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

Timothy R Walsh, John Efthimiou, Brigitte Dréno

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.

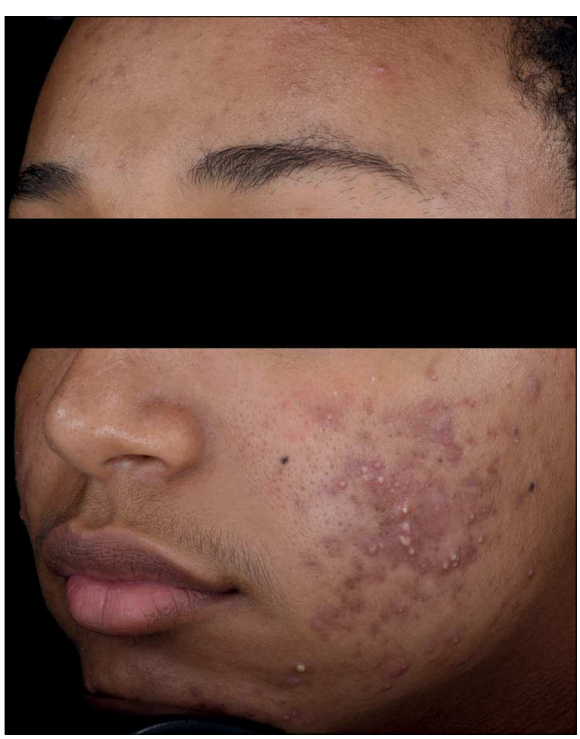

Figure 1: **Example of patient with severe acne likely to be treated with an oral antibiotic**

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

killing in vitro, an effect not reported in vivo.[23,43] The relative contribution of their antibacterial and anti-inflammatory properties in the treatment of acne remains to be completely elucidated.[43] Although low-dose oral antibiotics are used in the treatment of acne, this type of treatment has not been studied in detail, so robust conclusions cannot be drawn, particularly with regard to the overall benefit-to-risk ratio and implications for antibiotic resistance.[17]

Antibiotic use and resistance: a global issue

Although there is an enormous antibiotic load in the dermatology community, quantitative information on the use of antibiotics to specifically treat acne is very limited. In the USA, dermatologists represent 1% or less of the physician population, but prescribe almost 5% of all antibiotics.[44] Roughly 8% of all antibiotics prescribed in the UK are thought to be for dermatological indications.[45] Crucially, no longitudinal studies of topical or oral antibiotic use in acne exist. The fact that people with acne often take prolonged courses of a single antibiotic, typically 3–6 months, will result in exposure at varying concentrations and potentiate resistance.[43,46] Further research is needed to accurately determine antibiotic use in the treatment of acne and whether any differences in country or patterns of use exist.

Although not specific to acne, recent publications have highlighted the fact that use of antibiotics is still increasing globally. From 2000–10, use of 16 groups of antibiotics across 71 countries increased by 36%.[47] The latest data from the European Centre for Disease Prevention and Control on systemic use of antibacterials in the community (ie, outside hospitals) provide further evidence to support this increase. Belgium, Malta, and the UK all reported a substantial increase in antibiotic use between 2007 and 2011, but no country provided any evidence for a significant decrease (figure 2).[48]

Antibiotic resistance is a continuing issue worldwide.[49] Margaret Chan, WHO Director-General, said, "a post-antibiotic era means, in effect, an end to modern medicine as we know it".[50] In her annual report, Sally Davies, England's Chief Medical Officer, stated: "antimicrobial resistance is a ticking time bomb not only for the UK but also for the world".[51] The excessive use and misuse of antibiotics has played an important part in the development of antibiotic resistance.[52] Worryingly, antibiotics are prescribed when they are not needed or are misused as much as 50% of the time.[33] Drug-resistant strains of bacteria are thought to be annually responsible for 5000 deaths in the UK, 25 000 deaths in Europe, and 23 000 deaths in the USA.[52,53]

Crucially, few new agents have been discovered since 1987,[54,55] which might, in part, be due to woefully inadequate levels of funding. For example, less than 1% of available public and charitable research funding in the UK was awarded for research on antibiotics between 2008 and 2013.[56] One of the three strategic aims in the UK's 2013–18 antimicrobial resistance strategy is to stimulate the development of new antibiotics, diagnostics, and therapies.[57] Additionally, a new collaboration involving all seven UK research councils, the Department of Health and other government departments, the Wellcome Trust, and other relevant organisations, has been launched with the aim to boost research into microbial resistance.[58]

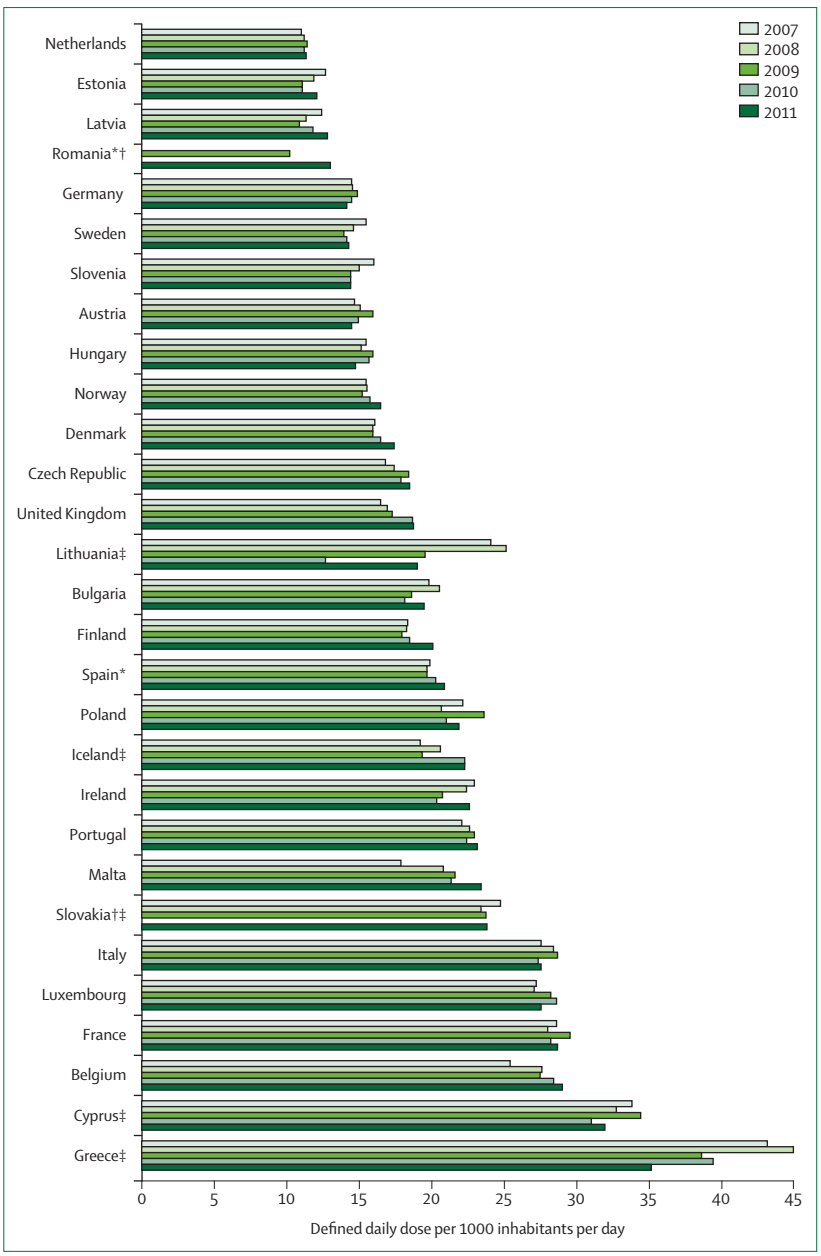

Figure 2: **Consumption of antibacterials for systemic use in the community for European Economic Area countries 2007–11, expressed as defined daily dose per 1000 inhabitants per day[48]**
Reproduced from reference 48, by permission of the European Centre for Disease Prevention and Control. *Romania and Spain provided reimbursement data (ie, not including use without a prescription and other non-reimbursed courses). †Romania (2007, 2008, 2010) and Slovakia (2010) did not report data for these years. ‡Cyprus (2007–11), Greece (2007, 2008, 2010), Iceland (2010, 2011), Lithuania (2007–09, 2011), and Slovakia (2011) provided only total care data (ie, including the hospital sector).

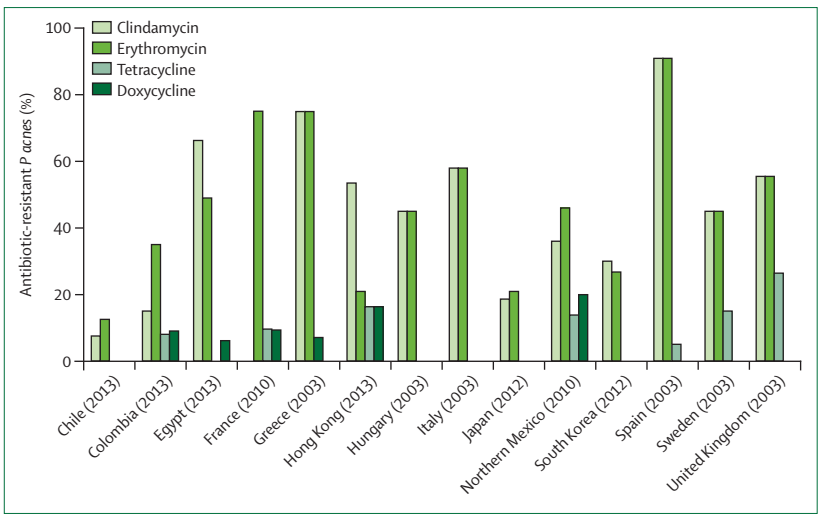

Figure 3: **Topical and oral antibiotic-resistant *Propionibacterium acnes* isolated from acne patients in different countries**[8-10,47-52]

At the end of 2014, the US President's Council of Advisors on Science and Technology reported a proposed initiative involving three strategies to address the increasing problem of antibiotic resistance: better control through stewardship of antibiotic use, improved surveillance of antibiotic-resistant pathogens, and the development of new, more effective antibiotics.[59] In the UK, the National Institute for Health and Care Excellence released draft guidelines on antimicrobial stewardship for consultation, which recommended monitoring and assessment of antimicrobial prescriptions, prescription reason documentation, and patient discussions about why an antimicrobial might not be the best option.[60] In their editorial,[61] Carl Nathan and Otto Cars highlight that the health-care community has not kept pace with the ability of many pathogens to develop resistance to antibiotics, which is a major global concern. This commentary includes a call to action suggesting that doctors could act not only individually and medically, but also collectively, to persuade elected officials to respond to expert panel recommendations and national leaders' directives with the legislation, regulation, enforcement, and cooperation needed to ensure appropriate use of antibiotics. Also very encouraging is *The Lancet* Series on antimicrobial access and resistance examining interventions known to work, which, in synergy with a more transparent prescribing culture, could help to prevent the apparent inexorable march of antimicrobial resistance.[62]

Antibiotic resistance in acne

In 1976, no evidence of topical or oral antibiotic-resistant *P acnes* existed in more than 1000 people with acne.[63] However, the overall incidence of *P acnes* resistance increased from 20% in 1978 to 62% in 1996.[64–67] Increases in *P acnes* resistance have now been reported in all major regions of the world, although the data for different antibiotics used and for different regions and countries remains incomplete.[38] Many countries have reported that over 50% of *P acnes* strains are resistant, particularly to topical macrolides (figure 3).[23,25–27,38,68–73] When clinicians consider different treatment options, they should be aware that antibiotic resistance is as important in the use of topical antibiotics as oral antibiotics.[25–27,68–73]

A correlation exists between the emergence of resistant *P acnes* and antibiotic use.[17,27,74] Importantly, countries with low resistance levels have restricted antibiotic use to treat acne, which emphasises the need to reduce their use at a global level.[27,75] Data from Hong Kong provide evidence of a link between the development of antibiotic-resistant *P acnes* and increased age, a longer duration of acne, and a longer duration of antibiotic treatment.[70] In another study[74] done in Japan, resistance of *P acnes* to antibiotics increased with disease severity. Antibiotic treatment is not a prerequisite for the development of antibiotic resistance.[27,70] Resistant *P acnes* can spread to the skin of untreated contacts, which strongly correlates with antibiotic prescribing patterns.[27]

Consequences of antibiotic use in treating acne

Resistance, cross-resistance, and topical antibiotic failure

The potential negative consequences of antibiotic use to treat acne are numerous (figure 4).[17,27,76–80] Resistance in *P acnes* mainly arises from chromosomal point mutations.[34,74,81] Non-resistant *P acnes* are killed or growth is slowed, while resistant *P acnes* grow and proliferate.[33,52] *P acnes* does not usually acquire resistance from other bacteria or transfer resistant determinants to other bacteria.[27,74,82,83] Resistant *P acnes* strains can emerge quickly—for example, topical clindamycin monotherapy results in an increase in resistant *P acnes* count to more than 1600% of baseline values by week 16.[84] Resident flora, such as *P acnes,* are naturally resilient, so resistant variants can remain long after antibiotic treatment has stopped.[17] Cross-resistance is also a growing global concern.[69,70]

Resistance of *P acnes* to antibiotics can manifest as a reduced response, no response, or a relapse.[17] Because resistance does not directly translate into treatment failure, acne is not a classic bacterial infection—partly due to the fact that antibiotics exert anti-inflammatory properties in addition to their antibacterial actions, and that the importance of infection versus inflammation in each patient is not known and not generally understood.[17,85] Topical macrolides are now less effective in the treatment of acne. A review[86] of controlled trials provided convincing evidence showing that the efficacy of topical erythromycin on the reduction in both inflammatory and non-inflammatory lesions significantly decreased over time. The authors concluded that the reduction was probably related to the development of resistant *P acnes*. As a consequence of the reduced efficacy of erythromycin in reducing lesions over time, the use of erythromycin to treat acne is decreasing.[75,87]

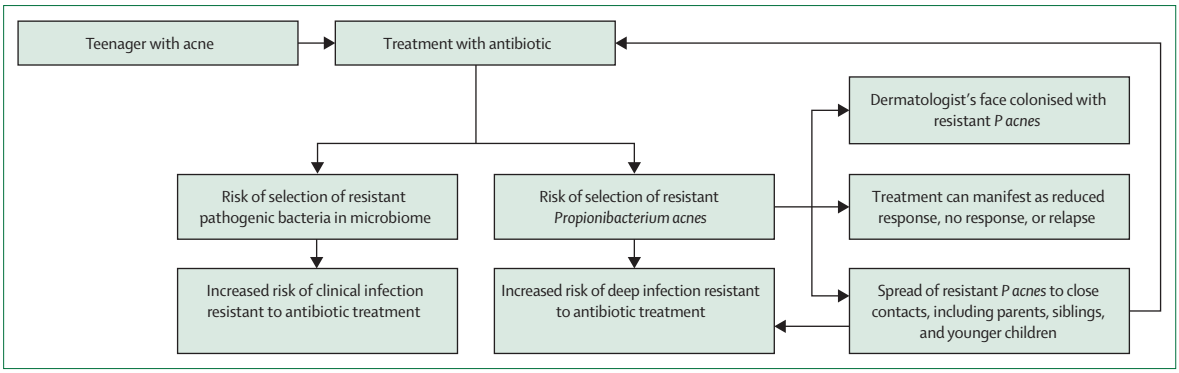

Figure 4: **Potential consequences of antibiotic use to treat acne**[4,10,76–80]

Selection pressure on the steady-state microbiome

Although acne-causing bacteria do not always respond to antibiotics, their use exerts selection pressure on non-target bacteria, which could develop antibiotic resistance and continue to grow and flourish.[17,45,52] For over a decade, treatment of acne with topical erythromycin for 3 months has been known to be sufficient to select resistant pathogenic bacteria. Mills and colleagues[76] found that erythromycin-resistant, coagulase-negative staphylococci were isolated from the facial skin of 87% of patients at baseline versus 98% by week 12. During a 12 week regression phase, when the antibiotic was removed, the number of erythromycin-resistant, coagulase-negative staphylococci only decreased slightly. Importantly, the average density of resistant bacteria significantly increased with erythromycin treatment versus placebo, with no change during regression. Over the 12 week treatment period, increases in resistant bacteria were also recorded on the untreated back and in the anterior nares. Almost all resistant isolates were highly resistant to erythromycin. The development and spread of such highly resistant bacteria could potentially have serious consequences.

Levy and colleagues[77] showed that colonisation and resistance of *Streptococcus pyogenes* in the oropharynx is associated with antibiotic therapy in people with acne. Patients treated with topical antibiotics, oral antibiotics, or both, had more than three times the risk of *S pyogenes* colonisation compared with patients not given antibiotic therapy (p=0·003). Importantly, use of oral only or topical only antibiotics resulted in similar increases in colonisation. A total of 85% of *S pyogenes* cultures grown from individuals using antibiotics were resistant to at least one tetracycline antibiotic versus 20% from those not using antibiotics (p=0·01). Again, this could contribute to difficult-to-control infections.

Emergence of resistant pathogenic bacteria has also been observed with clindamycin treatment. In people with acne, 18·8% of *P acnes* strains and 51·7% of *S epidermidis* strains were resistant to clindamycin. Over 80% of individuals who had clindamycin-resistant *P acnes* also had clindamycin-resistant *S epidermidis*.[74] Although *S epidermidis* is a ubiquitous member of the skin microbiota, it can possess pathogenic features. *S epidermidis* is frequently isolated from patients with opportunistic infections, and is a causative agent of hospital-acquired infections.[88]

Resistance can emerge quickly. After only 4 weeks of topical erythromycin use, the aerobic flora of the face is dominated by erythromycin-resistant, coagulase-negative staphylococci. By week 12, erythromycin-resistant *S epidermidis* is the dominant species of staphylococci.[89]

Collateral damage to the steady-state microbiome

The effects of topical and oral antibiotics on the steady-state microbiome differ. Although the use of topical antibiotics tends to result in antibiotic resistance confined to the skin of the treated site, treatment with oral antibiotics can lead to antibiotic resistance in commensal flora at all body sites.[17] The development of antibiotic resistance, as a result of the treatment of an individual's acne, can therefore promote the proliferation of opportunistic pathogens elsewhere in the body, so substantial collateral damage to the steady-state microbiome is a major concern, particularly for *S aureus* and MRSA.[52,76] In fact, erythromycin-resistant *S aureus* carriage rates in the anterior nares increase from 15% to 40% after 12 weeks of erythromycin treatment.[76]

We should remind ourselves that staphylococci bacteria are a major cause of health-care-associated infections. MRSA causes illnesses ranging from skin and wound infections to pneumonia and bloodstream infections that can cause sepsis and death. According to the US Centers for Disease Control and Prevention, MRSA has a threat level of serious, and erythromycin-resistant group A streptococcus and clindamycin-resistant group B streptococcus have a threat level of concerning.[52]

Although clindamycin and doxycycline are commonly used to treat acne, they are also treatments for MRSA.[45] Furthermore, clindamycin shows good tissue penetration, and can be used to treat several serious infections (eg, osteomyelitis and cellulitis).[90–92] The development of resistance to either of these antibiotics, due to their use instead of alternative acne treatment options, could limit their efficacy in future.[45]

Panel: **Strategies from the Global Alliance to Improve Outcomes in Acne to reduce antibiotic resistance in *Propionibacterium acnes* and other bacteria[4]**

First-line therapy

- Combine topical retinoid with antimicrobial (oral or topical)

If addition of antibiotic is needed:

- Limit to short periods; discontinue when only slight or no further improvement
- Oral antibiotics should ideally be used for 3 months
- Coprescribe benzoyl peroxide-containing product or use as washout
- Do not use as monotherapy
- Avoid concurrent use of oral and topical antibiotics
- Do not switch antibiotics without adequate justification

Maintenance therapy

- Use topical retinoids, with benzoyl peroxide added if needed
- Avoid antibiotics

Treatment of acne with antibiotics has been shown to increase the risk of common infections. In a retrospective cohort study[78] involving 84 977 individuals with acne treated with a topical antibiotic, oral antibiotic, or both, the odds ratio of developing an upper respiratory tract infection diagnosed by a general practitioner was 2·15 times higher compared with patients not treated with antibiotics ($p<0·001$). These findings were supported by a subsequent cross-sectional study,[93] in which 66·7% of patients on oral antibiotics for their acne self-reported an episode of pharyngitis in the previous 30 days, compared with 36·2% of individuals not given any oral antibiotics.

The dermatology community and all physicians treating people with acne should recognise the important effects of antibiotic resistance. Individuals receiving an antibiotic for their acne who develop a more serious illness[77,78,93] are likely to be seen by non-dermatology colleagues. This might provide insight into why the use of antibiotics, in particular topical antibiotics, to treat acne has not dramatically declined in the past 10 years.

Opportunistic infections

Evidence exists showing that *P acnes* can induce chronic and recurrent infections (with periods of relapse), such as endocarditis, mediastinitis after cardiac surgery, prosthetic joint infections, and breast implant infections.[80,94–96] Mutations conferring *P acnes* resistance to rifampicin—an anti-biofilm, active antibiotic used to treat such infections—have been reported in 2013 and 2014.[80,97] The spread of resistant *P acnes* to an untreated contact could lead to the development of a resistant infection in someone less able to cope with the disease (eg, an elderly, immunosuppressed patient having cardiac surgery or another major surgery).[27,80]

Alternatives to antibiotics in the treatment of acne

Antibiotics still form a major part of acne therapy, despite the low availability of evidence-based data and few clinical trials on topical antibiotic monotherapy.[23,45,98] Importantly, microbiology is not consistently done across all studies.[84,99] Moreover, detailed microbiological investigation, including bacterial counts, typing, and minimum inhibitory concentration levels and molecular analysis, have been rarely done together.[84] Many dermatologists might not fully appreciate the role of their specialty in potentially fuelling the problem of antibiotic resistance.[44] However, antibiotic stewardship is a multidisciplinary initiative and is there to ensure that patients receive the right antibiotic, given in the correct way, in every case. Efforts to enhance the responsible use of antibiotics have been shown to improve outcomes and save money.[52]

Data to support the apparently practical and sensible recommendation not to use topical and oral antibiotics concurrently are limited, although this approach is recommended by international guidelines.[17,23,100] The Global Alliance to Improve Outcomes in Acne, which brings together experts in the treatment of acne from around the world, has suggested several different strategies to reduce antibiotic resistance in *P acnes* and other bacteria (panel). The Alliance has reached a consensus that combination of a topical retinoid and antimicrobial agent (eg, BPO, an effective non-antibiotic antimicrobial agent) is preferred as first-line therapy for almost all people with acne (figure 5).[17] BPO is recommended as an addition to the topical treatment regimen when long-term antibiotic use is necessary, because it is a highly efficient bactericidal agent that will minimise the development of resistance at sites of application.[101–103] Topical antibiotics act relatively slowly on *P acnes* and have a poor suppressive effect compared with BPO; oral antibiotics are generally considered to be more effective than topical antibiotics. BPO is the most potent bactericidal agent against *P acnes* with evidence suggesting its use with a topical antibiotic improves efficacy and reduces the risk of antimicrobial resistance.[10,17,21,104] BPO rapidly reduces the number of sensitive and resistant strains of *P acnes* at the application site.[17,105] Treatment with adapalene and BPO reduced both antibiotic-sensitive and antibiotic-resistant *P acnes* counts after only 4 weeks. The number of erythromycin-resistant and clindamycin-resistant *P acnes* was reduced by several orders of magnitude, while *P acnes* resistant to one or more tetracycline decreased to levels close to total eradication.[99] Findings from the past 10 years have shown that acne improvement can be maintained with topical retinoids or combination of topical retinoid and BPO following initial treatment with antibiotics.[106–108]

Restriction of the use of topical antibiotics

Topical antibiotics should not be used as monotherapy. Their use in treating mild-to-moderate acne must be combined with a topical retinoid, BPO, or a fixed-dose combination of topical retinoid and BPO to provide

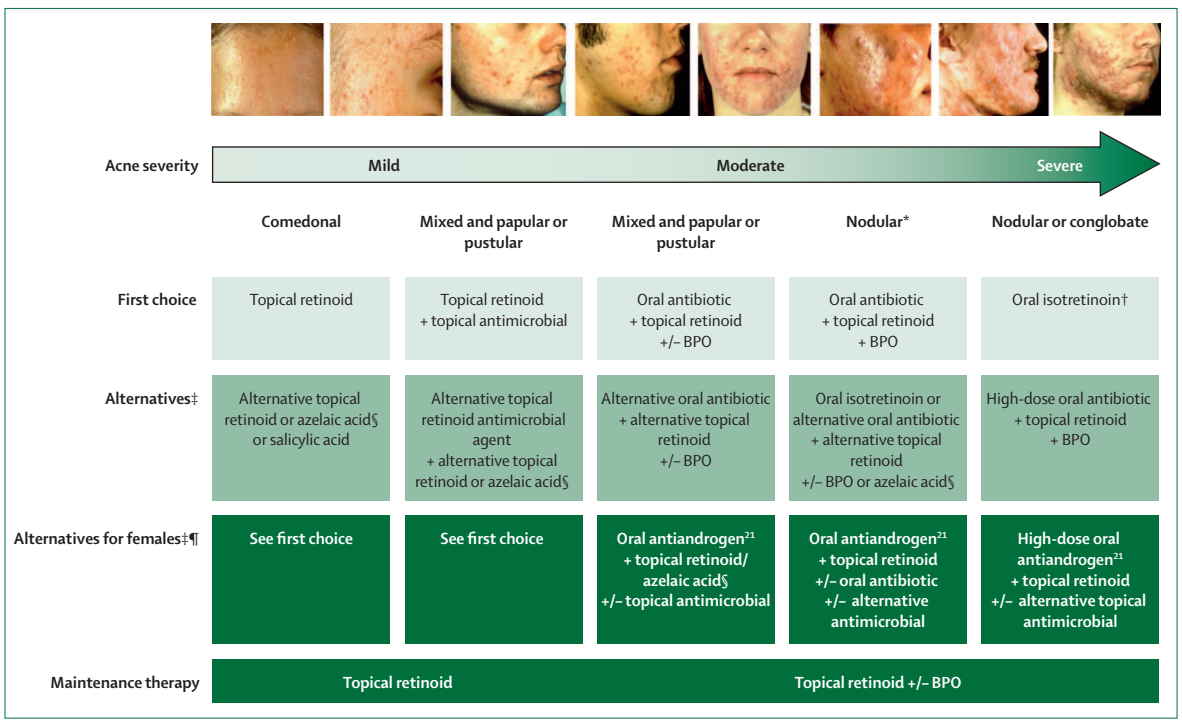

Figure 5: **Global Alliance to Improve Outcomes in Acne treatment algorithm[4]**
BPO=benzoyl peroxide. Reproduced from reference 17, by permission of Elsevier. *With small nodules (less than 0·5 cm). †Second course in case of relapse. ‡Consider physical removal of comedones. §No consensus on this alternative recommendation; however, in some countries azelaic acid prescription is appropriate practice. ¶For pregnancy, options are limited.

synergistic, faster clearance, and be limited in duration. To reduce antibiotic resistance, it is recommended that BPO or a topical retinoid should always be added when long-term topical antibiotic use is necessary (panel, figure 5). Topical and oral antibiotics should never be used concurrently. Ideally, BPO should be used in combination with a topical retinoid instead of a topical antibiotic to stop their use in acne and minimise the effects of resistance.[17]

The efficacy of topical antibiotics continues to be much debated. As an example, clindamycin monotherapy—even without resistance—is on the low end of the acne efficacy spectrum, with evidence showing an effect similar to vehicle.[109] Despite this evidence, clindamycin use is thought to continue unabated.[75] However, use of erythromycin, the topical antibiotic associated with the highest level of *P acnes* resistance, is now decreasing.[26,75,87]

Combination of a topical retinoid with an antibiotic does not have the same effect as combining it with BPO. For example, although treatment with clindamycin phosphate and tretinoin, and clindamycin phosphate and BPO reduced total *P acnes* counts over a 16 week period, overall reductions in clindamycin-resistant and erythromycin-resistant *P acnes* counts were only observed in the clindamycin phosphate and BPO arm. In the same study, treatment with clindamycin phosphate and tretinoin resulted in an increase in erythromycin-resistant counts from baseline to week 16.[110]

Restriction of the use of oral antibiotics

Oral antibiotics still have a role in the treatment of moderate-to-severe acne. However, they must always be combined with a topical retinoid, BPO, or a fixed-dose combination of topical retinoid and BPO, which has the advantage of a larger spectrum of activity. To reduce antibiotic resistance, it is recommended that BPO should always be added when long-term oral antibiotic use is necessary (panel, figure 5).[17] Since BPO is bactericidal, it kills the bacteria and reduces the likelihood of resistance.[17,33] Some restrictions on the use of oral antibiotics are in place, which aim to reduce the risk of antibiotic resistance. In some countries, minocycline has been reserved for hospital prescription use only.[111] In some countries, 100 mg doxycycline is the maximum licensed daily dose and 300 mg lymecycline is the maximum licensed daily dose.[112]

Oral antibiotics should be used carefully to treat acne, ideally for no longer than 3 months, as evidenced by different clinical studies that show little advantage in using them for a longer duration.[106,113,114] Although these studies did not have the same objectives, use the same antibiotics, or assess the same lesion type, they each provide information about the duration of oral antibiotic use. Despite guidelines recommending that oral antibiotics be used only for 3 months, the mean duration of oral antibiotic use is 129 days, 17·5% of courses are longer than 6 months, 7% of courses are at least 9 months in duration, and 57·8% of all qualifying oral antibiotic

courses do not include a concomitant topical retinoid.[17,46] Current international recommendations include restriction of the duration of antibiotic use to 3 months, avoidance of the use of topical and oral antibiotics concurrently, and addition of BPO to regress emergence of resistant bacteria. The inclusion of a topical retinoid to improve outcomes and for maintenance therapy, adding BPO if needed, has previously been recommended.[17] However, the amount of scientific evidence supporting the 3 month duration of antibiotic treatment and the avoidance of combined use of topical and systemic antibiotics remains very small.

What does the future hold?

Antibiotic resistance in *P acnes* and other non-target bacteria as a result of topical antibiotics use in the treatment of acne is a major and increasing concern.[26,52,69,76] The challenge is to curtail topical macrolide use, either alone or in combination with oral antibiotics. In combination with a topical retinoid, BPO provides a suitable alternative and reduces the likelihood of the emergence of antibiotic resistance.[17] Oral antibiotics still have a place in the treatment of more severe acne, as long as the rules are followed.[17] The prevalence of antibiotic-resistant *P acnes* strains is much lower than that reported for topical antibiotics across many countries.[25–27,69,70,72] Furthermore, no link between cycline use, bacterial resistant strains, and failure of acne treatment has been shown so far. Further investigation into the use of sub-antimicrobial dose cyclines is clearly needed, particularly as the risk of developing antibiotic resistance is expected to be lower.[17,18]

Crucially, the study of antibiotic-resistant *P acnes* is associated with a variety of different methodological issues.[75] Furthermore, the relative abundance of *P acnes* is similar in people with acne and healthy individuals, with certain strains highly associated with acne and other strains enriched in healthy skin.[115] The culture of a few isolates from a disease lesion or healthy skin, therefore, might not provide an accurate and unbiased measurement of the association between different strains and the disease or antibiotic resistance.[75]

Detailed microbiological antibiotic resistance studies in people with acne are urgently needed and, particularly, comprehensive studies involving both microbiologists and dermatologists. There is also a need to revisit other antibiotic classes, such as the β lactams. The minimum inhibitory concentration susceptibility of *P acnes* to a variety of antibiotics should be tested across the globe, using routine methods, preferably with the addition of sebaceous fluid. Moreover, partial or whole genome sequencing, as shown in other therapy areas, will allow improved characterisation of drug-resistant organisms, establishment of effective versus ineffective antibiotics, and rapid comparison of resistant organisms isolated in the same centre and even around the world.[116]

Antibiotic resistance through inappropriate antibiotic use can have a huge effect on the individual. In fact, the emotional and social impact of acne is more substantial than for some diseases that are generally considered more serious.[117] Suicidal ideation and mental health problems are common in adolescents with acne (twice as common in girls and three times as frequent in boys) and become more frequent with increasing acne severity.[118] Findings from a 2014 study[119] have also shown that acne can develop in young children, so the effect of antibiotic resistance in these subgroups should be actively considered. There is now, more than ever, a need to treat acne with effective alternatives to antibiotics to minimise the chance of developing resistance, which has already reached worrying levels.

Limitations of current evidence base

So far, very few controlled, detailed clinical and microbiological studies investigating the use of antibiotic regimens, or comparing the outcomes with use of antibiotics for different lengths of time (eg, 1 *vs* 2 *vs* 3 *vs* 4 months) have been done in people with acne, and even fewer studies relating microbiology to clinical outcomes are available. Additionally, little evidence exists on the clinical and microbiological consequences of antibiotic resistance in *P acnes* and the dermatological and non-dermatological microbiome and collateral damage. Few controlled trials investigating efficacy, safety, and antibiotic resistance of oral or topical antibiotics have been done, and detailed microbiology data are limited. Finally, antibiotics are thought to work principally through their anti-inflammatory effects; however, this remains to be clearly shown in clinical studies. A few studies have suggested that low-dose oral antibiotics are beneficial because of their anti-inflammatory effects without selective pressure on resident bacteria, but no detailed clinical and microbiological investigations have been undertaken, and such studies are much needed, given the associated risks.

Summary of treatment recommendations

Topical antibiotics used to treat mild-to-moderate acne should be limited in duration or avoided. Ideally, BPO combined with a topical retinoid should be used instead of a topical antibiotic to stop their use in acne and minimise the impact of resistance. Topical antibiotics should not be used as monotherapy. Topical and oral antibiotics should never be used concurrently. Oral antibiotics still have a role in the treatment of moderate-to-severe acne, but only in combination with a topical retinoid, BPO, or a fixed-dose topical retinoid and BPO combination, and ideally for no longer than 3 months. To limit antibiotic resistance, BPO should always be added when long-term oral antibiotic use is necessary (panel, figure 5). Acne improvement can be maintained with topical retinoids or a topical retinoid and BPO combination.[4]

Contributors
All authors reviewed the literature, interpreted the information, agreed the recommendations to be provided, helped draft the Review, and subsequently updated it as appropriate. All authors contributed equally to this Review.

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Declaration of interests
JE has served as a consultant for Havas Life Medicom. BD has served as a consultant, investigator, and speaker for Galderma, Meda, Fabre, and La Roche Posay. TRW declares no competing interests.

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