

## Stemming the tide of antimicrobial resistance: implications for management of acne vulgaris

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Acne can cause substantial distress, decreased self-confidence and increased rates of depression and suicidal ideation.<sup>(1)</sup> Topical and oral antibiotics are commonly used to treat acne, due to both antimicrobial and anti-inflammatory mechanisms of action but they are not always effective and alternatives are available.<sup>(2)</sup> Whereas topical antibiotics predispose to overgrowth of antibiotic resistant bacteria on treated skin sites, oral antibiotics increase the numbers of resistant bacteria not only on the skin but at all body sites with resident commensal microflora. Examples include overgrowth of resistant strains of *P. acnes*<sup>(3)</sup> and coagulase-negative staphylococci on the skin<sup>(4)</sup> as well as coliforms in the gut. Resistance emerges not only in treated patients but also in close contacts.<sup>(3, 4)</sup>

A strong case has been made for reducing antibiotic prescribing in primary care but relatively little emphasis has been placed on antibiotic prescribing for acne.<sup>(5)</sup> However, skin conditions account for 8% of primary care antibiotic prescribing and there is rising concern about 'collateral damage to the steady-state microbiome' of long-term antibiotic use in young people.<sup>(3)</sup>

A recent analysis of the Clinical Practice Research Datalink (CPRD) examined primary-care consultations and prescriptions administered for acne.<sup>(6)</sup> This suggested that GPs prescribe long courses of oral antibiotics at 31% of first consultations for acne,<sup>(6)</sup> although it is not clear whether this is due to GP prescribing habits or pressure from patients. Over 90% of acne is managed in primary care in the UK<sup>(7)</sup> placing primary care clinicians in a key position to address the problem of rising antimicrobial resistance fuelled by antibiotic prescriptions for acne.

### Effective non-antibiotic alternatives

The aetiology of acne is complex. Although *P. acnes* is strongly implicated in pathogenesis, acne is not an infection and effective antimicrobials do not eliminate *P. acnes* from the skin. A primary defect in sebum production triggers hyperproliferation of follicular keratinocytes resulting in inflammation via multiple pathways.<sup>(8)</sup> The relative importance of antibacterial versus anti-inflammatory actions of antibiotics in the management of acne remains unclear.

Benzoyl peroxide (available over-the-counter in many countries) is an effective non-antibiotic antimicrobial agent that can be used alone or in addition to antibiotics. It acts as a bactericidal agent that is equally effective against antibiotic resistant and susceptible strains of *P. acnes* and can also reduce the development of resistance within the resident skin microflora. It has limited impact at controlling selective pressure from oral antibiotics at body sites other than the area of application.

Topical retinoids, such as adapalene (Differin®), isotretinoin (Isotrex®) and tretinoin, act on abnormal keratinisation and also have anti-inflammatory properties. They are potentially skin irritant, which can lead to early abandonment of treatment unless appropriate advice to mitigate this is given.<sup>(1)</sup> See Box 1 for a summary of treatment guidelines and Box 2 for resources providing information for patients, including advice on mitigating local reactions to topical agents.

For some women, combined oral contraceptives (particularly 3<sup>rd</sup> generation) or co-cyprindiol (Dianette®) can be effective alternatives to antibiotics, particularly when combined with topical treatments.<sup>(9)</sup> However, co-cyprindiol should be discontinued three to four menstrual cycles after the acne has resolved.<sup>(10)</sup>

### How to avoid antibiotic resistance

The UK guideline suggests that either benzoyl peroxide or a topical retinoid, such as adapalene (Differin®), should be used first line.<sup>(10)</sup> For moderate acne which is localised, a fixed dose combination topical product is recommended when benzoyl peroxide or topical retinoid monotherapy is ineffective. Oral antibiotics with topical benzoyl peroxide are recommended if the acne is more widespread or risk factors (e.g. scarring) are present.

Three recently published evidence-based guidelines from the USA, Canada and Europe agree with UK guideline in recommending that neither topical nor oral antibiotics should be used as monotherapy.<sup>(11-13)</sup> Although the use of fixed-dose combination of benzoyl peroxide/adapalene (Epiduo®) has increased in recent years, combination clindamycin/benzoyl peroxide (Duac®) and erythromycin (Zineryt®) remain by far the most commonly prescribed topical preparations for acne in England and Wales.<sup>(14)</sup> Rates of resistance to erythromycin and clindamycin in *P. acnes* isolates from countries which use topical antibiotics for acne extensively vary from 45-91%, strongly implicating topical use in the emergence of resistance.<sup>(3)</sup>

There have been few head-to-head comparisons of topical therapies including fixed dose combinations vs. oral antibiotics so their comparative efficacies, especially in moderate acne, are not certainly known. Until such information becomes available, it would seem preferable to avoid oral antibiotics, except when justified by severity, distribution of lesions, scarring or other risk factors. Expert consensus and current guidelines recommend keeping courses of antibiotics relatively short, with a maximum duration of three to four months. Whilst the acne may not be cleared after this time in all patients, most should be sufficiently improved to switch to a topical non-antibiotic maintenance regimen that will continue to reduce the number of lesions and prevent recurrence.

Consideration of earlier referral to secondary care can be considered in preference to extending treatment duration with antibiotics or trying various different ones. Oral isotretinoin may avoid the need for multiple courses of antibiotics and, despite recent concerns expressed in the media about rising rates of prescribing, reviews have not shown an increase in depression following initiation of isotretinoin.<sup>(1)</sup> However, prescriptions for oral isotretinoin are still administered under the supervision of a consultant dermatologist due to potential serious adverse effects which include the very high risk of teratogenicity.

### Summary

Despite the continued popularity of antibiotics for acne, effective alternatives are available to minimise their use and reduce the impact of acne prescribing on the spread of antibiotic resistant bacteria. Antibiotics still have an important role to play, especially in managing more severe inflammatory acne, but only as part of a regimen that includes benzoyl peroxide. In mild to moderate acne, topical retinoids and benzoyl peroxide alone or in combination are effective if used regularly. Advice on minimising skin irritation may increase adherence.

### Box 1. Summary of guidance

Adapted from NICE – CKS guideline on acne vulgaris

First-line therapy	<ul style="list-style-type: none"> <li>Single non-antibiotic topical drug in people with limited acne which is mild and unlikely to scar: benzoyl peroxide or a retinoid, e.g. adapalene (Differin®), isotretinoin (Isotrex®) or tretinoin</li> </ul>
Second-line therapy	<ul style="list-style-type: none"> <li>Fixed dose combination topical retinoid with benzoyl peroxide (Epiduo®) or fixed dose combination topical antibiotic with benzoyl peroxide (Duac) or topical retinoid</li> </ul>
Third-line therapy	<ul style="list-style-type: none"> <li>An oral antibiotic or (in women) a combined oral contraceptive if acne is more extensive.</li> </ul> <p>For oral antibiotics:</p> <ul style="list-style-type: none"> <li>Limit to short periods (ideally 3-4 months)</li> <li>Do not use as monotherapy</li> <li>Use alongside topical retinoids to expedite response</li> <li>Co-prescribe benzoyl peroxide-containing product (limits resistance at site of application only)</li> <li>Avoid concurrent use of oral and topical antibiotics</li> </ul>
Maintenance therapy	<ul style="list-style-type: none"> <li>Use topical retinoids, with benzoyl peroxide added if needed</li> <li>Avoid antibiotics</li> </ul>

### Box 2. Resources to promote effective use of topical treatments

Resource	Advice
NHS Choices <a href="http://www.nhs.uk/Conditions/Acne">www.nhs.uk/Conditions/Acne</a>	Includes a guide to choosing different treatments
Patient.co.uk <a href="http://patient.info/health/acne-leaflet">patient.info/health/acne-leaflet</a>	Includes advice that treatments may take 4-6 weeks to work. Includes basic advice about dealing with side effects

British Association of Dermatologists patient information leaflet on acne <a href="http://bad.org.uk/for-the-public/patient-information-leaflets/acne">bad.org.uk/for-the-public/patient-information-leaflets/acne</a>	Comprehensive advice, including advice that treatments may take 4-6 weeks to work. Includes basic advice about dealing with side effects
Healthtalk.org <a href="http://healthtalk.org/young-peoples-experiences/acne">healthtalk.org/young-peoples-experiences/acne</a>	More extensive advice on all aspects of acne treatments, including advice on dealing with common side effects. Includes interviews with young people with acne

Word count currently 954 without boxes or 1190 including boxes

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