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Contents: The treatment of acne vulgaris: an update

The treatment of acne vulgaris: an update

While acne vulgaris affects 80% of adolescents, it can also occur later in life.¹ It may lead to scarring or hyperpigmentation and substantial disfigurement.² Acne sufferers are also more likely to be depressed or anxious.¹ This *Bulletin* discusses the general approach to acne management and considers recent issues surrounding treatment. It will not attempt to evaluate every possible drug combination in acne.

What causes acne?

Acne is a disease of the pilosebaceous follicle, consisting of skin lesions mainly on the face, back and chest. Increased sebum production and keratinous debris cause a blockage of the pilosebaceous duct. This produces a lesion called a comedo, which can be either open (blackhead) or closed (whitehead). Some comedones evolve into inflammatory lesions (papules, pustules, nodules or rarely granulomatous lesions). Inflammation may be caused by proliferation of the anaerobe *Propionibacterium acnes*.³ Diet (e.g. chocolate) or poor skin cleansing do not worsen acne.¹

How should acne be managed?

The main aims of treatment are:

- to reduce the number of lesions
- to reduce the impact of psychological stress, and
- to prevent scarring.

A structured approach to the management of acne requires an understanding of the cause, the

SUMMARY

- * The main aims of acne treatment are to reduce the number of lesions, reduce the impact of psychological stress and prevent scarring. Patient counselling is an important part of disease management.
- * Treatment should be started as early as possible with patients reassessed every two to three months initially. A response may take months and in some cases treatment may need to be continued for several years.
- * Early referral of patients with severe acne, for treatment by a dermatologist, may help to prevent scarring.
- * Mild acne should initially be treated with topical agents. Drug choice depends on whether comedonal or inflammatory lesions predominate. Benzoyl peroxide or a topical retinoid are first choice agents, depending on tolerance, formulation and cost.
- * Oral antibiotics should be added to topical therapy in moderate to severe acne. Tetracycline or oxytetracycline are first choice agents as they are effective and inexpensive. An adequate dose of an oral antibiotic should be given for at least three months before deciding a patient has failed to respond.
- * Minocycline and doxycycline have not been shown to be more effective than tetracycline or oxytetracycline and are more expensive. As reports of *P. acnes* resistance to minocycline are rare, it may be tried in patients who fail to respond to first choice agents.
- * Erythromycin is best reserved for patients in whom other antibiotics are unsuitable, as propionibacterial resistance to this drug is relatively common.

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severity, the type of lesions present and the treatment options available. Therapy should be started at an early stage to prevent scarring. Drug choice depends on previous treatment, patient acceptability and the type of lesion which predominates (comedonal or inflammatory). Ideally, an effective anti-acne treatment should reduce the number of both types of lesion."

Limitations of evidence

Although evidence supports the use of certain drugs in acne, good quality data are lacking for many drugs. Blinding is difficult with topical agents and motivated, self-selecting trial subjects are not representative of most acne patients.

Clinical trials in acne should use objective outcome measures, e.g. separate counts of inflamed and non-inflamed lesions.⁴

In some studies, it is not clear whether these measures were the primary endpoints. Therefore, drug use in acne is also based upon the clinical experience of dermatologists and GPs, as well as individual patient factors.

How should mild acne be treated?

Mild acne consists of open and closed comedones and some papules and pustules.⁵ Initially, a single topical preparation should be used.

Topical **benzoyl peroxide** is an established and highly effective antimicrobial, with slight anti-inflammatory activity.⁶ For an antibacterial effect, the lowest strength preparation may be as effective as higher strengths.⁷ It has a comparatively mild anti-comedonal effect,⁶ which is greatest at higher strengths.⁷ As skin irritation may occur, lower strengths are tried first and increased gradually if needed.⁷

The **topical retinoids** (vitamin A derivatives), **tretinoin**, **isotretinoin** and **adapalene** cause superficial skin peeling which unblocks follicles, making them particularly suitable for comedonal acne. However, **tretinoin** causes a low-grade

irritant dermatitis, with erythema and scaling, in most patients.⁶ To minimise this, a low strength preparation should be used initially, every two to three nights, gradually increasing the strength and frequency as tolerated (maximum twice daily), i.e. 0.025% cream, then 0.01% gel, then 0.025% gel.²

Despite varying degrees of anti-inflammatory effect,⁶ studies have shown **adapalene**⁹ and **isotretinoin**¹⁰ to be as effective as tretinoin. However, they may cause less skin irritation than tretinoin.⁶

A randomised controlled trial compared **benzoyl peroxide** (5% gel for four weeks then 10% gel for four weeks) and tretinoin (0.1% cream, not available in the UK) in 147 patients with acne vulgaris.¹¹ Both agents were equally effective at reducing comedones, but benzoyl peroxide produced a greater and more rapid effect on inflammatory lesions. However, tretinoin can take three to four months to produce a maximum response. Benzoyl peroxide seems to be as irritant as topical isotretinoin but less irritant than tretinoin.⁶

Patients prescribed a topical retinoid should be told:

- Redness and skin peeling may occur for several days but usually settles with time.
- Acne may worsen for the first few weeks.⁷
- To avoid ultraviolet lamps and minimise exposure to sunlight.
- To allow peeling [e.g. from benzoyl peroxide] to subside before using a topical retinoid.

Topical retinoids should not be used in pregnancy and women of childbearing age must use adequate contraceptive precautions while using a retinoid.⁸

While **topical antibiotics** reduce numbers of *P. acnes* within hair follicles, their precise mechanism of action is unclear.⁴ They are not as irritant as benzoyl peroxide gel, but may rarely cause contact dermatitis.⁴ However, it should be noted that topical antibiotics are no more effective than benzoyl peroxide or tretinoin in mild to moderate acne.^{4,8} Although they

reduce inflammatory lesions, their effect on comedones is less consistent.⁴

Clindamycin and **erythromycin** are the most commonly used topical antibiotics. Tetracycline may be less acceptable because it stains skin and clothing.⁷ There is no evidence to suggest superior efficacy of any topical antibiotic, although development of resistance to *P. acnes* may determine drug choice.

In view of the limited clinical evidence for **azelaic acid** and **nicotinamide**, their place in therapy is unclear. Azelaic acid may be an alternative to benzoyl peroxide or tretinoin where skin irritation is a problem.⁷

Choice of topical agent

Topical retinoids or **benzoyl peroxide** are first choice agents for mild comedonal acne. Selection is based on tolerance, formulation and cost. Benzoyl peroxide is cheap, and may also be bought from pharmacies.

In mild inflammatory acne, **benzoyl peroxide** is the topical agent of choice. The place in therapy of **topical antibiotics** is not well defined. Some specialists recommend using a topical antibiotic in combination with benzoyl peroxide in patients who have not responded after two months of benzoyl peroxide (no more than 50% improvement). They may also be considered as single agent therapy in those who cannot tolerate benzoyl peroxide. Measures to avoid antibiotic resistance should be adopted (see table 1). Patients with mild acne who fail to respond to the above regimens may require an oral antibiotic (see below).

How should moderate to severe acne be treated?

Moderate acne encompasses more frequent papules and pustules with mild scarring.⁷ Severe acne also includes nodular abscesses, and leads to more extensive scarring.⁵ Treatment of moderate to severe acne requires the use of both systemic and topical agents.

Oral antibiotics are the mainstay of systemic therapy. While their precise mechanism of action is unclear,⁴ they are thought to exert their effect by inhibiting *P. acnes*, although some may also have a direct anti-inflammatory action.² Drug choice depends on likely adverse effects, resistance, previous antibiotic exposure and cost.

First choice antibiotic agents are tetracycline or **oxytetracycline** (500mg twice daily) as they are effective and inexpensive.^{2,8} **Minocycline** (100mg daily, in one or two divided doses) and **doxycycline** (100mg daily) are more expensive (see **table 2**) and have not been shown to be more effective than tetracycline or oxytetracycline. However, they may be useful when compliance is a problem as they are less likely to interact with food and milk. Once daily dosing is unlikely to offer much benefit over twice daily regimens.

Minocycline has been the subject of recent safety concerns. This follows case-reports of rare but serious reactions, such as systemic lupus erythematosus (SLE), autoimmune hepatitis, serum-sickness-like reaction and **pneumonitis**.¹⁵⁻¹⁷ Irreversible pigmentation has also been reported.* In view of its high cost and potential for adverse effects, minocycline **should be reserved for patients who fail to respond to tetracycline or oxytetracycline**.^{8,15}

Since all tetracyclines can harm developing bones and teeth, they should not be given to children under twelve years, to pregnant women or breastfeeding mothers. Effective contraception should be used if they are prescribed for women of childbearing age. **Tetracyclines** may also cause contraceptive failure during the first few weeks of therapy.^{8,19}

Erythromycin (500mg twice daily) is also used but, as resistance is common, it is best reserved for patients in whom other antibiotics are unsuitable."

Use of benzoyl peroxide in combination with topical or oral antibiotics has been suggested to reduce the numbers of resistant

- *P. acnes* resistance to antibiotics has been associated with a poor treatment response, but has not been proven.
 - **In 1996**, a GP study of 1,000 skin swabs taken from acne patients found that 25% of swabs had strains of *P. acnes* which were resistant to antibiotics.
 - Most data on resistance relate to *in vitro* measurements and are difficult to interpret in terms of clinical effect. Minocycline is unstable in bacteriological culture medium and so measurement of resistance to minocycline is unreliable. Reported resistance to minocycline is rare.
 - Most tetracycline resistant strains of *P. acnes* are cross-resistant to doxycycline. Most erythromycin resistant strains are cross-resistant to clindamycin.
- Measures to minimise antibiotic resistance**
- Do not prescribe antibiotics if a non-antibiotic topical preparation will suffice.
 - Use adequate doses of antibiotics.
 - Avoid concomitant oral and topical use of antibiotics from different classes.
 - Do not continue treatment for longer than necessary (but give an adequate course to allow a response).
 - If acne returns, reuse the same drug if the previous response was satisfactory with that agent.
 - Stress to patients the importance of good compliance.

Table 1. Antibiotic resistance.^{8,12-14}

propionibacteria^{12,14} (see also **table 1**). There is evidence that a combination of benzoyl peroxide with topical erythromycin is more effective than topical erythromycin alone at reducing *P. acnes*.²⁰ This is also the case for erythromycin resistant strains.²⁰ In addition, the combination is synergistic against inflammatory lesions,²¹ but does not appear to prevent patients from acquiring resistant strains of *P. acnes*.²⁰

Concomitant use of benzoyl peroxide with oral antibiotics seems reasonable, especially as resistance of *P. acnes* to benzoyl peroxide has not been reported. There do not appear to be any clinical studies of the effect of this combination in reducing resistant strains of *P. acnes*.

Androgens increase production of sebum and may worsen acne. **Anti-androgen** therapy may benefit women with a hormonal influence to their acne, e.g. premenstrual flare.² **Dianette** (containing ethinylloestradiol 35mcg and 2mg cyproterone) is licensed for severe acne that is refractory to prolonged oral antibiotic therapy. It may be useful in women who also wish to use oral contraception.

Treatment duration and referral

For most topical agents, at least two months of treatment is needed before a response can be determined, although some drugs

may take several months to achieve maximum response. **Treatment** should be reassessed every two to three months and, if effective, continued until it is clear that new lesions are not developing.³ For some patients this may take several years. **Once** this is achieved, an attempt should be made to gradually discontinue drug therapy.³

Courses of topical antibiotics should last at least six months. While a response to an oral antibiotic is usually seen after three months, it may take four to six months for maximum response. Some patients may even need to take them for two years or more.* **An adequate, dose of oral antibiotic should be given for at least three months before deciding a patient has failed to respond.**

Patients with nodulocystic acne are at greatest risk of scarring. They should be referred promptly to a dermatologist, who may prescribe oral **isotretinoin**. This drug is highly effective at reducing sebum secretion and a 16 to 20 week course leads to remission in most patients.³ It can only be prescribed by, or under the supervision of, a dermatologist because it may cause serious adverse effects. **As it is highly teratogenic, women of childbearing age should use effective contraception for four weeks before starting, during treatment and for at least four weeks after stopping this drug.**

Other reasons for referral include: scarring, pigmentation, poor treatment response, severe psychological stress,¹⁴ late onset acne or unpleasant side-effects from current acne therapy.

Patient counselling

Effective patient counselling is important in acne. Patients must be clear about how to use their medication, common side-effects, likely timescale for improvement and that treatment may be needed for months or even years.^{3,14} Topical agents should be applied to the 'spots' and areas between them, in order to prevent the development of new lesions.¹⁴ Patients **should avoid abrasive cleansers and vigorous scrubbing, as this may worsen acne by provoking inflammation.**³

Patient involvement in choice of topical drug treatment is vital. Products must be cosmetically acceptable to the patient, otherwise they may not be used. Generally, **gels and solutions are good for oily skin but may sting sensitive or dry skin.** Creams are suitable for sensitive or **dry skin** but may make oily skin more 'greasy'. Lotions are thinner than creams and are useful for large or hairy areas.²²

Conclusions

Although it may seem a trivial complaint, acne can be extremely distressing for many patients. Initially, mild acne should be treated with topical agents. Drug choice depends on whether comedonal or inflammatory lesions predominate. In more severe disease, addition of systemic drugs to topical therapy is required. **Oral antibiotics** are the mainstay of treatment for moderate to severe acne. Early referral of those with very severe acne may prevent scarring.

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Table 2. Comparative costs of some oral antibiotics for acne.
(Prices are based on *Chemist & Druggist* and the *Drug Tariff*, October 1999).

Drug	Cost of 28 days therapy
Tetracycline - 500mg twice a day	
Tetracycline tablets 250mg	£2.13
Tetracycline capsules 250mg	£5.36
Achromycin capsules 250mg	£5.36
Oxytetracycline - 500mg twice a day	
Oxytetracycline tablets 250mg	£3.92
Terramycin tablets 250mg	£3.84
Doxycycline - 100mg once a day	
Doxycycline capsules 50mg	£14.60
Doxycycline capsules 100mg	£6.90
Vibramycin capsules 50mg	£15.48
Vibramycin Acne Pack capsules 50mg	£17.80
Vibramycin capsules 100mg	£14.63
Vibramycin-D dispersible tablets 100mg	£17.19
Minocycline - 100mg daily in one or two divided doses	
Minocycline tablets 50mg	£10.49
Minocycline tablets 100mg	£12.59
Minocycline capsules 50mg	£17.20
Minocycline capsules 100mg	£14.74
Minocin MR modified-release capsules 100mg	£17.62
Erythromycin - 500mg twice a day	
Erythromycin tablets 250mg	£12.32
Erythrocin tablets 250mg	£14.83
Erythrocin 500 tablets 500mg	£15.29
Erythroped A tablets 500mg	£18.52
Ilosone tablets 500mg	£34.91
Ilosone capsules 250mg	£35.08
Tiloryth capsules 250mg	£22.69
Erymax capsules 250mg	£21.65

N.B. Doses quoted are those recommended in the BNF for acne treatment.

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Useful information sources

Acne Support Group
Howard House,
The Runway, Ruislip,
Middlesex, HA4 6SE
Tel: 0208-841 4747 (patients)
0208-841 13400 (professionals)
Website: www.stopspots.org

'acne...Key Facts'
Patient information leaflet produced by the British Association of Dermatologists available on the internet at: www.skinhealth.co.uk

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Telephone: 0151-794 8146/8140/8143/8145 Fax: 0151-794-8139/44

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