Fortnightly Review

Acne vulgaris

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Acne vulgaris is a multifactorial disease affecting the pilosebaceous follicle and characterised by comedones, papules, pustules, nodules, and scars. Acne affects 95% and 83% of 16 year old boys and girls respectively,¹ but it is clearly no longer a problem confined to teenagers: recently, attendance at general practitioner surgeries for this condition and referral for specialist opinion has significantly increased among people aged over 20.^{1,2} This shift in the incidence of acne away from schoolchildren to an older age group has produced a much more demanding and articulate group of patients with high expectations for improvement. Simple attention to hygiene is no longer enough, and antiseptic washes so popular 20 years ago are perceived as ineffective by many sufferers and most clinicians. Neither will comments such as "You will probably grow out of it" suffice.

A detailed understanding of the pathogenesis of acne was developed in Europe and the United States during the 1960s and '70s. Follicular keratinisation, seborrhoea, and colonisation of the pilosebaceous unit with *Propionibacterium acnes* are central to the development of lesions. Genetic and hormonal factors also play a role, possibly by optimising the follicular environment suitable for the growth of *P. acnes* or by influencing the inflammatory response and thus the nature of the lesions. Such understanding has led to the use of keratolytics, antibiotics, sebum reducing agents, and antiandrogens and oestrogens (in some women) but has not contributed to the emergence of specifically designed drugs or treatments.

Aims of treatment

The aims of treatment are to prevent scarring, limit the disease duration, and reduce the impact of the psychological stress that may affect over half of sufferers.³ Treatment should be started at an early stage to prevent scarring since there is little effective treatment for improving acne scars already present. More acne sufferers are unemployed compared with controls matched for age, sex, and social group,⁴ and so long term economic benefits may possibly result from

FIG 1—Mild acne vulgaris

Summary points

- Acne is as common as it was 20 years ago but is now less severe in teenagers and affects more people in their 20s and 30s, who have high expectations of treatment
- Topical treatments are effective for mild to moderate acne, and oral antibiotics (and anti-androgens for women) are helpful for moderate acne
- For severe acne high dose oral antibiotics can be used, but oral isotretinoin has a rapid effect and a high rate of long term remission
- Isotretinoin is only available through hospital dermatologists because of its side effects
- Early treatment and regular review are necessary to prevent scarring

effective treatment. Studies of quality of life have concentrated on the added value of treatment in the worst cases,⁵ but for most sufferers there is little patient based information from which to recommend treatment. Thus, any review of the management of acne vulgaris must reflect clinical trial evidence of effectiveness. On this basis, it is possible to divide treatment in terms of severity and the age and sex of the sufferer, with severity being the most powerful determinant.

ACNE SEVERITY

Severity of acne can be graded for therapeutic studies according to the Leeds grading scale,⁶ but in the general treatment of acne vulgaris most doctors would divide the condition into mild, moderate, and severe. Mild disease consists of open and closed comedones and some papules and pustules, while moderate acne encompasses more frequent papules and pustules with mild scarring. Severe disease contains all of the above plus nodular abscesses and leads to more extensive scarring which may be keloidal in some cases.

Treatment of mild acne

Topical preparations are the mainstay of treatment for mild acne vulgaris (see box). These are popular with patients, but their slow benefit needs careful explanation to encourage good compliance.

Benzoyl peroxide is a potent oxidising agent with antibacterial and keratolytic properties. It does not induce any change in the resistance pattern of aerobic bacteria to antibiotics; it also prevents such resistance when used concomitantly with topical erythromycin.⁷ Benzoyl peroxide is applied daily in lotions or creams

Topical treatment for mild acne

- Benzoyl peroxide 2.5-10% once daily
- Azaleic acid 20% twice daily
- Tretinoin 0.1-0.25% once daily
- Isotretinoin 0.05% once or twice daily
- Clindamycin 1% twice daily
- Erythromycin 2% and 4% with zinc acetate 1.2% twice daily
- Tetracycline 4% twice daily

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BMJ 1994;308:831-3

in concentrations of 2.5-10% w/v. There have been no adequate dose response trials to show increased efficacy of higher concentrations. The main adverse effects are bleaching of clothes, transient skin irritation, and occasional allergic contact dermatitis. It can be used long term and in conjunction with oral antibiotics for moderate acne vulgaris.

Azelaic acid is keratolytic, causes alterations in the free fatty acid composition of skin surface lipids, and significantly reduces the follicular bacterial density.⁸ It can cause local irritation and photosensitisation, and the data sheet presently limits treatment to a maximum of six months.

Topical retinoid preparations are useful for mild to moderate acne and can be applied once or twice daily. Tretinoin is supplied as cream or lotion from 0.01-0.025% and isotretinoin as a 0.05% gel. Both preparations have comedolytic effects. Side effects include erythema, desquamation, occasional hyperpigmentation or hypopigmentation, and sensitisation of the skin to sunlight. These products are derivatives of vitamin A, and there have been reports of malformed infants born to women who have used topical retinoids during early pregnancy.⁹ However, one study suggested a relative risk of 0.7 for having a baby with a major congenital anomaly, although the 95% confidence interval was 0.2 to 2.3%.¹⁰ These figures do not take into account the possible risk of less serious congenital abnormalities, and topical retinoids must therefore be avoided during pregnancy.

Topical antibiotics are particularly useful in mild to moderate acne and in acne which is resistant to benzoyl peroxide. They affect the metabolic pathways of *P. acnes*. Topical preparations of clindamycin and erythromycin are similar in terms of efficiency¹¹ and are suitable for greasy skins due to their alcoholic base. Clindamycin in a lotion base is less irritating to dry or scaly skin and is preferred by many women in their mid-20s and older. Topical tetracycline is less effective and leaves a residue that may fluoresce under ultraviolet light, which could be a distinct disadvantage at the disco. The development of antibiotic resistance in *P. acnes* may limit the prescription of topical antibiotics.

Treatment of moderate acne

Oral antibiotics

Systemic antibiotics remain the mainstay of treatment, and tetracycline remains the treatment of first choice. To ensure adequate absorption, it should be taken half an hour before food and patients should avoid concomitant ingestion of milk or iron supplements. Erythromycin is less popular owing to frequent induction of resistance by *P. acnes* and *Staphylococcus epidermidis*.¹² Minocycline is the most widely prescribed systemic antibiotic for acne. Clinically, there is little difference between tetracycline and minocycline,

Treatment for moderate acne

Topical treatment

As for mild acne

Oral antibiotics

Tetracycline 500 mg twice daily

Minocycline 100 mg (slow release) once daily or 50 mg twice daily

Doxycycline 100 mg once daily

Trimethoprim 300 mg twice daily

Erythromycin 500 mg twice daily

Oral antiandrogen

Cyproterone acetate 2 mg with ethinyloestradiol 35 µg once daily

Treatment for severe acne

High dose oral antibiotics

Tetracycline or erythromycin 1.5-2 g daily in divided doses

Minocycline 100 mg twice daily

Oral retinoid

Isotretinoin 1 mg/kg body weight daily

but the lack of dietary restriction is said to increase compliance with minocycline. Doxycycline or trimethoprim are further alternatives. Antibiotic courses should last for at least three months before assuming failure of response. Adverse effects of oral antibiotics include gastrointestinal upset, vaginal candidiasis, gram negative and pityrosporum folliculitis, and hyperpigmentation from high dose minocycline.

Hormonal treatment

The sebaceous gland is an androgen target organ, and moderate acne may respond to antiandrogens. There is little evidence to support any hormonal disturbance in girls with acne, but 46% of women who develop or continue with acne between the ages of 18 and 32 have minor increases in circulating testosterone and suppression of sex hormone binding globulin.¹³ Treatment with the antiandrogen cyproterone acetate 2 mg with ethinyloestradiol 35 µg is equally effective as oral tetracycline but may take three to six months to produce a beneficial effect when used alone.¹⁴

Greater success has been reported with 50 mg or 100 mg of cyproterone acetate from days 5 to 15 of the menstrual cycle alongside ethinyloestradiol 35 µg from days 5 to 26.¹⁴ Combined contraceptive pills containing norethisterone or levonorgestrel may aggravate acne, but those with desogestrel or gestodene do not. Contraceptive pills containing cyproterone acetate are ideal for women who require treatment for mild or moderate acne and who also wish to use oral contraception. Alternative hormonal approaches for the treatment of acne vulgaris include bromocriptine, spironolactone, and gonadotrophin releasing hormone antagonists, but there is only limited evidence from clinical trials to support their use.

REASONS FOR FAILURE OF RESPONSE

Rapid induction of antibiotic resistance in *P. acnes* accompanied by relapse of acne has been found with topical erythromycin and clindamycin and systemic tetracycline, erythromycin, and doxycycline.¹² Only systemic minocycline seems free from this problem so far. Concomitant topical use of benzoyl peroxide may prevent the induction of antibiotic resistance, but this has only been shown for *Staphylococcus epidermidis*.⁷

Macrocomedones or large whiteheads are blocked and swollen pilosebaceous units. These lesions tend to persist and usually progress to inflamed papules or pustules. Systemic antibiotics and topical treatments have little effect. The best treatment is hyfrecation or fine cold point cautery after local anaesthesia with anaesthetic cream.¹⁵

Treatment of severe acne

High dose antibiotics such as tetracycline or erythromycin 1.5-2 g daily or minocycline 200 mg daily may be used in severe acne, but the oral retinoid isotretinoin is much more effective.

ISOTRETINOIN

Isotretinoin is reserved for prescription by hospital based dermatologists because of several serious adverse effects. Its mechanism of action is complex, but there is

FIG 2—Moderate acne vulgaris

FIG 3—Severe acne vulgaris

FIG 4—Severe cystic acne vulgaris. Such patients should be urgently referred for treatment with isotretinoin

a dramatic reduction in sebaceous gland activity and sebum production that leads to a significant decrease in the *P. acnes* population. Cutaneous retinol concentrations are increased and may reflect a metabolic interference with endogenous vitamin A.¹⁶ The drug has also been shown to alter the sex steroid metabolism in women with severe acne.¹⁷ In the early phase of treatment isotretinoin may cause a transient exacerbation of the patient's skin condition by exacerbating neutrophil mediated inflammatory processes through proinflammatory priming of neutrophils.¹⁸ Patients suitable for isotretinoin treatment are those with severe nodular or cystic acne; moderate acne that is resistant to conventional treatment (that is, the patient having received two courses of oral antibiotics at the correct dose for the correct length of time); and acne of late onset in the mid-20s or 30s (acne at this age is often resistant to oral antibiotics). Delays in starting isotretinoin treatment for patients with severe acne can result in substantial scarring, so it is important that such patients are referred urgently to dermatology departments.

The ideal dose of isotretinoin is 1 mg per kg body weight daily because relapse is more likely if lower doses are prescribed. Most patients require a four month course, but 15% need longer treatment of up to 10 months.¹⁹ Forty per cent of patients are cured of their acne and need no further treatment, and a further 21% need topical treatment alone. In the remaining 39% relapse occurs within three years of stopping treatment: 16% require oral antibiotics, and 23% require further courses of isotretinoin.²⁰ Although isotretinoin is expensive, its use in moderate to severe acne vulgaris is considerably more cost effective than long term rotational antibiotics.²¹

Adverse reactions

Adverse reactions to isotretinoin are common. Mucocutaneous reactions such as cheilitis, xerosis, blepharoconjunctivitis, and epistaxis are dose related and occur in most cases. Indeed, the absence of any such problems suggests poor compliance. Hypertriglyceridaemia, hypercholesterolaemia, and disordered hepatic function are less common, but plasma lipids and hepatic function should be monitored during treatment. Unfortunately, pretreatment lipid concentrations are unhelpful in predicting the degree of elevation of plasma cholesterol and triglycerides while on the drug.²² Myalgia and arthralgia occur in both male and female patients and may limit sporting activity. About 10% of those with this musculoskeletal syndrome develop asymptomatic, small hyperostotic lesions of the spine.²³ Rare side effects include photosensitivity, diffuse alopecia and changing of the hair character, anaemia, and leucopenia. Staphylococcal skin infections may occur late in treatment as a result of lowered concentrations of skin lipids, which allow colonisation of xerotic scale by this organism. Benign intracranial hypertension is a rare but serious adverse effect of both isotretinoin and tetracyclines; concomitant use of these two drugs is therefore contraindicated. Isotretinoin is highly teratogenic with its main effects on the developing neurological and cardiovascular systems, and all women who are at risk must take adequate contraception and provide a negative pregnancy test before treatment is started.

Acne fulminans

Acne fulminans is a rare, very severe variety of acne due to an immune complex reaction to *P. acnes* that most commonly affects adolescent boys.²⁴ Patients develop severe eruptive and ulcerative scarring lesions,

fever, debilitation, arthralgia, leucocytosis, and a high erythrocyte sedimentation rate. Osteolytic bone lesions can arise, most frequently in the clavicle, sternum, long bones, and ilium.²⁵ Inpatient treatment with high dose systemic steroids is necessary, and in patients taking oral isotretinoin temporary withdrawal of this treatment is usual. While systemic steroids rapidly control the skin lesions and systemic symptoms, the drugs need to be continued for two to four months because both acne and musculoskeletal symptoms tend to relapse if the dose is reduced too quickly. Severe scarring is an inevitable consequence.

Cysts and scars

Although treatments for acne vulgaris are initiated in order to prevent scarring, some patients present with scars or lesions that are likely to scar. Fluctuant cysts may be frozen with liquid nitrogen or may be aspirated and then injected with triamcinolone suspension. Unfortunately, these procedures frequently cause deep scars. Intralesional triamcinolone can be helpful in reducing keloid formation if injected into early lesions. Overall there is little effective treatment for scars already present. Dermabrasion has declined in popularity because of the risk of blood borne infection in the operating theatre.

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(Accepted 18 November 1993)