

Acne

Amanda M M Oakley MBChB FRACP DipHealInf

Introduction

Acne affects about 85% of teenagers but may persist into the 40s, especially in women. In a sample of adolescents from schools in New Zealand, acne was present in 91% of males and 79% of females.¹ It tends to persist for six to eight years without treatment.

Pathogenesis

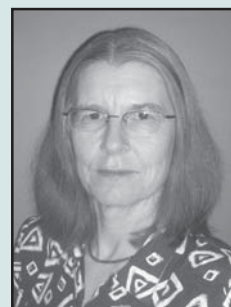
Acne is multifactorial. There is a genetic predisposition, perhaps relating to the number, size and activity of sebaceous glands. Sebum production increases at adrenarche, often noted a year or so prior to menarche in females. Acne is often associated with seborrhoea although not all those with seborrhoea develop acne.

Non-inflammatory acne lesions commence as the microcomedo. This is an accumulation of sebum beneath a bottleneck formed by sticky shed keratinocytes blocking the proximal portion of the follicle. As the comedo expands the follicle wall may rupture, extruding its contents into the surrounding dermis and provoking an inflammatory response.

Normal follicular bacteria include *Staphylococcus epidermidis* and *Propionibacterium acnes*. *P. acnes* produce pro-inflammatory mediators and lipases, contributing to acne lesions.

Severe disease is more likely in those with endocrine disorders particularly polycystic ovaries (PCOS), Cushing's syndrome and in the presence of excess androgens. However, most acne affects those with normal levels of circulating androgens. There is an increased production of dehydroepiandrosterone at adrenarche, stimulating local production of dihydrotestosterone (DHT) within the sebaceous gland via 5- α reductase activity. DHT stimulates sebum production.

Clinical Associate Professor Amanda Oakley is Clinical Director of the Department of Dermatology of Health Waikato and in private practice in Hamilton. She has a particular interest in teledermatology and online medical education, preparing online courses in dermatology for the University of Auckland and managing the New Zealand Dermatological Society's successful website at <http://www.dermnetnz.org>. She has wide clinical interests.



Ethinyl oestradiol at a dose of greater than 50mcg suppresses sebum production by opposing androgens within the sebaceous gland and by inhibiting ovarian production of androgens.

History

Take note of the following factors that are important in the management of acne:

- Age of onset of acne and its duration;
- In females, menstrual and oral contraceptive history;
- Prescription and over-the-counter medications used and their effect;
- Cosmetics and sunscreens;
- Skin sensitivity and dryness (especially if atopic);
- Presence of depression and poor self-esteem.

Clinical examination

Acne presents with non-inflammatory and inflammatory lesions and may affect the face, neck, chest, back and/or upper arms. Although the skin is often oily, the patient may report dryness due to concurrent atopic dermatitis, seborrhoeic dermatitis or contact irritant dermatitis from topical antiacne therapy.

Visible non-inflammatory lesions are blackheads (open comedones) and whiteheads (closed comedones).

Blackheads are discoloured because of melanin deposition within the keratin core blocking the follicle. Whiteheads can be seen more readily by stretching the skin. Large ones (>2mm diameter) are known as macrocomedones and are associated with treatment-resistant disease.

Inflammatory lesions are papules (<5mm diameter), pustules, nodules (>5mm) and cysts (deep fluctuant lesions filled with pus and serosanguinous fluid). The pus is sterile and represents a neutrophilic response. As the lesions resolve, postinflammatory erythema may persist for weeks and pigmentation to months or longer. Deep inflammation may result in permanent pitted, atrophic or hypertrophic scarring.

Standard photographs are available to grade the severity of inflammatory acne, for example the Leeds Acne Grading Technique. As a minimum, record whether it is 'mild', 'moderate' or 'severe' in affected sites.

- Mild acne is defined as non-inflammatory lesions (comedones), a few inflammatory (papulopustular) lesions, or both.
- Moderate acne is defined as more inflammatory lesions, occasional nodules, or both, and mild scarring.
- Severe acne is defined as widespread inflammatory lesions; nodules, or both, and scarring; moderate acne that has not settled with

six months of treatment; or acne of any objective severity with serious psychological upset.

Acne variants

Acne mechanica: localised acne provoked by mechanical or frictional obstruction of the follicle, for example by a chin strap or violin.

Acne excoriée: acne in which the lesions have been picked out resulting mainly in excoriations, often associated with an anxiety disorder or obsessive-compulsive tendencies.

Acne medicamentosa: acne induced by anabolic steroids, phenytoin, lithium, isoniazid, B vitamins, iodides and many other drugs.

Acne cosmetica: acne provoked by greasy and occlusive face creams or pomades.

Acne conglobata: severe nodulocystic acne with sinus tract formation.

Acne fulminans: nodulocystic acne accompanied by ulceration and granulomatous plaques, fever, arthralgia, myalgia and prostration. There is often neutrophil leucocytosis, mild anaemia and elevated ESR and C-reactive protein. Radiographic investigations may reveal osteolytic lesions, most often within the clavicle or sternum. Acne fulminans may be occasionally induced by oral isotretinoin.

Infantile acne: comedones and inflammatory lesions arise most often in boys three to 12 months of age. It may scar.

Occupational acne: acne provoked by cutting oils and hydrocarbons in the workplace.

Chloracne: extensive macrocomedones and inflammatory lesions in unusual sites sometimes persisting years after exposure to halogenated aromatic hydrocarbons such as those found in pesticides.

Differential diagnosis

Acne is usually straightforward to diagnose. However, it may be confused with other follicular eruptions. Uninflamed lesions include milia, sebaceous hyperplasia, adnexal tumours and keratosis pilaris. Inflamed lesions include rosacea, perioral dermatitis, bacterial folliculitis and

pseudofolliculitis barbae (shaving rash). Miliaria may look similar but is non-follicular.

Malassezia folliculitis results in monomorphic superficial papulopustules. There are no comedones. Variants include acne aestivalis, steroid acne and neonatal acne (now called neonatal cephalic pustulosis).

Investigations

Hormonal investigation is warranted only when the presentation is unusual or other signs of hyperandrogenism in females such as hirsutism or irregular periods.

- Elevated DHEAS indicates and adrenal source of excessive androgens and may arise in congenital adrenal hyperplasia or adrenal tumour.
- Elevated total testosterone indicates an ovarian source, most often PCOS and rarely a tumour; arrange pelvic ultrasound scan.

Management

Patients with severe acne (as defined above) at any site and adults with persistent acne should be referred early to a dermatologist for consideration of oral isotretinoin therapy (see below). Commence treatment with standard therapy as described below, especially if there is a wait of several months for an appointment.²

Mild acne in males and females

Advice given to the patient should include the advice to wash the affected areas twice daily with mild soap or a non-soap cleanser twice daily, to avoid the use of greasy face creams (moisturisers, sunscreens etc.) and to choose non-oily products if they wish to use make-up.

Antiseptic cleansers are popular and may be beneficial. They may contain cetrimide, chlorhexidine and/or triclosan. Other acne cleansers are based on salicylic acid (a keratolytic) or benzoyl peroxide.

Topical agents are generally sufficient for mild comedonal and inflammatory acne. None are subsidised by PHARMAC. There is evidence to sup-

port the use of topical benzoyl peroxide, azelaic acid (available over the counter), antibiotics and retinoids (requiring a prescription).³ Two or more agents from different classes of medication applied at different times of day are probably more effective than a single product once or twice daily.

Any of these agents may irritate, sting or dry the skin especially in those who have a history of any kind of eczema or atopic disorders. In general, these adverse effects are minimised by applying the agent very sparingly at first, and may be treated by the application of a light non-comedogenic moisturiser (petrolatum is best avoided as it is too occlusive). Tell the patient to treat all areas affected by acne rather than just applying the product to active spots, and that it may take weeks to months to observe significant improvement.

Benzoyl peroxide is probably the least expensive choice and is suitable for comedonal and inflammatory lesions. The patient can choose cream, gel, lotion, and wash formulations (Benzac, Brevoxyl, Clearasil Ultra, PanOxyl and other brands). It may bleach clothing and occasionally results in contact dermatitis.

Azelaic acid (Skinoren Cream and Acnederma Lotion) appears less effective but is sometimes better tolerated. In addition, it may help to lighten postinflammatory hyperpigmentation or concurrent melasma.

Clindamycin (Topicil Solution) and erythromycin (Eryacne gel, Stiemylin solution) reduce the number of inflammatory lesions. Benzoyl peroxide and/or topical retinoids should be prescribed as well to reduce the risk of bacterial resistance.

Topical retinoids are possibly the most effective agents for comedonal acne but are also effective for inflammatory lesions. Adapalene is probably the best tolerated (Differin Gel or Cream), but tretinoin (Retin A Cream) or isotretinoin (Isotrex Gel) may be preferred. They should be applied at night to reduce degradation by sun exposure. Protect treated skin from sun exposure because

retinoids thin the normally protective stratum corneum. If inflammatory lesions appear to flare, reduce how often the retinoid is applied and add in benzoyl peroxide; the flare resolves with continued usage.

In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used in pregnancy or by women of childbearing age who are not taking adequate contraceptive precautions. However, dietary intake of retinoids has been shown to have a greater influence on serum retinoid levels than facial application.

Arrange to review your patient at three months, while they are still using the product. If effective, treatment should be continued as stopping will likely result in rapid recurrence of acne lesions. If results are disappointing, add a second agent or consider oral therapy.

Moderate acne in males

Oral antibiotics with anti-inflammatory properties should be added to benzoyl peroxide and/or a topical retinoid. Additional topical antibiotics are of no benefit. Suitable fully subsidised antibiotics include doxycycline (Doxine), erythromycin (E-mycin) and trimethoprim (TMP). They are generally well tolerated when prescribed for six months or so (review after three months). They have little effect on comedones.

Doxycycline 50 to 100mg once or twice daily may cause photosensitivity. This may be less likely if taken in the evening compared to a morning dose. It is best taken after a meal to reduce nausea, and with a full glass of water to reduce the risk of oesophagitis. Minocycline 50 to 100mg twice daily has a part-charge but may be more effective because of better penetration into the sebaceous apparatus and reduced bacterial resistance. It has been associated with an increased risk of developing headache, arthralgia, systemic lupus erythematosus, hepatic dysfunction and pigmentation. Lymecycline 300mg daily may also be used but is

unsubsidised. Tetracyclines should not be used in children under nine years of age and are best avoided in those under 12.

Erythromycin 400mg twice daily has a higher risk of bacterial resistance than tetracyclines but it can be used in children. Gastrointestinal upset is less likely if it is taken with milk or food. Trimethoprim 300mg daily is less often prescribed but also may be effective.

Moderate acne in females

Tetracyclines may harm bones and teeth and should not be taken by pregnant or breastfeeding women. They may cause contraceptive failure during the initial weeks of treatment, although this is disputed. About 5% of women complain of vulvovaginitis and anticandidal therapy may be required.

Combined oral contraceptive pills (OCP) can be very effective for comedonal and inflammatory acne, particularly if there are premenstrual flares, whether or not there are detectable hormonal abnormalities. Ethinyl oestradiol/cyproterone (Estelle 35, Diane 35) may be more effective if improvement is inadequate on a standard OCP or the patient has PCOS.

Spironolactone 25 to 200mg daily reduces sebum production and improves acne in women. It is usually combined with OCP to reduce irregular menstruation and reduce risk of feminising a male fetus. This may be a progesterone-only pill if oestrogen is contraindicated.

Antiandrogenic therapy takes three to six months to be effective in acne and is often continued for several years.

Isotretinoin

PHARMAC subsidy requires the prescription to be by a dermatologist (not just on their recommendation). Its use by other doctors is discouraged because it is a major teratogen and its potential adverse effects are somewhat complicated to manage. It is cost-effective for those with severe and/or persistent disease, when com-



Figure 1. Acne on brown skin



Figure 2. Comedonal acne



Figure 3. Adverse effects of retinoids

pared to long courses of other less effective topical and systemic agents.

Contraceptive advice must be provided to girls and women of childbearing potential as any isotretinoin in early pregnancy runs a 50% risk of birth deformities; if they are sexually active, hormonal contraception and condoms are required until a month after the drug has been stopped. Monitoring may include pre-treatment and two-monthly measurement of serum β -HCG. Fasting lipids, liver function and blood count are also recommended as the drug may rarely induce hypertriglyceridaemia, hepatic enzyme abnormalities and neutropaenia.

The daily dose varies from 0.1 to 1mg/kg/day and is titrated according to the severity of acne, response



Figure 4. Inflammatory acne



Figure 5. Nodulocystic acne



Figure 6. Scarring from infantile acne

to treatment, adverse effects and patient preference.

Adverse effects are universal and tolerance of these quite variable. The dose of isotretinoin can be reduced or treatment interrupted if necessary.

- Dry lips, nostrils, skin should be anticipated and treated using non-soap cleansers, lip balm and thick emollients.

- Retinoid dermatitis presents as patchy or discoid-pattern dry red plaques, most often on the dorsal aspect of the hands and forearms but may arise on any site. It usually quickly responds to moderate potency topical steroids and increased use of emollients.
- Thinned skin may abrade more easily and appear slow to heal. Waxing should be delayed until the course of treatment is completed but shaving can be continued. Sun sensitivity is likely to increase so fair skinned individuals should be reminded of the need to cover up and apply sunscreens when outdoors.
- Staphylococcal infection complicates wounds, lip fissures, dermatitis and excoriated pimples and may result in paronychia. Standard antibiotic therapy may be necessary.
- Artificial tears provide relief to dry, gritty or red eyes, which may paradoxically become watery and may not tolerate contact lenses.
- Tiredness, muscle and joint aches and headaches may be treated with paracetamol and are a common reason for reducing the dose of isotretinoin, especially once the acne has improved. They may be accompanied by mood changes: parents sometimes report their teenagers to be more grumpy than usual (frequently denied by the patients themselves!).
- There is uncertainty whether the drug itself can cause depression; several studies of acne patients have found there is an overall reduction in depression and suicide in those treated with isotretinoin. However as a group, acne patients have a higher risk of depression

and it is also possible that there may be some individuals that have unexplained psychiatric reactions to the drug.⁴ Medsafe requires prescribers to discuss depression with male and female patients, who then must sign a specific informed consent form.

Drug interactions are rarely a problem. Tetracyclines are best avoided in case the combination causes raised intracranial pressure. Vitamin A could aggravate retinoid adverse effects.

Although isotretinoin is a remarkably effective medication, acne may persist (especially macrocomedones), recur after treatment has been stopped (20%) or flare during treatment, sometimes severely.

Secondary changes

Postinflammatory erythema, hypopigmentation and hyperpigmentation are common. Anti-acne treatment may need to be more aggressive in darker skinned patients. The pigmentation may reduce with topical retinoids, azelaic acid, glycolic acid and/or hydroquinone.

Management of scarring should wait until the acne is in remission, and surgery should be delayed for a minimum of six to twelve months after a course of oral isotretinoin. Topical retinoids may reduce the severity of scarring but this is not proven. Intralesional triamcinolone acetonide may be cautiously injected into hypertrophic scars. Ice pick scars may appear less obvious after surgical subcision. Dermabrasion or laser resurfacing may smooth out contours. Collagen or hyaluronic acid implants may be injected into shallow atrophic scars. However, these methods rarely eradicate the scars completely.

References

1. Pearl A, Arroll B, Lello J, et al. The impact of acne: a study of adolescents' attitudes, perception and knowledge. *N Z Med J* 1998; 111:269-271. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9734528
2. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, Shalita AR, Thiboutot D. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* 2003; Jul;49 (1 Suppl):S1-37. Review. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12833004
3. Sarah Purdy BMJ Clinical evidence. Acne vulgaris. Available at: http://www.clinicalevidence.com/ceweb/conditions/skd/1714/1714_background.jsp
4. Acne, Isotretinoin and Depression. Prescriber Update Article Medsafe June 2005. Available at: <http://www.medsafe.govt.nz/Profs/PUarticles/isotretDTB.htm>