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How to treat acne

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Key concepts:

- An inflammatory response to *P. acnes* results in papules, pustules and inflamed nodules
- Acne severity (mild, moderate or severe) may be based on the number, type and distribution of lesions
- Benzoyl peroxide, topical retinoids or topical antibiotics are suitable for mild acne
- Oral antibiotics may be suitable for moderate acne
- Combined oral contraceptives may be effective for moderate acne in women
- Isotretinoin may be suitable for severe acne, although it has many adverse effects and requires close monitoring and management - isotretinoin is a major teratogen, it is essential that women taking isotretinoin do not get pregnant

Acne is a common skin condition most prevalent in adolescents, affecting approximately 80% of people at some stage between the ages 11 to 30 years.[1, 2, 3] In a sample of New Zealand adolescents, 91% of males and 79% of females were affected by acne.[2, 3] Acne can also occur later in life and is present in approximately 5% of women and 1% of men over the age of 25 years.[1]

Acne can lead to dyspigmentation, scarring and psychological problems, especially anxiety and depression.[1] The aims of treatment are to reduce or clear skin lesions and prevent scarring and psychological sequelae.[1, 3]

An inflammatory response to *P. acnes* results in papules, pustules and inflamed nodules

Increased sebum production occurs following the increase in androgen production at puberty. Hyperkeratinisation of the hair follicle prevents normal keratinocyte shedding, which then blocks the follicle resulting in open comedones (blackheads) and closed comedones (whiteheads).[5, 6] *Propionibacterium acnes* colonises the follicle and breaks down sebum into free fatty acids and peptides. Papules, pustules and inflamed nodules occur due to a variable inflammatory response to *P. acnes* and the chemicals it releases.[1]

Acne diagnosis is based on history and examination

The diagnosis of acne is primarily based on history and examination.[5] Factors to consider when taking a history include:[2]

- Age of onset of acne and its duration
- Menstrual and oral contraceptive history in females
- Skin sensitivity and dryness (especially if atopic)
- Use of topically applied products such as cosmetics, cleansers, sunscreens, hair products and moisturisers that might be irritant or occlusive
- Use of other topical products, especially corticosteroid preparations
- Prescription and over-the-counter acne medicines used and their effect
- "Recreational" use of steroids e.g. gym use
- Presence of depression and/or poor self-esteem

Examination and assessment of severity

Acne may present as non-inflammatory, inflammatory or a mixture of both.

School students survey

In a survey of New Zealand secondary school students, 14.1% of students self-reported having "problem acne" with female, Pacific and older students reporting this most often. Those with more severe self-reported acne, females and Māori or Pacific students), were more likely to report difficulty in accessing medical treatment for acne (i.e. they reported that they wanted treatment but were unable to access or afford treatment from a doctor or specialist).[4]

Hormonal investigations for acne in women

Acne in women may be due to a condition that causes excessive androgen production such as polycystic ovary disease (PCOS). If signs of hyperandrogenism (e.g. hirsutism or irregular periods) are present consider hormonal investigation or referral.[2, 7, 8] (see BPJ 12, April 2008)

Non-inflammatory lesions include:

Closed comedones – 1 to 5 mm white papules without perceptible follicular orifice

Open comedones – 1 to 3 mm dark papules with visible follicular opening

Cysts – non-tender larger fluctuant dermal or subcutaneous swellings

Inflammatory lesions include:

Papules – inflamed palpable lesions less than 5 mm in diameter

Pustules – similar to papules containing pus

Nodules – larger, well or poorly defined red lumps that are often very tender

The severity of acne may be based on the number, type and distribution of lesions (Table 1).

Table 1: Severity of acne[7]

Severity		Description
Mild		Non-inflammatory lesions (comedones) predominate. A few inflammatory lesions (papules and pustules) may be present (generally less than 10)
Moderate		More papules and pustules (10–40) and comedones (10–40) present. The trunk may be mildly affected. Occasional nodules and mild scarring may also be present
Severe		Widespread inflammatory lesions, nodules and scarring present. Usually involving the face, chest and back. Moderate acne that has not settled after six months of treatment or acne of any severity that causes significant psychological distress is also classified as severe acne

Pharmacological treatment of acne – initial treatment depends on severity of acne

Initial treatment selection depends on the severity of acne. Initial management of mild acne is with topical therapies (benzoyl peroxide, topical retinoids and topical antibiotics). Oral antibiotics and/or hormonal treatments are added for moderate acne, and severe acne may require oral isotretinoin.

Mild acne: benzoyl peroxide, topical retinoids or topical antibiotics are suitable

Benzoyl peroxide and the topical retinoids (adapalene, tretinoin and isotretinoin) are usually considered first line for mild acne. Topical antibiotics, which can be used in conjunction with benzoyl peroxide or a topical retinoid, may be useful for mild inflammatory acne.[1] Topical treatments for acne are not currently subsidised. Topical agents should be applied as a thin smear to all areas affected by acne as they are much less effective as spot treatment.

Benzoyl peroxide

Benzoyl peroxide is an effective agent for comedonal and inflammatory acne. It is available over the counter in a range of formulations (e.g. washes, creams, gels) and strengths (2.5–10%).

The most common adverse effect of benzoyl peroxide is skin irritation, i.e., dryness and sometimes redness. This can be minimised by starting with a lower strength product and increasing.[8] Lower strength products (2.5–5%) are effective and cause less irritation than higher strength formulations (10%).[3] Patients should be advised that benzoyl peroxide can bleach clothes, towels, bedding and hair.

Azelaic acid may be used for mild comedonal acne. It causes less irritation than benzoyl peroxide but is generally believed to be less effective.[2, 7, 8]

Topical retinoids: adapalene, tretinoin, isotretinoin

Topical retinoids inhibit comedone formation and therefore prevent the formation of new acne lesions. They are useful for treating inflammatory and non-inflammatory acne.[9] Topical retinoids available in New Zealand are adapalene, tretinoin and isotretinoin. While they all are similarly effective, adapalene may be better tolerated.[1, 8]

As with benzoyl peroxide, skin irritation is also common with topical retinoids and can limit their use for some people.[1] This can be minimised by slowly increasing the frequency of application over time, starting with application every second or third day and increasing as tolerance develops. Initially applying topical retinoids for shorter durations may also minimise skin irritation, for example, by washing the application off after a period of time (e.g. 20 minutes or more).[1, 9] Irritation may be exacerbated by applying excess amounts of topical retinoids and patients can be advised that a pea sized amount is sufficient for application to the whole face.[9]

Topical retinoids are applied at night because they are degraded by sun exposure. Sun protection during the day is also recommended because they can thin the stratum corneum.[2] There have been case reports of birth defects in infants born to mothers who used topical retinoids during pregnancy and for this reason they are not recommended for use in pregnancy.[9] However, there is thought to be no increase in circulating retinoid levels above normal, when used according to usual directions.

Topical antibiotics: clindamycin and erythromycin

Topical antibiotics are effective for mild inflammatory acne but have little effect on comedones. Monotherapy with topical antibiotics is not recommended because this can cause bacterial resistance.[1, 9] Combining treatment with benzoyl peroxide or topical retinoids prevents resistance and is more effective for clearing acne lesions.[7]

Clindamycin and erythromycin are the topical antibiotics available in New Zealand.

They usually cause less irritation than benzoyl peroxide and topical retinoids but may occasionally cause mild irritation and burning.[9]

One product that combines clindamycin and benzoyl peroxide (Duac Once daily) can be applied once daily at night. Otherwise separate products can be combined by using one in the morning and one at night. If treatment includes a topical retinoid, this should usually be used at night.[1]

Usually topical antibiotics should not be used for extended periods of time as bacterial resistance is more likely. Consider stopping topical antibiotics after approximately six to twelve weeks of treatment and continue the benzoyl peroxide or topical retinoid alone.[1]

Practice points for topical treatments:

- Apply to all areas of skin prone to acne – the main effect of topical treatments is preventing new comedones developing[7]
- Use for at least six weeks before deciding if treatment is effective – topical treatments prevent new lesions therefore adequate time is required to allow current lesions to resolve
- Continued improvement may occur for up to six months of continuous use
- Different formulations can be chosen depending on skin type – creams for dry sensitive skin, gels and topical solutions for oily skin[1]

Glossary of topical acne medications

Benzoyl peroxide

2.5% – Benzac AC gel, PanOxyl Acne gel

4% – Brevoxyl cream

5% – Benzac AC gel, Benzac AC wash, Clean and Clear Continuous Control Acne Cleanser, Clearasil Ultra Acne Treatment cream, PanOxyl Acne gel

10% – Benzac AC gel, PanOxyl Acne gel

Azelaic acid

20% – Acnederm Lotion, Skinoren cream

Topical retinoids:

Adapalene

0.1% – Differin gel, Differin cream

Isotretinoin

0.05% – Isotrex gel

Tretinoin

0.05% – Retin-A cream, Retinova cream

Topical antibiotics:

Erythromycin

2% – Stiemycin topical solution

4% – Eryacne gel

Clindamycin

1% – Topicil solution

1%, with 5% benzoyl peroxide – Duac Once Daily gel

Moderate acne: oral antibiotics are recommended

Oral antibiotics are appropriate for moderate acne and for acne that has not responded to topical therapy. They inhibit the growth of *P. acnes* and also have direct anti-inflammatory effect.[10] Tetracycline antibiotics such as doxycycline are usually the first line choice. Erythromycin-resistant *P. acnes* is common and for that reason erythromycin is usually reserved for treating acne in children, pregnant women and those with a hypersensitivity to tetracyclines.[9] Trimethoprim 300 mg daily may also be effective.

Oral antibiotics should be used in combination with a topical retinoid or benzoyl peroxide.[2, 6, 9] Short courses (however not usually less than three months) are now recommended over longer courses because of the risk of antibiotic resistance.[8] They may be prescribed for four to six months and may be tapered and discontinued once acne improves. Use of benzoyl peroxide or topical retinoids may help maintain improvements once oral antibiotics are stopped.[10] If acne relapses, treat with the same antibiotic as previously used.

Doxycycline and minocycline are usually taken at a dose of 100 mg to 200 mg daily. Photosensitivity and oesophagitis are common side effects of doxycycline. Vaginal thrush affects 5% of women treated with oral antibiotics. Minocycline is associated with other rare side effects such as blue-gray pigmentation, drug-induced lupus and hepatic dysfunction and for this reason is usually reserved for second line use.[2, 9] If minocycline is used for longer than six months, liver function tests will be required every three months.[11] Tetracyclines are not suitable for pregnant or breastfeeding women, or for children under 12 years old as they may harm bones and teeth of the unborn or developing child.[1]

When used for acne, erythromycin is taken at 400 mg twice daily. It may cause nausea and should be taken with food.[2]

Interaction with combined oral contraceptives

It is thought that gut flora develop resistance to non-enzyme inducing antibacterials (all antibacterials apart from rifampicin and rifabutin) after three weeks of treatment. For this reason, women taking the combined oral contraceptive do not require additional precautions (e.g. condoms) after three weeks of treatment with an antibiotic.[12]

Moderate acne: combined oral contraceptives may be effective for acne in women

Hormonal treatment of acne may be suitable for women who have premenstrual flares of acne, have acne that is resistant to conventional treatment, those with hormonal abnormalities, or women with acne that also require hormonal contraception.[1] Combined oral contraceptives containing cyproterone (e.g. Estelle) may be more effective than other oral contraceptives and are suitable for women with PCOS. However any oral contraceptive containing oestrogen is likely to have positive effects on acne.[7]

A therapeutic response may be seen after one cycle but usually takes up to six cycles to see a full response.[7]

Isotretinoin for severe acne

Acne that has not responded to topical or oral therapy or acne that is severe on presentation may require treatment with isotretinoin. Isotretinoin can be a complex drug to use, as it has many adverse effects, requires monitoring and is a major teratogen. Isotretinoin should only be prescribed by doctors who have been educated in its safe and effective use. Patients may require referral to a dermatologist.

Patients should receive extensive verbal and written information regarding the medication, its risks, adverse effects and requirement for monitoring. They should be reviewed regularly during the course of treatment.

Isotretinoin is effective because it is active against all four contributing factors to acne.

Isotretinoin:[13]

- Reduces the size and secretions of sebaceous glands
- Prevents the formation of comedones
- Reduces colonisation of the skin by *P. acnes*
- Reduces associated inflammation

Results are unpredictable and highly variable. A single course of isotretinoin may result in prolonged remission of acne.[8] Acne is resolved in approximately 40% of patients after one course, 40% may have acne that recurs at low severity and usually responds to topical therapy or occasionally oral antibiotics are required and 20% of patients may need a further course of isotretinoin.[7]

Contraindications to isotretinoin

Isotretinoin can not be used by women who are pregnant or breastfeeding, or by people who have severe hepatic impairment, hyperlipidaemia or hypervitaminoisis A.

Concomitant use of isotretinoin with tetracycline antibiotics should be avoided as it may increase the risk of raised intracranial pressure.

Table 2: Common adverse effects of isotretinoin and ways to minimise these[2, 15]

Problem	Solution
Acne flare – sometimes very severe	Mild acne flare may occur initially and usually improves with continued treatment. Severe flare may require a reduced dose or discontinuation of isotretinoin. Oral erythromycin and/or systemic steroids may be required.
Dry skin, lips and nostrils	Use non-soap cleansers, lip balm and thick emollients
Skin fragility, delayed wound healing and sun sensitivity	Use sunscreen and cover up in the sun (especially fair skinned people) Avoid waxing but shaving can be continued with shaving cream
Dry, irritable eyes and contact lens intolerance	Use artificial tears and wear glasses or change to “dry eye” contact lenses if contact lens are not tolerated
Retinoid dermatitis – patchy or discoid-pattern dry red plaques often seen on the hands and forearms	Increase use of emollients. Moderate potency topical steroids are useful
Paronychia and staphylococcal infection of wounds, dermatitis and lip fissures	Treat with topical (fusidic acid) or oral antibiotics (flucloxacillin)
Tiredness, muscle and joint aches, headache	Paracetamol or a reduction in dose (especially if acne is improving) Severe headache (especially if accompanied by visual changes) should be investigated for benign intracranial hypertension

Dosing

Patients may be initiated on 0.5 mg/kg/day for two to four weeks and then maintenance therapy can be continued at 0.1–1 mg/kg/day depending on response and tolerance.[14] A cumulative dose over the treatment course of between 120 mg/kg and 150 mg/kg is associated with an increased likelihood of prolonged remission.[7] Therefore a treatment course may last four to six months, depending on the daily dose. The maximum cumulative dose per course is 150mg/kg. If a further course is required, there should be a minimum of eight weeks between courses.

Adverse effects are often dose dependent and may be minimised with lower dose treatment for a longer time period.[7] See Table 2 for management of adverse effects associated with isotretinoin.

Significant adverse effects include abnormal liver enzymes, hypertriglyceridaemia, cytopaenias and depression.[2]

Transient increases in liver enzymes may occur but often return to normal with continued treatment. Liver function should be checked before and one month after the start of treatment and then three monthly.[16] If liver enzymes rise greater than two and a half times normal levels, investigation into other possible causes of liver dysfunction (e.g. viral hepatitis, alcohol) is required and the dose of isotretinoin may need to be reduced or the drug stopped altogether.[15]

Some patients may have a small increase in triglyceride or cholesterol levels. Levels may resolve on reduction of dose, discontinuation of therapy or modification of diet.[15, 16] Triglyceride levels in excess of 9 mmol/L have been associated with pancreatitis. Isotretinoin should be stopped if triglyceride levels are rising or if symptoms of pancreatitis develop.[16] Fasting lipids should be measured at baseline, one month after the start of therapy and at the end of therapy.[16]

Rarely isotretinoin causes reversible cytopaenias. A complete blood count is required at baseline and one month after commencing treatment. Further complete blood counts should be done if the patient presents with high fever, sore throat, petechiae or unusual bruising.[15]

There has been ongoing debate as to whether isotretinoin causes mood disorders. Studies so far have proved inconclusive as it has not been possible to accurately distinguish between mood change due to acne or due to isotretinoin.[17] Patients should be counselled about mood changes and closely monitored during treatment.[3]

Isotretinoin is a teratogen

A major concern with isotretinoin use is its teratogenic effect. A single exposure during pregnancy can result in embryopathy and severe birth defects including ear abnormalities, central nervous and cardiovascular system defects.[6, 7] Long term cognitive and developmental effects may be present even if central nervous system abnormalities are not obvious.[15]

For this reason, every attempt to prevent pregnancy should be made, including: [17]

- Obtaining a current sexual history in ALL females of child bearing potential, whatever their age or likely behaviour
- A negative pregnancy test (preferably blood) is required in the two weeks before initiation and isotretinoin can be started on the second or third day of the next menstrual period
- Pregnancy tests are required monthly at each prescription
- Two forms of contraception are recommended for females (e.g. a hormonal contraceptive and a barrier method such as condoms) one month before, during and one month after treatment.

  NB: The progesterone-only pill may be less reliable during isotretinoin therapy and is not recommended

- Female patients should be advised to consult their GP, pharmacist or dermatologist if they have knowingly had unprotected sex during isotretinoin

therapy so that emergency contraception can be considered

- If a foetus is exposed to isotretinoin offer counselling regarding termination of pregnancy as early as possible
- Male and female patients should not donate blood during, and for one month after finishing isotretinoin treatment, because of this risk

It is recommended patients sign a consent form indicating they have understood potential adverse effects of isotretinoin and for females, the importance of not becoming pregnant while on therapy. A copy of this form is available in *bestpractice* Decision Support acne module or can be downloaded from the bpac website: **www.bpac.org.nz** keyword: isoconsent

Images contributed by NZ DermNet, the website of the New Zealand Dermatological Society: **dermnet.org.nz**

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