

Acne

Lynn Lambert*

^aAmayeza Info Centre

*Corresponding author, email: lynn@amayeza-info.co.za

Abstract

Acne vulgaris is a common skin condition with a high prevalence in teenagers and young adults. It is a condition of the pilosebaceous follicles, resulting in comedones, papules, pustules or nodules which occur primarily on the face, but which may also present on other areas of the body. Although acne is not physically disabling, its psychological impact is highly significant, contributing to low self-esteem, depression and anxiety. As a result, there is a significant demand for effective acne therapies.

Keywords: acne, topical retinoids, topical antibiotics, oral antibiotics, oral isotretinoin, hormonal treatment

Introduction

Acne vulgaris (acne) is an extremely prevalent skin disorder which affects adolescents and young adults.^{1,2} The highest prevalence appears to be in adolescents. However, it may persist into or develop in adulthood.²

The psychological effects of embarrassment and anxiety can impact on the social lives and employment of affected individuals, since scarring associated with acne can be disfiguring and lifelong.² It has a greater negative effect on the emotions and social functioning of teenagers than conditions such as asthma and epilepsy. It was confirmed in a study that successfully treating acne in affected patients resulted in a significant improvement in self-esteem.^{1,2}

This highlights the importance of an appropriate and effective choice of medical treatment, capable of clearing the condition completely, or bringing about a significant improvement in those who do not experience complete clearance.^{1,2} Understanding the pathophysiology of this condition is imperative when deciding on a course of treatment. Pathogenetic factors represent specific targets for treatment. It has been proved that a combination of treatment, directed at different pathogenetic factors, achieves better results than different treatment methods which target the same factors.¹

Acne is a chronic inflammatory condition of the pilosebaceous units (hair follicles and their accompanying sebaceous gland), resulting in the formation of comedones, papules, pustules, nodules and/or cysts.^{3,4} Acne affects approximately 80% of people aged 11–30 years, of whom roughly 60% are sufficiently affected to seek medical treatment. Typically, acne lesions

develop at the onset of puberty. Therefore, girls tend to develop acne at an earlier age than boys.⁴

The formation of a comedo is a typical sign of acne development. It consists of a widened hair follicle, filled with keratin skin debris, bacteria and sebum (oil). A comedo may be closed or open. A closed comedo, called a whitehead, has an obstructed opening to the skin, and may rupture to cause a low-grade inflammatory skin reaction in the area. An open comedo, called a blackhead, has a wide opening to the skin, and is capped with a blackened mass of skin debris.⁵

Acne typically affects those areas of the body with the largest, most hormonally responsive sebaceous glands. This includes the face, neck, chest, upper back and upper arms. Typical acne lesions include open comedones, closed comedones and inflammatory lesions. In addition to these, scarring and post-inflammatory hyperpigmentation can occur, which can be greatly distressing to patients, and is most common in patients with darker complexions. An individual macule with hyperpigmentation may take several months or more to resolve without treatment.²

Pathogenesis

Although the sequence of events leading to the development of an acne lesion is not fully understood,² the microcomedo is the primary lesion in acne. Although not visible to the naked eye, histological analysis has revealed hyperkeratosis of the intrafollicular sebaceous ducts and dilatation of the sebaceous glands. Approximately 30% of facial follicles in the acne-prone patient are in this state at any given time. An additional concept is that of the inflammatory microcomedo, still invisible to the naked eye, but which shows inflammation on histological examination.

Table 1: The differential diagnosis of acne³

Bacterial folliculitis	Abrupt eruption Spreads with scratching or shaving Variable distribution
Drug-induced acne	The use of androgens, adrenocorticotrophic hormone, bromides, corticosteroids, oral contraceptives, iodides, isoniazid, lithium and phenytoin
Hidradenitis suppurativa	Double comedo It starts as a painful boil Sinus tracts
Miliaria	“Heat rash” in response to exertion or heat exposure Nonfollicular papules, pustules and vesicles
Perioral dermatitis	Papules and pustules confined to the chin and nasolabial folds Clear zone around the vermilion border
Pseudofolliculitis barbae	Affects curly haired persons who regularly shave closely
Rosacea	Erythema and telangiectasias No comedones
Seborrhoeic dermatitis	Greasy scales and yellow-red coalescing macules or papules

This lesion forms an important target in the treatment of acne, especially as far as maintenance treatment is concerned.¹

Acne is typified by the eruption of a comedo within the follicle.³ The four main factors leading to the formation of acne lesions are:¹⁻³

- Increased sebum production by the sebaceous glands, in which androgens play an important role.
- Hyperkeratinisation of the follicle or follicular hyperproliferation, leading to a microcomedo which eventually enlarges into a comedo.
- The presence of the bacterium, *Propionibacterium acnes*, within the follicle.
- Inflammatory and immunological reactions.

Current therapies target these four factors in order to achieve control of acute acne flare-ups and long-term maintenance.³

Evaluation

Acne is diagnosed by the identification of lesions.³ While the presence of comedones is the primary sign, acne can present with a variety of skin lesions, such as inflammatory papules, pustules, nodules, cysts, conglobate lesions, sinuses, scars or ulcers. Several other skin diseases present with very similar looking skin lesions. Therefore, making a diagnosis is not as straightforward as it may seem. It is important to ascertain whether or not comedones are present because these are virtually diagnostic of acne vulgaris, and it is difficult to make a diagnosis of acne in their absence. Furthermore, the presence of comedones is lacking in other conditions which may mimic acne. While acne involves the face mostly, it often extends onto the trunk, most often the back, and can also affect the upper arms, thighs and even the buttocks. The scalp is rarely involved, even though it is richly supplied with sebaceous glands.^{1,3} The differential diagnosis of acne is outlined in Table 1.

Other factors

Patients should be advised that other factors may exacerbate acne. These include external factors, diet, family history and stress.²

External factors

Although soap, detergent and astringent remove sebum from the skin surface, they do not alter the production of sebum. Repetitive mechanical trauma caused by scrubbing with these agents may worsen the disorder by rupturing comedos, promoting the development of inflammatory lesions. Thus, patients with acne should refrain from rubbing their faces or picking their skin. Clothing such as turtleneck sweaters, bra straps, shoulder pads, orthopaedic casts and sports helmets can all cause acne mechanica, in which occlusion of the pilosebaceous follicles leads to comedone formation. Pomade acne is associated with the use of occlusive, oil-based hair products.

Diet

The potential role of diet in acne is controversial. An association between acne milk intake was found following questionnaire-based evaluations, in which subjects were required to recall their dietary intake and self-diagnose acne and disease severity. It was suggested that the natural hormonal components of milk or other bioactive molecules in milk can exacerbate acne. However, the relationship between dairy products and acne has not been evaluated in any randomised trials.

There is no reliable evidence that the ingestion of chocolate is associated with the increased prevalence or severity of acne. Data on the favourable effects of dietary factors, such as zinc, omega-3 fatty acids, antioxidants, vitamin A and dietary fibre, on acne, are limited. Further studies are necessary to determine the roles of these supplements in acne vulgaris.

Family history

Individuals with close family members with acne are at increased risk of developing acne. A more than threefold higher risk in individuals with affected first-degree family members has been demonstrated in case-control studies. There is often a positive family history in cases of very severe acne, but the role of genetics in mild acne is uncertain, owing to its almost ubiquitous occurrence in young adolescents.

Stress

It is commonly believed, by both patients and doctors, that psychological stress can exacerbate acne. It was found that acne severity, rather than sebum production, was exacerbated by stress, in particular around examination time.

Grading of acne

While a standardised method of grading acne severity is lacking, this is necessary because of the important role that it plays in treatment decisions.^{1,6} However, grading can be problematic and subjective. According to the South African acne guidelines, the simplest way of grading acne is based on the predominant type of lesion present on the skin, regardless of the number of lesions. Grading is performed according to the most severe lesions present (Table 2).¹

Table 2: The grading of acne

Grade	Presentation
Grade 1	Comedones only
Grade 2	Inflammatory papules present, in addition to comedones
Grade 3	Pustules present, in addition to comedones and/or inflammatory papules
Grade 4	Nodules, cysts, conglobate lesions or ulcers plus comedones, papules and/or pustules

Treatment options

The development of acne lesions is promoted by four main factors. The goal in the treatment for acne is to target one or more of these factors, as well as the grading of the acne that presents.⁶ A summary of the approach to medical therapies for acne is provided in Figure 1.^{3,6}

Topical therapies

Topical retinoids

Topical retinoids (adapalene, isotretinoin, tretinoin and tazarotene) are effective in treating acne in which comedones, papules and pustules are present, but are ineffective in treating severe pustular or deep nodular cystic lesions.⁷ These agents target the microcomedo level, which forms the earliest precursor of visible acne lesions.¹ They act by normalising keratinisation and inhibiting comedone formation. Topical retinoids are unlikely to cause systemic toxicity as they are minimally absorbed by the skin. However, their use in pregnancy is contraindicated, and women of childbearing age who are prescribed this option must use contraception.⁷ Topical retinoids can be used as monotherapy for noninflammatory acne, or as combination therapy with antibiotics (oral or topical), to treat inflammatory acne. After the treatment goals have been reached, they are useful for maintenance treatment.³ A common side-effect is shared by the different topical retinoids, in the form of initial irritation on application.¹ While adapalene appears to be the best tolerated topical retinoid in terms of irritation, there is no evidence that any formulation is superior to another.³ Topical retinoids should be applied before bedtime,⁷ and to the whole affected area, not just the lesions. This is because in addition to their therapeutic effect on visible lesions, their main action is preventative.¹ The frequency of application should be individualised, depending on response.⁷

Topical antibiotics

Topical antibiotics (clindamycin and erythromycin) are used for the treatment of mild to moderate inflammatory or mixed acne.^{3,7} Although they can be used as monotherapy, they are more effective in combination with topical retinoids. It is

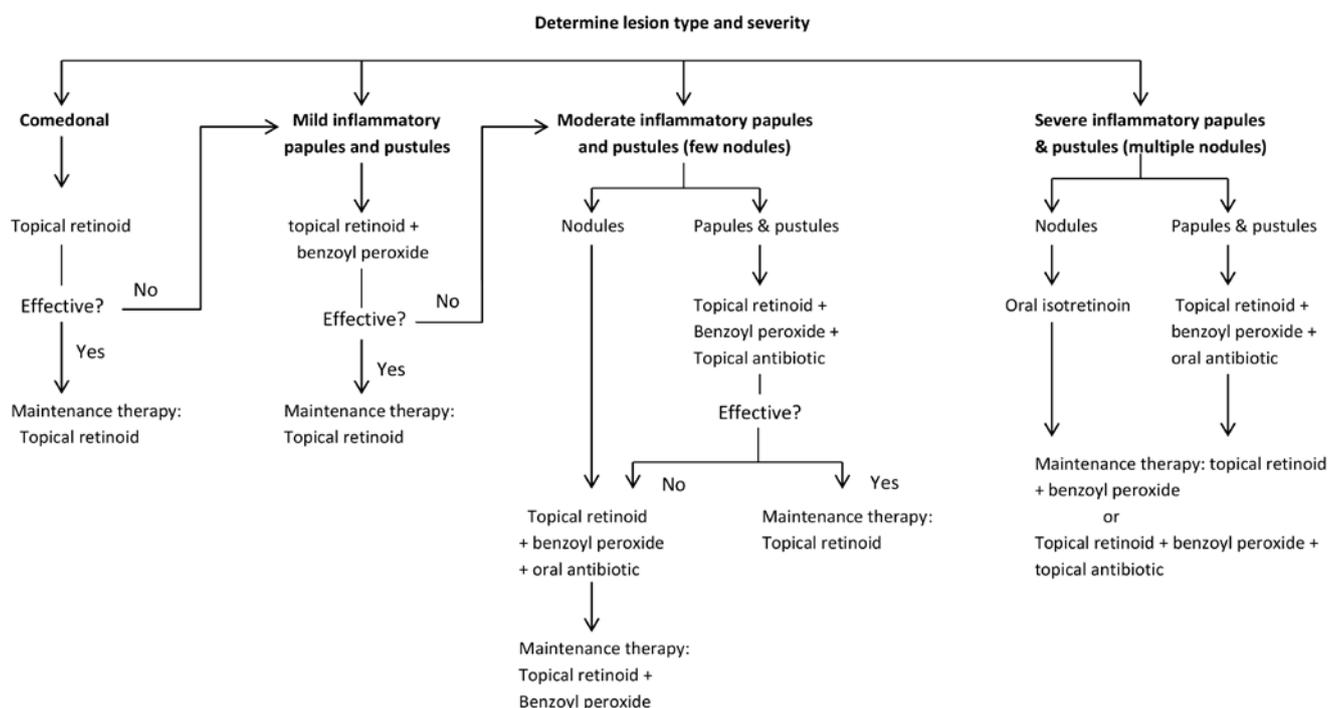


Figure 1: A treatment algorithm for the management of acne^{3,6}

Table 3: Oral antibiotics used to treat acne vulgaris^{3,6-8}

Drug	Recommended dose	Potential adverse effects
Doxycycline	<i>Initial:</i> 100 mg daily <i>Maintenance:</i> 50 mg daily	Gastrointestinal disturbances (dose-related) Photosensitivity Contraindicated in pregnancy and in young children
Erythromycin	<i>Initial:</i> 750–1 000 mg daily in divided doses, and decreased gradually according to the clinical response to 250 mg once or twice a day	Gastrointestinal intolerance
Minocycline	<i>Initial:</i> 100–200 mg daily <i>Maintenance:</i> 50 mg daily	Vestibular toxicity (dizziness, vertigo and tinnitus) Pigmentation of the skin/scars Contraindicated in pregnancy and in young children
Lymecycline	300 mg twice a day	Gastrointestinal upsets Headaches Contraindicated in pregnancy and in young children

recommended that benzoyl peroxide is added to this regimen to minimise the risk of antibiotic resistance.³

Topical over-the-counter preparations

Benzoyl peroxide has bactericidal activity, and is not known to increase bacterial resistance. It is most effective in treating mild to moderate mixed acne when used in combination with topical retinoids.³ Azelaic acid is suitable for treating mild to moderate acne because it has an antimicrobial effect on *P. acnes*, and an influence on follicular hyperkeratosis. Salicylic acid is used as an exfoliating agent. It has a positive effect on comedones.⁷

Oral antibiotics

Antibiotics (doxycycline, lymecycline, minocycline and erythromycin) are the most common form of treatment for moderate to severe acne.¹ Oral antibiotics improve inflammatory acne by inhibiting the growth of *P. acnes* within the pilosebaceous unit.⁶ While they are effective in treating acne, they have the potential for bacterial resistance. Therefore, it is recommended that benzoyl peroxide is added to any regimen containing an oral antibiotic. Erythromycin has a higher rate of resistance, and tetracycline is usually preferred for this reason.³ Once the individual treatment goals have been met, the oral antibiotics can be discontinued and replaced with topical retinoids for maintenance therapy.³

Oral antibiotics also exhibit non-antibacterial activities, such as the inhibition of bacterial lipases, anti-inflammatory activity and immunosuppression. The needless use of antibiotics should be avoided, and should only be considered to treat moderate to severe acne.¹ Oral antibiotics produce more rapid clinical improvement than topical preparations, but may induce side-effects such as vaginal candidiasis in women, or gastrointestinal distress in most patients.⁶ They should be used in combination, and not as monotherapy.¹ Oral antibiotics should be prescribed for a limited course to limit the emergence of antibiotic resistance⁶ (Table 3). The minimum duration of therapy is six weeks, continued daily for less than six months, with subsequent discontinuation as the acne improves. Some experts recommend limiting the treatment to 12–18 weeks because of antibiotic resistance.^{1,6}

Oral isotretinoin

Oral isotretinoin is used for the treatment of severe recalcitrant acne, and represents the most effective choice of therapy as it targets all of the pathophysiological factors.^{1,3} It is the drug of choice, owing to its high incidence of success in the treatment of severe acne. Its benefits far outweigh the risks involved.¹ Used as monotherapy, the usual dosage for severe treatment-resistant acne is 0.5–1.0 mg/kg per day for 20 weeks, or a cumulative dose of 120 mg/kg.^{3,6} Isotretinoin is a potent teratogen, and is associated with foetal abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, thymus and parathyroid glands. Therefore, negative pregnancy tests are mandated before therapy is initiated. Thereafter, monthly tests should be performed immediately after the last dose has been taken, and one month after the last dose has been taken. It has been suggested that the use of isotretinoin worsens depression and increases the risk of suicide, but a causal relationship has not been established in this regard. Laboratory monitoring during therapy is required. This includes obtaining a complete blood count and fasting lipid panel, and measuring the liver transaminase levels. Common adverse effects include headaches, dry skin and mucous membranes, and gastrointestinal upset.³

The following measures can be taken to mitigate against the risk of teratogenicity which accompanies the use of isotretinoin. The patient must:

- Adhere to strict contraception for a month before starting the treatment, undergo a pregnancy test before starting treatment, then start the medication on the third day of her next menstrual period.
- Be encouraged to use effective contraception during treatment, and for one month after the last dose of isotretinoin has been taken.
- Be made fully aware of the risks associated with the use of isotretinoin.
- Be asked whether or not she has provided written consent to use the medication, to indicate that it is understood that a therapeutic abortion would be compulsory should she fall pregnant during treatment.

Hormonal treatment

Androgens stimulate increased sebum production, which contributes to the formation of acne. Hormonal therapies should be considered as a treatment option in patients with evidence for hyperandrogenism.⁶ Women without hyperandrogenism can also benefit from this treatment as it reduces androgen production or blocks the androgen receptors, which leads to significant improvement in, or clearing of, the condition.^{1,6}

Combination oral contraceptives are often effective in treating mild forms of acne in women, but anti-androgen combination oral contraceptives are recommended for the more severe forms, e.g. a cyproterone-ethinylestradiol combination.

Hormonal therapy represents an effective choice for women who also require oral contraception. It may also be considered in women with normal serum androgens, but who present with persistent inflammatory papules, nodules on the lower face, and/or prominent acne flares at menstruation.¹

Conclusion

Acne can be extremely distressing, and can impact severely on quality of life. A comprehensive assessment of the patient is required to determine the most effective course of acne treatment. The treatment of acne should involve counteracting follicular hyperproliferation, increased sebum production,

P. acnes proliferation and inflammation. The choice of treatment also depends on whether comedonal or inflammatory lesions predominate. Treatment goals in patients with acne should include the prevention of scars, the reduction of psychological morbidity, and the resolution of noninflammatory and inflammatory lesions. Optimal results are seen when treatment is individualised on the basis of clinical presentation.

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