINE, and three older systematic reviews[2–4] have been published. Other searches done were acne (title) AND antibiotic (title), which identified 107 publications, 63 of which were published after 2000, and acne (title) AND therapy (title) NOT insulin, which identified 749 publications, 287 of which were published after 2000. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

The number of publications found is relatively low as compared with other therapy areas. For example, a search using terms pneumonia (all fields) AND resistance (all fields) provides 7622 publications, 1694 of which are reviews. The development of antibiotic resistance as a result of antibiotic use in people with acne is a relatively unexplored area where further research is needed. This large, comprehensive systematic review has been done to highlight the importance and concern in this area, to discuss the scientific literature currently available, and to propose recommendations to be internationally implemented. Such a systematic and comprehensive analysis has previously not been undertaken.

Causes and pathogenesis of acne

Acne is a chronic inflammatory disorder of the skin associated with comedones, papules, pustules, nodules, and erythema, which can lead to scarring. It is very common, affecting almost 80% of adolescents and young adults aged 11–30 years.[5–7]

The pathogenesis is complex, but the pilosebaceous unit is the target organ, which accounts for the distribution of acne primarily on the face, chest, and back—the areas with the highest concentration of pilosebaceous glands.[6,8–10] The most notable pathophysiological factors that affect the development of acne are sebaceous gland hyperplasia with seborrhoea, altered follicular growth and differentiation, *P acnes* colonisation of the follicle, and inflammation and immune response.[8,11–15]

Of these factors, altered follicular growth and differentiation and sebaceous hyperplasia are thought to be the most important because, together, they induce the microcomedo, the primary lesion of acne. The microcomedo can develop into either a non-inflammatory comedo or become inflamed and present as a papule, pustule, or nodule. *P acnes* is a skin commensal that is present in small numbers in most post-pubertal individuals, and is found in increased numbers in abnormal skin environments—ie, increased sebum and abnormally desquamated corneocytes in the sebaceous follicles of people, including those without acne.[14,16] Additionally, androgens are thought to contribute to the pathogenesis of acne by affecting the growth of follicular corneocytes.

Acne is clearly not primarily an infectious disease and simply killing *P acnes* might improve acne, but will not necessarily result in disease resolution or cure.[17] The importance of the antibacterial and anti-inflammatory effects of antibiotics in acne is unclear,[18,19] and their individual contribution to clinical efficacy remains unknown. However, antibiotics are thought to work largely by inhibiting inflammation,[10] although this has not been reported in vivo, but rather has been suggested by large amounts of in-vitro data showing that antibiotics have actions independent of bacterial killing. Inflammatory events have been shown to precede hyperkeratinisation, and *P acnes* is thought to contribute to inflammation via activation of toll-like receptors on the membranes of inflammatory cells.[20] Additionally, oxidised lipids in sebum can stimulate production of inflammatory mediators, which further drives the inflammatory process.

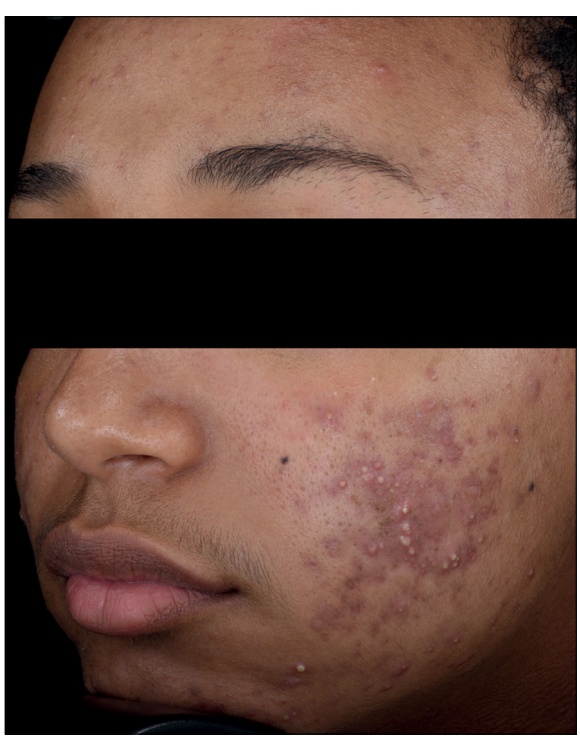

Figure 1: **Example of patient with severe acne likely to be treated with an oral antibiotic**

Antibiotics used in the treatment of acne

Both topical and oral antibiotics are traditionally used in the treatment of acne.[17,21,22] Erythromycin and clindamycin, two of the longest used and most commonly prescribed topical antibiotics, are still frequently prescribed because side-effects are typically minor.[21–24] Topical antibiotics are usually used in the treatment of mild-to-moderate acne.[17] However, despite their modest efficacy, their use continues and antibiotic resistance associated with topical antibiotic use, particularly macrolides, is an increasing concern.[23,25–27] Cyclines are the most commonly used oral antibiotics and tend to be used for the treatment of moderate-to-severe acne (figure 1).[17,23] As a result of increasing levels of resistance, use of oral erythromycin and other macrolides should be restricted to cases where cyclines are contraindicated or not well tolerated.[21,23] Use of oral clindamycin is associated with potentially serious gastrointestinal complications, and the need for periodic liver and kidney function test monitoring during prolonged therapy.[28–31] Furthermore, European guidelines specifically state that oral clindamycin is not generally recommended for the treatment of acne.[32] Cyclines, macrolides, and clindamycin are all bacteriostatic antibiotics so their use only slows bacterial growth and bacteria retain the potential to become resistant.[23,33] However, antimicrobial therapies that maximise bactericidal effects (eg, BPO) are essential because they kill the bacteria and thus reduce the likelihood of bacteria developing antibiotic resistance.[17,33]

Historically, topical antibiotics have been largely used for their antimicrobial properties.[17] Antibiotic use directed against *P acnes* has been a mainstay of acne treatment for over 50 years.[34] *P acnes* seems to play an integral part in the development of acne lesions both early and late in the pathophysiological process.[35] It contributes to the development of retentional lesions by increasing the proliferation of keratinocytes and the expression of proteins implicated in the differentiation of keratinocytes. Additionally, *P acnes* strongly activates innate immunity via toll-like receptor 2 and protease-activated receptors—expressed by keratinocytes—which induces the production of proinflammatory cytokines and matrix metalloproteinases.[35–37] Although acne is not an infection, antibiotic use reduces the number of *P acnes* present on the skin and in the pilosebaceous follicles, and results in clinical benefits.[1,17,21]

Oral antibiotics (particularly cyclines) also have substantial anti-inflammatory properties, which could have an important role in addition to their antimicrobial effects in acne,[18,23] as they do in other areas of medicine where infection and inflammation can chronically coexist.[38–42] However, oral antibiotics have only been shown to inhibit inflammation independent of bacterial