Acne vulgaris

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Acne may be common, but it causes considerable distress and doctors should treat it effectively, not trivialise it

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Acne vulgaris is common and affects nearly all adolescents and adults at some time in their lives. Although overall health is not impaired, acne is not a trivial disease; it can produce cutaneous and emotional scars that last a lifetime.[1 2] Numerous psychological problems stem from acne, even resulting in decreased employability in adulthood.[3] Fortunately, acne is eminently treatable, and this review provides an outline of current treatments.

Summary points

- Acne is a multifactorial disease which, although not life threatening, has profound effects on patients
- The microcomedo is the primary lesion in acne
- Reduction of comedones and *Propionibacterium acnes* is the main aim of treatment
- Most effective acne regimens treat inflammatory and comedonal acne lesions with a combination of antibacterial and retinoid drugs

Sources and selection criteria

A literature review augmented my extensive experience of the topic. I used Entrez PubMed for all literature searches.

Pathogenesis

Acne has a complex aetiology, involving abnormal keratinisation, hormonal function, bacterial growth, and immune hypersensitivity.[1 2] The disease is limited to pilosebaceous follicles of the head and upper trunk because the sebaceous glands in these regions are particularly active. The primary acne lesion is the "blackhead" (microcomedo), an impaction and distension of the follicle with improperly desquamated keratinocytes and sebum. The stimulus for comedogenesis is uncertain.

At puberty, when androgens stimulate the production of sebum, pre-existing comedones become filled with lipid and may enlarge to become visible. Subsequently, some patients also begin to show signs of inflammation. Comedones that become inflamed are nearly always clinically invisible before the pimple develops.

Inflammatory acne is the result of the host response to the follicular inhabitant *Propionibacterium acnes*,[1 4] which is a member of the normal flora and is a harmless commensal, largely incapable of tissue invasion or serious infection. The organism metabolises sebaceous triglycerides, consuming the glycerol fraction and discarding free fatty acids. As a consequence of growth and metabolism, *P acnes* produces neutrophil chemoattractants. *P acnes* also activates complement and is generally inflammatory when brought into contact with the immune system .

Assessment of disease severity and impact on patient

The first step in treating acne is to determine the severity of the disease. In diabetes and hypertension (for example), severity of disease and response to treatment can both be measured quantitatively; but such measurements have only limited benefits in acne. Moreover, the severity of acne is often overestimated by the patient and minimised by the doctor. Teenagers in particular are stigmatised by fairly trivial acne. In their eyes, severe acne can mean ruination. Thus, simple pimple counts are only partly useful; it is of little benefit to clear 95 of 100 lesions if the patient is left with several disfiguring nodules.

Grading schemes that rely solely on lesion counts are of greater use in clinical studies than in clinical practice. It is better to focus on the most severe lesions present, because adequate treatment for them covers all lesser lesions. Acne can be classified into four main types: purely comedonal—that is, non-inflammatory acne—mild papular, scarring papular, and nodular or scarring acne.

Dispelling popular misconceptions

Child patients (and usually their parents) hold common misconceptions about acne that need tackling before treatment begins. Firstly, they often blame themselves for the disease. However, acne does

not come from bad behaviour nor is it a disease of poor hygiene. Patients (and parents) need to realise that acne has nothing to do with lack of cleanliness. The black tip of a comedo is oxidised sebum,[2] not dirt, and it cannot be removed by scrubbing. Vigorous washing may actually make things worse.

Secondly, despite parental admonitions, diet has never been shown to have much effect on acne. Thirdly, patients need to understand that topical treatments work by preventing new lesions, not shrinking ones that have already formed. Thus, the treatment should be applied faithfully to all skin that may be affected, not just to visible lesions.

Treatment regimens should be simple

Many doctors seem tempted to use as many as five or six treatments. I believe, however, that most acne can be treated effectively with two drugs, or at most three, at any one time. Failure to respond to a regimen within four to eight weeks should prompt a substantial change in drugs, not merely the addition of another product. Besides adding expense with little benefit, complex regimens are usually more irritating and present problems with compliance.

Comedonal acne

Non-inflammatory acne is the mildest form of disease but can be the hardest to treat. Comedones are usually firmly seated in the follicle, and, if untreated, they cannot often be expressed without some degree of violence. Tretinoin, isotretinoin, adapalene, and tazarotene are topical retinoids which, if applied daily, inhibit formation of comedones and usually clear even severe comedonal acne within a few months.[5] The only major drawback is irritation, which is greatest after a few weeks, but the irritation usually requires no more than simple moisturising. Because their skin is inherently irritable, patients with atopic diseases may not tolerate topical retinoids, even if they apply a moisturiser. Azelaic acid is a dicarboxylic acid with modest antibacterial and comedolytic effects. It is the least irritating preparation. The side effect of hypopigmentation may be desirable in some patients: in dark skinned patients, inflammation results in hyperpigmentation, which could otherwise remain for weeks or months.

Box 1: Typical treatment regimens for acne

Comedonal acne

- Topical tretinoin, adapalene, or tazarotene applied daily
- Salicylic acid
- Azelaic acid

Mild papulopustular acne

- Benzoyl peroxide
- Topical gel preparations of benzoyl peroxide with either clindamycin or erythromycin
- Oral doxycycline or minocycline 75-100 mg twice daily plus topical retinoid

Severe papulopustular or nodular acne

- Oral doxycycline or minocycline plus topical retinoid
- Isotretinoin 1 mg/kg a day

Box 2: Solutions for acne that is resistant to treatment

- Investigate compliance
- Increase frequency of topical therapy
- Begin or increase oral antibiotic dosage
- Search for hormonal derangement
- Begin oral isotretinoin therapy

Inflammatory acne

Topical treatment

Mild papulopustular acne rarely results in scarring and typically is responsive to aggressive, twice daily, topical treatment. Usually, two drugs are prescribed—an antibacterial and a comedolytic. Benzoyl peroxide 2.5-10% is extremely effective against *P acnes*. Its major disadvantage is irritation, which can be minimised by using lower concentrations in a cream vehicle. Topical erythromycin and clindamycin are available as alcoholic solutions, lotions, creams, and gels, all of which are about equally effective.[6] A combination of clindamycin and benzoyl peroxide in gel form is superior to a topical antibiotic alone.[7] Azelaic acid 20% cream is also an effective alternative to topical macrolide preparations.[8 9]

During the past two decades many reports have documented the acquisition of antibiotic resistance by *P acnes* during treatment of acne.[7 10 11] The problem is most often seen with topical clindamycin and erythromycin, and I now find neither of these drugs useful unless combined with benzoyl peroxide. When resistance is suspected, culture and susceptibility testing are not needed. Failure to respond to topical treatment within four to eight weeks should automatically prompt a change in treatment. Other options for resistant *P acnes* include oral antibiotics and isotretinoin.

Oral treatment

Acne that is resistant to topical treatment or that manifests as scarring or nodular lesions typically requires oral antibiotics.[8 9] Many of the antibiotics useful in acne also have an anti-inflammatory activity, which is nearly as important as their effect on the *P acnes* itself. Oral erythromycin used to be a common treatment for acne, but the rise of resistance has greatly reduced its utility.[8 9 11]

Many doctors prefer to start with tetracycline at 1 g a day in divided dose. I often find this insufficient and usually begin with doxycycline or minocycline at 75-200 mg a day. Lower doses of doxycycline and minocycline—for example, 20 mg or 50 mg—are available and are useful for maintenance treatment. Acquired resistance to minocycline and doxycycline is less common than to erythromycin but is still a concern, and use of these drugs should be limited to those patients who truly need them. Patients are instructed to take the drug with food—this minimises stomach complaints and maximises compliance, albeit with a slight decrease in absorption. Patients should be warned that they may get sunburnt more easily. Rarely, a hypersensitivity syndrome ranging from urticaria to drug induced lupus can be caused by minocycline.[12] Onset of symptoms, especially early in minocycline

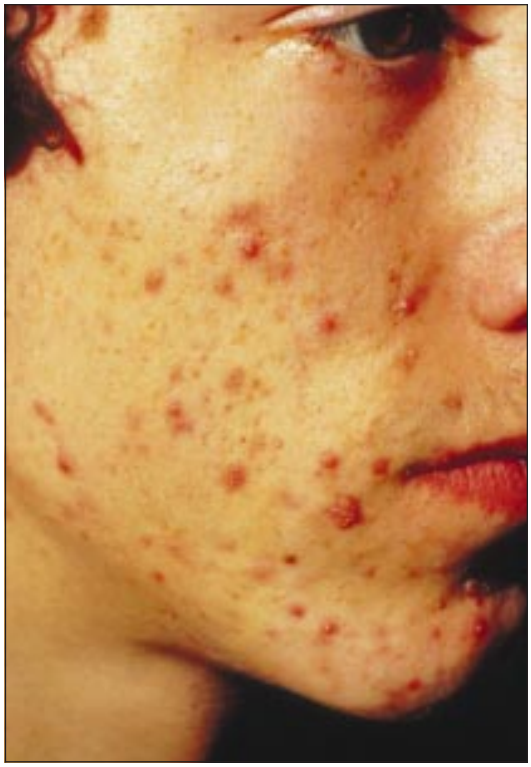
treatment, should prompt evaluation. In the vast majority of patients, oral antibiotics may be continued for months or years with little concern—the safety record of these drugs in acne goes back decades.

If minocycline or doxycycline cannot be used, alternatives include co-trimoxazole and ciprofloxacin. Risk of acquiring resistance to these drugs after long term use has not been studied, but it is clearly a concern, and use of these drugs should be minimised. In general, cephalosporins and penicillins are not very effective in treating acne. The increased cost of some of these newer drugs may make using isotretinoin an attractive option if long term treatment is anticipated.

Because all acne begins with follicular impaction, a topical comedolytic such as tretinoin, tazarotene, or adapalene should be added to oral antibiotic regimens, and most patients greatly benefit from such addition. Even with combination therapy, the physician should not expect to see maximal improvement in under at least six to eight weeks. When the patient's acne has been controlled to a satisfactory level, maintenance treatment may be begun. Topical treatment with retinoids or benzoyl peroxide is often sufficient for long term control.

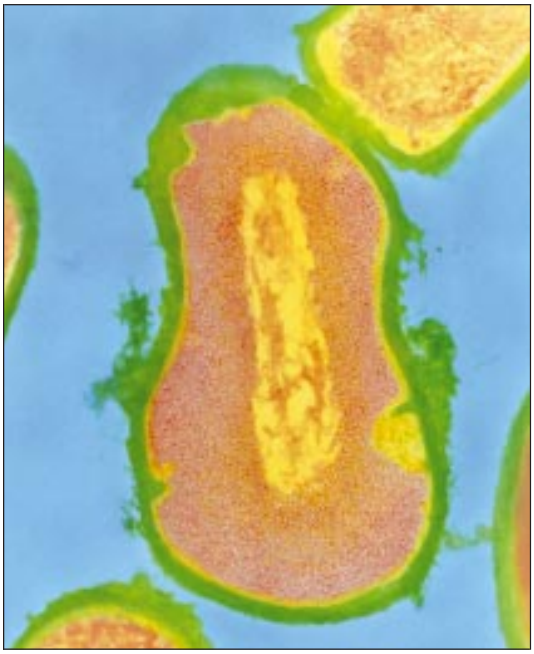
Hormonal treatment

Women with masculinisation have a higher incidence of acne, but it is wrong to assume that any woman with acne has a hormonal derangement. In fact, androgen levels do not correlate with acne severity among people with acne.[13] Acne resistant to treatment, especially in a woman with irregular menses, should be investigated with, at least, measurements of total and free testosterone as well as dehydroepiandrosterone sulphate. If these levels are raised, four approaches may be taken: suppression with low dose oral corticosteroid; oral contraception; cyproterone acetate; or spironolactone.[14]



DR ZARA/BPP/SPL

Acne vulgaris in an adolescent



DR KARI LOUNATMAA/SPL

Propionibacterium acnes

Isotretinoin

Isotretinoin revolutionised the treatment of severe acne about 20 years ago. It is a synthetic retinoid that inhibits differentiation of sebaceous glands, corrects the keratinisation defect in the follicle, and also has some anti-inflammatory activity. Its major indication is severe nodular acne, but it is commonly used for severe acne that is resistant to oral antibiotics as well.

Side effects of isotretinoin are mostly dose related and are not always trivial.[15] Most patients complain of dry skin, lips, and eyes. In dry seasons, it is common to see epistaxis and mild flares of atopic dermatitis due to the drug. About a third of patients show raised triglyceride levels during the first month of treatment. Usually, modifying the diet or reducing the dosage keeps the triglyceride level from rising too high. Thinning of hair is uncommon but can be particularly distressing. Rarely, patients complain of myalgias while taking isotretinoin and show substantial rises in levels of muscle derived aminotransferase. Typically these patients are engaging in vigorous exercise. Because

Box 3: Adverse effects of oral isotretinoin

Common

- Dry skin
- Hyperlipidaemia
- Initial flare of acne

Uncommon

- Alopecia
- Myalgia
- Pseudotumour cerebri
- Visual
- Depression (link not confirmed)

Additional resources

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www.skincarephysicians.com/acnenet/ (a sensible and accessible website endorsed by the American Academy of Dermatology)

doctors rarely request measurement of creatine kinase, drug related hepatitis is often incorrectly diagnosed. Restriction of exercise and reduction of dose usually correct the problem. Depression is a rare adverse effect of isotretinoin, but a convincing link to the drug has not been documented.[16] Decreased night vision may be measured but is rarely noticed by the patient. Finally, patients with severely inflamed lesions, especially those on the back and chest, may have a severe flare of disease accompanied by systemic complaints similar to those seen in acne fulminans. Prednisone 20-40 mg a day, along with low starting doses of isotretinoin, is indicated in such patients.

The most important side effect of isotretinoin is teratogenicity.[15] Two means of birth control, one either hormonal or surgical, are required for all fertile women taking the drug and should be continued for one menstrual period after treatment is stopped. After a course of isotretinoin, fertility and fetal development are normal once circulating isotretinoin levels return to normal.[15] There are no known deleterious effects on male fertility.

Patients should be monitored routinely. Pretreatment tests should include a lipid profile aspartate aminotransferase, complete blood count, and in the case of women, two negative pregnancy tests. At one month these tests should be repeated. If the results are normal and the dose of isotretinoin is not increased, only the pregnancy test needs be repeated each month.

The correct dosage of isotretinoin is controversial, and there is a point at which greater efficacy is outweighed by an increase in side effects. I prefer to use 1 mg/kg a day. Lower dosages often require longer than the standard four or five months of treatment and have a higher long term failure rate.

Acne and pregnancy

Erythromycin, topical or oral, is safe in pregnancy, although oral erythromycin is often poorly tolerated in patients whose lower oesophageal sphincter is already relaxed by pregnancy. Benzoyl peroxide rapidly decomposes into benzoic acid and hydrogen peroxide and is also safe. Topical tretinoin in pregnancy is theoretically safe as circulating vitamin A blood levels do not change with topical tretinoin treatment. However, many doctors avoid its use until after childbirth. No increase in fetal abnormalities has been seen in women using topical tretinoin while pregnant.[17]

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Commentary: A UK primary care perspective on treating acne

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In the United States, many patients with skin disease are treated predominantly by dermatologists. In the United Kingdom, patients often turn first to community pharmacists and then to their general practitioner. Acne can be managed in primary care provided that the general practitioner has adequate training and experience, but this is not always the case. Dermatology remains an area with high levels of referral to specialist services, and this demand outweighs capacity.[1]

No national UK guidelines exist for treating acne, although some trusts and health boards have local ones. The *BNF* (*British National Formulary*) and the *MeReC Bulletin* provide some information,[2] and the National Institute for Clinical Excellence provides advice on referral to secondary care.[3] Also, increasing numbers of general practitioners are developing a special interest in dermatology.

The principles of treatment suggested by Professor Webster are logical. A holistic approach is important with topical treatment for mild disease, a combination of oral and topical treatment for more troublesome disease, and oral isotretinoin for severe disease and when other treatment fails.

As the microcomedo is a precursor of many acne lesions it is reasonable to introduce a topical retinoid (or retinoid-like drug, such as adapalene). Such drugs reverse formation of comedones. Retinoids should be used early on and continued throughout much of the treatment programme. In contrast to the United States, the topical retinoid tazarotene is not licensed for acne. A topical retinoid can be used in the evening and an antimicrobial agent in the morning. It is important to emphasise the benefit of benzoyl peroxide, which may reverse the increasing problems of resistance to *Propionibacterium acnes*. Benzoyl peroxide can be used in combination with oral and topical antibiotics or during "antibiotic holidays" (breaks from antibiotic use).

We agree that when an oral antibiotic is needed, oxytetracycline is the first choice. More expensive preparations are not proved to be more effective. As a second line drug, minocycline is worth trying. General practitioners should be aware of the possible side effects, especially drug induced lupus.[4] General practitioners in the United Kingdom prescribe minocycline in a dose of 100 mg a day but American dermatologists regularly prescribe 200 mg a day. Generic trimethoprim is both effective and inexpensive.

Patients should be warned to expect little improvement in the first month, but thereafter they should expect about 20% improvement a month. After successful control of the disease, maintenance treatment with topical agents is essential. Oral antibiotics should be reintroduced if the acne occurs.

Women with acne who need the contraceptive pill for gynaecological reasons are often prescribed cyproterone acetate and oestrogen (Dianette) and topical treatment. Oral isotretinoin is highly effective at treating acne, but in the United Kingdom it can be prescribed only in secondary care because of its teratogenicity and the risk of adverse psychiatric events. In the United States the prescribing of oral isotretinoin and contraceptive advice is very proscriptive. UK guidelines are expected soon. The idea of prescribing oral isotretinoin in the community is a matter of debate. If general practitioners with a special interest in dermatology were able to prescribe isotretinoin it may reduce the waiting time for secondary care. However, any small changes in the threshold for prescribing isotretinoin could have serious financial implications for the NHS.[5]

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Corrections and clarifications

Randomised trial of endoscopy with testing for Helicobacter pylori compared with non-invasive H pylori testing alone in the management of dyspepsia
In this paper by K E L McColl and colleagues (27 April, pp 999-1002), we inadvertently published the wrong date for when we finally accepted the paper for publication. The correct acceptance date was 20 December 2001 [not 2 February 2002].

A time for global health
In this editorial by Richard Smith (13 July, pp 54-5), we managed to mangle a currency conversion. In the second sentence of the third paragraph, $119bn is £76bn (exchange rate at time of writing this correction), not £158bn, which is patently wrong, even with the recent shifting exchange rates. We should also have followed our policy, in place since 1 January 2002, of including a conversion to euros (which would be €121bn).