Chapter 2
Antibiotics in the Management of Acne

Alison M. Layton

2.1 Antibiotics in Acne

Antibiotics available for the treatment of acne embrace topical and oral therapies. Topical antibiotics represent 46.6 % of the acne topical market and oral antibiotic prescriptions account for 63.2 % of the market for systemic acne treatment [1, 2].

Table 2.1 summarises the randomised controlled studies on topical antibiotics used for acne as monotherapy and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions.

Table 2.2 summarises the randomised controlled studies on topical fixed-dose combination agents used for the treatment of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions.

Table 2.3 summarises the randomised controlled studies on systemic antibiotics used for the treatments of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions.

2.1.1 Topical Antibiotics

Topical antibiotics have been shown to be effective in the treatment of acne, and those used over the last decade include clindamycin, erythromycin and tetracycline [3, 4]. They have been used in concentrations of 1–4 %, in a cream or lotion base. More recently topical 5 % dapsone has been introduced for the use of mild to moderate acne [5]. Topical antibiotics may theoretically impact on non-inflamed

A.M. Layton
Harrogate and District NHS Foundation Trust,
Lancaster Park Road, Harrogate HG2 7SX, UK
e-mail: alison.layton@hdft.nhs.uk

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Table 2.1 Summary of the randomised controlled studies on topical antibiotics used for acne as monotherapy and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions

	Inflamed lesions			Non-inflamed lesion		
	Comparison with other agents			Comparison with other agents		
Agents	Superior to	Equivalent to	Inferior to	Superior to	Equivalent to	Inferior to
Topical clindamycin		Benzoyl peroxide Azelaic acid Oral tetracycline Minocycline	Zineryt®	Topical tetracycline	Oral tetracycline Minocycline	Benzoyl peroxide Zineryt®
Topical tetracycline		Benzoyl peroxide	Topical clindamycin		Benzoyl peroxide	

Table 2.2 Summary of the randomised controlled studies on topical fixed-dose combination agents used for the treatment of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions

	Inflamed lesions			Non-inflamed lesion		
	Comparison with other agents			Comparison with other agents		
Agents	Superior to	Equivalent to	Inferior to	Superior to	Equivalent to	Inferior to
Duac®, clindamycin and benzoyl peroxide	Benzoyl peroxide				Benzoyl peroxide	
Epiduo®, adapalene and benzoyl peroxide	Benzoyl peroxide Adapalene	Duac®		Benzoyl peroxide Adapalene	Duac®	
Zineryt®, Erythromycin and zinc acetate	Topical clindamycin Minocycline	Oral tetracycline		Topical clindamycin Minocycline	Oral tetracycline	

lesions by reducing perifollicular lymphocytes which are involved in comedogenesis [6]; some have a direct anti-inflammatory action as a result of an antioxidant effect on leukocytes [7], but their main mechanism of action is through their ability to significantly reduce numbers and activity of *P. acnes* [8]. At a clinical level, this translates into topical antibiotics being most effective to treat inflammatory acne [9].

2.1.1.1 Topical Antibiotics as Monotherapy

Adequately powered randomised, controlled trials have demonstrated a 55–60 % reduction in mean inflammatory lesion count at 12 weeks but have clarified much less impact on non-inflammatory lesions [10]. The variation in vehicles used in individual products challenges comparisons between individual treatments and studies, but those available to date suggest that there is no overall consistent

Table 2.3 Summary of randomised controlled studies on systemic antibiotics used for the treatments of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions

	Inflamed lesions			Non-inflamed lesion		
	Comparison with other agents			Comparison with other agents		
Agents	Superior to	Equivalent to	Inferior to	Superior to	Equivalent to	Inferior to
Oral tetracycline		Benzoyl peroxide Topical clindamycin Zineryt® Azelaic acid Minocycline[a] Diane®			Benzoyl peroxide Topical clindamycin Zineryt® Azelaic acid Minocycline[a] Diane®	
Minocycline		Benzoyl peroxide Topical clindamycin[a] Oral tetracycline Doxycycline Lymecycline Diane®	Zineryt®		Topical clindamycin Oral tetracycline Doxycycline Lymecycline Diane®	Zineryt®
Doxycycline		Minocycline			Minocycline	
Lymecycline		Minocycline			Minocycline	
Erythromycin		Tetracycline	Erythromycin Stearate		Tetracycline	

[a]Acted quicker but no significant difference at end of trial

difference in clinical outcome from topical clindamycin compared to topical erythromycin in mild to severe acne [11–14]. In contrast to an overall improvement in severity demonstrated with topical clindamycin when compared to topical tetracycline [15, 16]. A detailed analysis of 144 clinical trials of topical antimicrobial therapy rejected over 50 % because of poor trial design [17]. Adequate conclusions could not be drawn from the remaining data because of huge variation in methodology and study design but benzoyl peroxide (BPO) emerged as a successful treatment and was similar in effectiveness to topical erythromycin and clindamycin and confirmed topical tetracycline as the least effective.

A further systematic review examined results from clinical trials using topical erythromycin and clindamycin for inflammatory acne with the implicit aim of establishing whether or not there has been a decrease in efficacy since their introduction of these agents in the mid-1970s. In 50 eligible trials identified, a gradual reduction in the efficacy of topical erythromycin was identified, whilst the efficacy of clindamycin over the same time frame remained stable. The authors postulated that the reduced efficacy of erythromycin probably related to the development of antibiotic-resistant propionibacteria [18].

2.1.2 Combination Therapy

The emergence of antibiotic-resistant *P. acnes* has led to many experts recommending against the use of antibiotics as monotherapy. Guidelines suggest that the use of topical antibiotics alongside BPO should be considered to avoid resistant strains of *P. acnes* emerging at a local level and to reduce the numbers of existing resistant strains already present. The addition of topical agents can also expedite efficacy such that the exposure to the antibiotic is limited.

2.1.2.1 Combining Topical Antibiotics with BPO

BPO is fully active against sensitive and resistant strains of *P. acnes*, and combining topical BPO with topical erythromycin or oral antibiotics results in less resistance both in vitro and in vivo [19]. A number of trials have demonstrated the benefit of combining topical antibiotics with benzoyl peroxide over using individual constituents as monotherapy [20–23].

Two large randomised, double-blind placebo-controlled trials from 2008 demonstrated that clindamycin 1.2 % and BPO 2.5 % gel significantly reduced lesion counts and demonstrated similar tolerability compared with the individual constituents used as monotherapy [24].

A more recent meta-analysis of randomised controlled trials using 5 % BPO and clindamycin versus 2.5 % BPO and clindamycin topical treatments in acne showed that the combination products out-performed the individual constituents in the treatment of inflammatory lesions and the reduction in non-inflammatory lesions [25]. This was most significant with the 2.5 % BPO and clindamycin compared with all other treatments. A further study demonstrated similar efficacy between 2.5 and 5 % BPO in combination with clindamycin but confirmed the 2.5 % BPO/clindamycin combination was better tolerated [26].

In one noncommercial community-based study, BPO monotherapy produced similar clinical efficacy when compared to a combination of BPO and erythromycin although the former caused greater skin irritancy [27].

2.1.2.2 Combining Topical Antibiotics with Zinc

Some topical antibiotics are available in combination with zinc. Whilst zinc itself is not effective in the management of acne [28], two placebo-controlled trials showed that erythromycin 4 % plus zinc 1.2 % was significantly better than placebo at reducing inflamed and non-inflamed lesions [29, 30] and superior to 1 % clindamycin lotion [31].

There is however evidence to suggest that antibiotic-resistant *P. acnes* will emerge when using this combination product over time [32]. One study comparing 1.2 % zinc/4 % erythromycin with oral tetracycline 250 mg twice daily demonstrated no difference in terms of lesion reduction regardless of type [29]. However, a study

comparing this combination product with oral minocycline 50 mg daily demonstrated superiority for the former with respect to reduction of inflamed and non-inflamed lesions [33].

A small single-blind study of patients with mild to moderate acne treated once daily with 1 % clindamycin plus BPO 5 % or erythromycin 4 % plus 1.2 % zinc acetate showed the former had a quicker onset of action and demonstrated significantly greater reduction in lesion count and inflammatory lesions [32].

2.1.2.3 Combining Topical Antibiotics with Retinoids

Topical retinoid and antibiotic combinations are also available and indicated for the treatment of mild to moderate acne.

There are a number of studies that have indicated that combining an antibiotic with a retinoid results in better efficacy and significantly faster clearance when compared to the individual constituent alone [34–37].

The addition of an antibiotic to a topical retinoid may also result in less irritancy [35, 36, 38, 39] although the combination of clindamycin and adapalene in one topical formulation appeared to produce a more irritant effect that when the separate products were used alone [34]. Clindamycin combined with the adapalene results in better efficacy and is associated with less irritation than a combination of clindamycin and tretinoin [40, 41].

The fixed combination products have the advantage of being easier to use but the disadvantage of being more expensive than the individual products they contain.

2.1.2.4 Other Topical Antibiotics Available

Topical 5 % dapsone alone or in combination with 4 % BPO or adapalene 0.1 % has been shown to be effective for mild to moderate acne but was less well tolerated when used in combination with adapalene [42].

2.1.2.5 Topical Versus Oral Antibiotics

Systematic reviews have identified comparative data on the use of oral versus topical antibiotics in acne management [10, 43], and some randomised controlled trials have studied the difference between these different routes of administration [44–46] As outlined previously, one large, randomised, controlled trial in a community care setting showed that topical Benzamycin® and its components given separately (erythromycin and 5 % benzoyl peroxide) were more effective than oral tetracycline and minocycline [27]. However, as oral antibiotics have a delayed onset of activity, shorter studies may introduce bias in favour of the topical agent [47].

Many of these studies were underpowered as well as too short, making it challenging to draw definitive conclusions.

2.1.3 Adverse Effects

2.1.3.1 Topical Agents

The most common side effect of topical antibiotic products for acne relates to primary irritant effects which often subsides with time and can be managed by reducing frequency of application, using emollients and if severe short-term application of a type I potency topical corticosteroid [48, 49]. Some topical therapies have a comparatively lower irritant profile than others. Certain antibiotic/benzoyl peroxide combinations are less irritating than benzoyl peroxide alone [50], possibly explained by the anti-inflammatory action of the antibiotic. Allergic contact dermatitis has been reported with BPO but is rare with other topical agents. From animal studies and much clinical experience, there is no evidence to support the claims that benzoyl peroxide and vitamin A acid induce skin carcinomas, and continued use of these two drugs can be supported [51, 52]. Benzoyl peroxide bleaches clothes and hair, and the patient must be informed of these inconvenient side effects.

One of the main concerns relates to the emergence of antibiotic-resistant strains of bacteria emerging with the use of topical antibiotics; this will be discussed in more detail later.

2.1.3.2 Oral Antibiotics

Oral antibiotics are the most widely prescribed agents in acne and are indicated for severe acne, moderate facial acne not responding to topical therapies and/or extensive truncal acne.

2.1.4 Mechanisms of Action

There are two main mechanisms of action for oral antibiotics; as well as their antibacterial activity, they have anti-inflammatory effects [53–58]. Tetracycline and erythromycin are bacteriostatic, especially in larger doses. In smaller doses oral antibiotics do not reduce the number of organisms, but they do affect their function. The magnitude of reduction of *P. acnes* achieved by oral antibiotics does not correlate well with clinical efficacy [59].

Support for the important role of antibacterial therapy in the management of acne includes the fact that *P. acnes* is integral to the mediation of inflammation in acne, successful treatment with antibiotics is associated with significant reductions in *P. acnes*, and colonisation of the skin with antibiotic-resistant strains of *P. acnes* may be associated with reduced clinical efficacy. Antibiotics can also inhibit various enzyme activities and modulate chemotaxis, lymphocyte function and proinflammatory cytokines, in particular TNF-α, IL-1 and IL-6 expression [56–58].

2.1.5 *Selecting Oral Antibiotics for Acne, Dose and Duration*

A number of publications have proposed how antibiotics should be administered to achieve optimal therapeutic response whilst avoiding antibiotic resistance [60]. Table 2.4 outlines oral antibiotics available and potential adverse effects. Suggestions include restricting the duration of antibiotics, use of combination regimens from the onset of therapy to expedite response and reduce duration of antibiotic exposure, utilisation of benzoyl peroxide either to reduce the emergence of or to treat existing antibiotic-resistant strains of *P. acnes* and avoidance of using chemically dissimilar antibiotics and regular switching of antibiotics.

Table 2.5 summarises these recommendations. The question of how long antibiotics should be given in acne has not been adequately researched in randomised, controlled trials, and recommendations made in publications are not backed by hard evidence. It has been stated that 3 weeks is required before any obvious improvement is noted [61, 62] and that a minimum of 3 months extending to 6 months in conjunction with topical therapy, which should include an anti-resistant agent, is required to achieve maximum benefit [60, 63]. However, one controlled study comparing five antimicrobial regimes for mild to moderate facial acne in the community suggested that maximum improvement was reached at 6 weeks with both oral antibiotics and topical BPO [27].

There is a paucity of randomised, controlled trials examining different dosages of antibiotics in acne. One nonrandomised, controlled study confirmed that patients on oral erythromycin in combination with topical 5 % BPO responded better on 1 g compared to 500 mg daily. The relapse rates within 1 year were also significantly lower in the high-dose group [63].

Table 2.4 Systemic antibiotics in the treatment of acne vulgaris: dosage and adverse effects

Antibiotic tetracyclines	Dosage	Adverse effects
Oxytetracycline	500 mg twice daily half hour pre food and not with milk; makes adherence to medication problematic for some	Common: GI upset
		Rare: onycholysis, photosensitivity, benign intracranial hypertension
Lymecycline (not available in the USA)	300–600 mg daily	As oxytetracycline but tolerated better
Doxycycline	100–200 mg daily	As oxytetracycline
		Photosensitivity (dose dependent)
Minocycline	100–200 mg daily	Rare but serious: headaches and dizziness associated with benign intracranial hypertension, pigmentary changes, autoimmune hepatitis/LE-like syndrome
Erythromycin	500 mg twice daily	Common: GI upset, nausea, diarrhoea
Trimethoprim	200–300 mg twice daily	Maculopapular rash
		Rare: hepatic/renal toxicity/agranulocytosis

Table 2.5 Strategies to avoid antibiotic-resistant propionibacteria emerging

Strategy to avoid propionibacterial resistance emerging	Comments
Avoid inappropriate use of topical and systemic antibiotics	Use oral antibiotics for 6–8 weeks in the first instance and only continue if clinical improvement continues
If extending the duration of oral antibiotics utilises combination therapy	Combine with an agent that reduces the likelihood of promoting antibiotic propionibacterial resistance, e.g. benzoyl peroxide
If repeated courses of antibiotics are required and the initial clinical response was favourable, reuse the same drug	This will avoid multiple resistant strains emerging
Avoid prescribing different oral and topical antibiotics concomitantly	This will avoid multiple resistant strains emerging
Consider using topical retinoids and non-antibiotic antimicrobials wherever possible	These do not promote resistant isolates and when used with antibiotics may achieve more rapid efficacy so reduce the duration of the antibiotic course and the exposure time to the antibiotic
Topical benzoyl peroxide (BPO) can be used for 7 days between antibiotic courses	BPO is fully active against sensitive and resistant strains of *P. acnes* and able to eradicate resistant isolates
Remember to check medical adherence	Poor adherence to antibiotic therapies promotes resistance

Further reports suggest that higher doses of tetracycline [64, 65] and oxytetracycline [66] are more effective in recalcitrant and severe acne. In patients with nonresponding disease, minocycline limited dose-response studies have shown that doubling the dose of minocycline to 200 mg/day is more effective than continuing on an average dose of 100 mg where acne has not responded [67]. Daily doses of doxycycline (100 mg), minocycline (100 mg) and lymecycline (408 mg) are said to be equally effective, provided *P. acnes* is not resistant to doxycycline and lymecycline [68–72]. Subtherapeutic doses of doxycycline have been reported as effective in the treatment of moderate acne via non-antimicrobial mechanisms of action [73].

A correlation between sebum excretion rate and degree of improvement was noted in a retrospective study examining 255 patients treated with oral oxytetracycline, erythromycin and minocycline. Interestingly, this correlation was not noted with trimethoprim. The higher the sebum extraction rate, the less well the patients responded to their systemic therapy. The authors hypothesised that this may relate to a dilutional effect of the antibiotic within the intrafollicular duct and as a result of this suggested that when the sebum excretion rate was greater than 2.5 μg/cm^2, a higher daily dosage of antibiotics might be required (lymecycline 600 mg, doxycycline and minocycline 200 mg) [74]. When prescribing higher doses of antibiotics, patients and physicians should be wary about increased adverse effects [60].

2.1.6 *Adverse Effects*

Cyclines (tetracycline, oxytetracycline, doxycycline, lymecycline, minocycline) have excellent efficacy and are the antibiotics of choice [48, 75–78]. The second-generation cyclines may aid adherence, and of these, lymecycline and doxycycline should be used in preference to minocycline [60].

Macrolide (erythromycin, azithromycin or clindamycin) prescribing for acne has increasingly fallen out of favour due to the emergence of antibiotic-resistant strains of *P. acnes* in line with extensive erythromycin usage in the past [60, 79].

Erythromycin remains the preferred option in female patients who are, or might become, pregnant or are breastfeeding [80] and in children varying from 8 to 12 years (depending on national licences). Tetracyclines are contraindicated in this latter context due to potential musculoskeletal problems and discoloration of dentition.

Clindamycin is highly lipophilic and very effective in acne, but adverse effects including diarrhoea seen in 5–20 % of cases and potential pseudomembranous colitis from overgrowth of *Clostridium difficile* have rightly discouraged prescribers from using it [81, 82].

Oral azithromycin has been reported to be effective for acne in four open and two investigator-blinded trials. Regimens have varied, but intermittent dosing schedules have been advocated (250 mg three times a week) due to the long half-life of 68 h [83, 84]. As azithromycin is commonly used to treat a variety of systemic infections, its use should also be restricted and discouraged in acne. This recommendation also applies to cephalosporins and fluoroquinolones although there are documented cases of acne that have improved with these agents [85]. Exceptions to this rule may include short-term use for extremely refractory disease and/or evidence of Gram-negative folliculitis where other agents are not acceptable.

Trimethoprim (400–600 mg/day) has similar efficacy to tetracycline [85] but does not have a licence for acne and is reserved as a third-line antibiotic for acne or for cases where there is proven resistance to other agents. It has been used successfully in cases that have become refractory to first- or second-line antibiotics over time [86–88]. Trimethoprim may also be used in young patients in whom tetracyclines are contraindicated. However, as trimethoprim is used for treatment of some potentially serious cutaneous and systemic infections, such as those caused by CA-MRSA, it is advisable to limit use to selected cases [88].

Response to systemic antibiotics is variable. Young males with marked seborrhoea and truncal acne respond less well than females with purely facial acne [78]. Patients who require antibiotics should be given 1 g/day of tetracycline or where indicated erythromycin in divided doses [63]. There is no evidence to support the need for this to be four times a day. The major disadvantage of tetracycline is the prerequisite for it to be taken half an hour before food and not with milk to avoid reduced absorption [89]. Second-generation tetracyclines, doxycycline, lymecycline or minocycline, are less likely to be affected by food [89–91] and can be taken once daily, which may enhance patient adherence. The perception that they are more active as a result of their lipophilicity resulting in greater concentration within the pilosebaceous duct is not supported by good evidence.

Table 2.4 outlines dosage regimens for systemic antibiotics recommended for the treatment of acne and considers potential adverse effects.

Many systematic reviews and publications have failed to find any evidence to suggest that there are any clinical benefits between any of the tetracycline antibiotics. In the Western world, minocycline is used very extensively. This may in part have resulted from claims that antibiotic-resistant *P. acnes* is less likely to emerge with minocycline use. However, with the increased use of minocycline, there has been an increased trend of minocycline-resistant *P. acnes* emerging [92–95].

A Cochrane review published in 2003 found no evidence to suggest that minocycline should be prescribed in preference to other tetracyclines [43]. Other reviews have confirmed that minocycline should not be used as first-line therapy [96]. There are many studies examining the efficacy of individual antibiotics against placebo; however, the methodology and quality of these studies are poor, and very few compare one active agent with another. A large randomised, controlled trial conducted in UK community practice demonstrated that oral minocycline and oral tetracycline were of similar efficacy to each other and comparable in terms of efficacy to topical BPO. Hence, given the cost and the increased side effect profile of oral minocycline, minocycline should not be the first choice of oral antibiotic therapy in acne [97].

2.1.7 Combining Oral Antibiotics with Topical Preparations

Oral antibiotics should not be used as monotherapy in acne and should always be combined with topical agents. Combining BPO with antibiotics results in superior efficacy, this may be in part due to the relative lack of activity when used as monotherapy against non-inflammatory lesions. There is also evidence that such combinations prevent, reduce or eliminate bacterial resistance and can achieve significant clinical improvement in patients already colonised with antibiotic-resistant strains of *P. acnes*. Intermittent usage of BPO during extended courses of antibiotics is recommended to eliminate resistant strains [60, 98].

Topical retinoids may also be safely combined with antibiotics and are likely to enhance efficacy by acting on the microcomedo and non-inflammatory lesions [98, 99]. The use of oral and topical antibiotics together does not offer any benefit and may select for multiple different resistant strains if chemically dissimilar preparations are used.

2.2 The Emergence of Antibiotic-Resistant Bacteria as a Consequence of Antibiotic Usage in Acne

2.2.1 The Incidence of Resistance

The issue of antibiotic-resistant *P. acnes* is a global phenomenon with a prevalence increasing from around 20% in 1978 to 62% in 1996. Cross-resistance between erythromycin and clindamycin is frequently observed [100–106]. There is evidence

in the literature to demonstrate a correlation between antibiotic-resistant *P. acnes* and clinical failure when prescribed antibiotics [27, 107, 108]. However, the association between colonisation and antibiotic-resistant strains is complex, and it is important to recognise that even if some specific antibiotic-resistant strain of *P. acnes* is identified microbiologically, it does not necessarily mean that the acne will be clinically resistant to this antibiotic. If the concentration of the antibiotic at the relevant skin site is equal to or greater than the minimal inhibitory concentration (MIC) of the relevant *P. acnes* strain, the patient will be clinically responsive. In addition, many antibiotics with anti-acne properties achieve efficacy via anti-inflammatory mechanisms of action [58] which can offset any problems resulting from antibiotic resistance.

A number of factors have been linked to increased antibiotic resistance in *P. acnes*; notably patient and physician behaviours can influence the development of resistance [109, 110]. Greater numbers of resistant *P. acnes* have been demonstrated on the skin of close contacts of acne patients using antibiotics compared with controls [111]. In addition clinicians working within the field of acne harbour significantly more resistant propionibacteria than clinicians working in an environment unrelated to acne. Given the fact that the resistance is due to a mutant gene [112] it is likely that *P. acnes* resistance is going to last for many years.

Luk et al. recently investigated the prevalence and pattern of antibiotic-resistant *P. acnes* and looked for any associated factors linked to harbouring resistant strains. Fifty-five percent of strains were found to be resistant to one or more antibiotics, and resistance rates were highest to clindamycin and erythromycin. Characteristics associated with antibiotic-resistant *P. acnes* included older age, duration of disease and duration of antibiotic treatment [101].

A health technology assessment conducted between 1998 and 2000 in general practice in the UK identified 18 % of acne patients with tetracycline-resistant strains of *P. acnes*, 47 % with erythromycin-resistant and 41 % with clindamycin-resistant strains [27]. Up to 61 % of patients referred to specialist acne clinics in Leeds, UK, had antibiotic-resistant *P. acnes* [2].

Although resistance is most frequently seen to erythromycin and clindamycin, resistance to more than one antibiotic is seen in 18 % of patients.

Table 2.5 outlines possible reasons to suspect resistance to antibiotic therapies. Antibiotic prescribing policies have been advocated in an attempt to control/reduce the levels of resistance (Table 2.5) [113].

A number of studies have confirmed negative consequences that have resulted from antibiotic usage in acne.

2.2.2 *Impact on Nontargeted Bacteria with Potential Consequences*

When antibiotics are administered for any reason, resistance can occur in both targeted and nontargeted bacteria. The resident flora may have the capacity to retain resistant variants long after the antibiotic has been withdrawn. In addition resistance gene pools are often shared by non-pathogens and pathogens.

Mills and co-workers assessed resistant bacteria in acne patients ($n = 209$) treated with topical erythromycin for a 12-week period in a randomised, double-blind, parallel study. The prevalence of erythromycin-resistant coagulase-negative Staphylococci on the face rose from 87 to 98 %; in addition the density of antibiotic-resistant organisms increased significantly, and the majority of isolates had high-level resistance [114].

Acne patients are frequently treated with multiple courses of antibiotics, and their flora is exposed to significant selective pressure for resistance development. Margolis et al identified that patients treated with antibiotics for acne had a 2.15 times greater risk of developing an upper respiratory tract infection compared with those not treated with antibiotics [115]. Levy et al. demonstrated colonisation of the oropharynx with resistant *S. pyogenes*, in association with antibiotic therapy in patients with acne [116].

2.2.3 *The Developments of Antibiotic-Resistant Strains of* P. acnes *Beyond the Patient in the Community*

Antibiotic use for acne may have consequences for the community. Antibiotic-resistant *P. acnes* are spread primarily by person-to-person contact, and the prevalence of resistant *P. acnes* in household contacts of patients with acne ranged from 41 % in Hungary to 86 % in Spain in one European study [94]. The ability for resistant organisms to move from acne patients to the community has particular importance as *P. acnes* can survive for long periods on inanimate surfaces at room temperature. A significant proportion of acne patients may be colonised by antibiotic-resistant strains before they receive any treatment.

There have also been an increasing number of reports of severe infections due to *P. acnes* including arthritis, endocarditis, endophthalmitis and adenitis. These infections are frequently associated with surgical procedures, predisposing conditions for *P. acnes* infection including malignancy, immunosuppression, trauma, diabetes and steroid therapy. *P. acnes* infections have been associated with a mortality rate of up to 5 % in the context of these clinical situations [117–122].

2.2.4 *Impact of Antibiotic-Resistant* P. acnes *on the Patient*

Resistance may manifest itself in the patient as reduced response or no response to antibiotic therapy and in some cases worsening of disease whilst on therapy.

A systematic review of the literature published in 1998 found a clear correlation between poor therapeutic response and presence of antibiotic-resistant *P. acnes*. It is estimated that harbouring antibiotic-resistant *P. acnes* can result in up to a 20 % nonresponse to therapy, and several studies have confirmed reduced efficacy in this

context [59, 112, 114, 123]. Cunliffe et al. showed a significantly significant association between clinical improvement, reduction in *P. acnes* counts and inhibition of antibiotic drug resistance [124].

2.2.5 *Impact of Antibiotic Therapeutic Efficacy Over Time*

One rigorous meta-analysis of efficacy data indicates that there has been a gradual decrease in the overall efficacy of topical erythromycin between 1977 and 2002 thought to have arisen due to the presence of antibiotic-resistant *P. acnes* [18].

2.3 Strategies for Preventing the Emergence of Antibiotic-Resistant *P. acnes* Over Time

Guidance on acne managements suggests that the duration of exposure to antibiotics should be minimised, and this can be achieved by combining treatment regimens to enhance efficacy and rate of response to treatment. This might be achieved by using a topical retinoid alongside an antimicrobial preparation. Other strategies can be adopted as in Table 2.5 [125].

2.3.1 *BPO as an Anti-resistant Agent*

BPO has the ability to rapidly kill bacteria, including both antibiotic-sensitive and antibiotic-resistant strains of *P. acnes.* There are no reports of antimicrobial resistance to BPO which makes it an ideal therapy for acne as not only does it provide clinical efficacy through a potent bactericidal, anti-inflammatory and some keratolytic/comedolytic action [126], but it also permits an approach that spares the use of antibiotics.

A recent study demonstrated that a BPO cleanser used daily can effectively reduce populations of antibiotic-resistant *P. acnes.* At baseline there were multiple resistances present to including erythromycin, tetracycline, doxycycline, minocycline and clindamycin. Total *P. acnes* counts and counts of each resistant strain decreased by >2logs at 3 weeks [127].

A fixed combination product containing 1.2 % clindamycin and 0.025 % tretinoin demonstrated much better effect on the reduction of total *P. acnes* as well as those demonstrating clindamycin resistance when compared to the impact of 1 % clindamycin alone [128]. This may well have resulted from the tretinoin facilitating higher concentration of antibiotic within the sebaceous follicles and/or resulting in

a change in the microenvironment of the microcomedo leading to less overall *P. acnes.*

A further strategy adopted to minimise the development of antibiotic-resistant *P. acnes* has been to exploit the anti-inflammatory actions whilst avoiding the antimicrobial effects by employing low, sub-antimicrobial doses of antibiotics. Doxycycline has been selected for this purpose as it is the tetracycline found to have the most potent action against matrix metalloproteinases (MMPs). A sub-antimicrobial dose of doxycycline (SDD) 20 mg twice daily downregulates MMPs and proinflammatory cytokines without decreasing microbial counts; this was first demonstrated in periodontal disease [129]. A small ($n=40$) double-blind placebo-controlled study of SDD (20 mg twice daily) in acne was associated with greater reductions in the numbers of comedones ($p<0.01$), inflammatory lesions ($p<0.05$) and total lesions at 6 months [73].

The duration of antibiotics should be limited in an attempt to avoid the emergence of antibiotic-resistant bacteria. In a multicentre, randomised, parallel-group investigator-blinded study of 152 acne patients, researchers demonstrated that the efficacy of antibiotic therapy for acne reached a plateau around 12–16 weeks depending on the antibiotic used. This supports an approach that then switches patients onto alternative maintenance therapy without the use of an antibiotic [130].

2.4 Conclusions

Antibiotics still have an important place in acne management; however, judicious use is advocated to ensure that the patient, close contacts and the wider environment are not compromised. Antibiotic-resistant *P. acnes* will emerge as a result of antibiotic use for acne, and this may result in poor therapeutic response and treatment failures. Strategies should be adopted to minimise risk of antibiotic resistance such that the therapeutic value of antibiotics can be preserved for acne and beyond. Topical antibiotics should be avoided as monotherapy and BPO should be employed as an effective anti-resistant agent in treatment regimens. Fixed-dose combinations should be considered in any acne regimen to achieve more rapid efficacy so avoiding unnecessary exposure to antibiotics.

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