

ACNE VULGARIS. GRADES OF SEVERITY AND TREATMENT OPTIONS

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Introduction

Acne is the most common skin condition treated by dermatologists. Acne is a polymorphic disease exhibiting a number of diverse lesions: comedones, papules, pustules, nodules, cysts, sinuses and scars. Despite this diversity, acne can be reduced to a two-stage sequence of events. Firstly an abnormal hypercornification and desquamation in the infundibular segment of the pilosebaceous unit (the infundibulum is the part of the hair follicle from the orifice of the sebaceous gland duct to the opening on the surface) leads to the formation of a comedo, initially without an inflammatory component; and later an inflammatory reaction results in disorganisation of the epithelial capsule.

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AETIOLOGY

There are four major aetiological factors involved in the pathogenesis of acne:

- ductal hypercornification
- increased sebum production under androgen control
- abnormal microbial activity in the pilosebaceous duct (colonisation with *Propionibacterium acnes*)
- inflammation

Proliferation of *P. acnes* within the occluded environment of comedo is associated with release of neutrophil and lymphocyte chemo-attractants which leads to the accumulation of these cells within the follicular epithelium and perifollicular infiltrate. *Propionibacterium acnes* activates complement and stimulates the release of several cytokines (Interleukin-1, IL-8, TNF- α).

The clinical presentation of acne in an individual patient reflects which of the above listed factors takes the upper hand. In some patients, non-inflammatory lesions in the form of closed and open comedones (white- and blackheads) predominate, in others, inflammatory lesions, papules, pustules, nodules, cysts, drainage sinuses form the picture. In the majority of patients, both types of lesions occur.

For treatment purposes, the classification of acne into mild, moderate and severe is sufficient. More elaborate scoring systems based on counting of different acne lesions are used for assess-

ment of efficacy of medications in clinical trials requiring statistical validity.¹ Acne is considered mild when there are mainly non-inflammatory lesions and only a few superficial inflammatory lesions. In severe acne, there are deep inflammatory lesions resulting in scarring. What lies between is called moderate acne. The therapeutic approach would depend on the type of the prevalent lesion, the extent of the involvement and the response to previous treatments.

Table 1 – International Acne Treatment Algorithm provides the recommendations for the treatment of acne depending on the severity. It is the consensus of opinions expressed during the 9th Congress of European Academy of Dermatology and Venereology in Geneva in 2002.² **Figures 1 to 3** demonstrate mild, moderate and severe acne.

MILD ACNE

In cases of mild acne, topical treatment is usually sufficient. It is necessary to

determine whether the condition is mainly comedonal, non-inflammatory or inflammatory, or a mixture of both types of lesions. Patients with mainly comedonal acne should be treated with a topical agent with significant comedolytic activity.

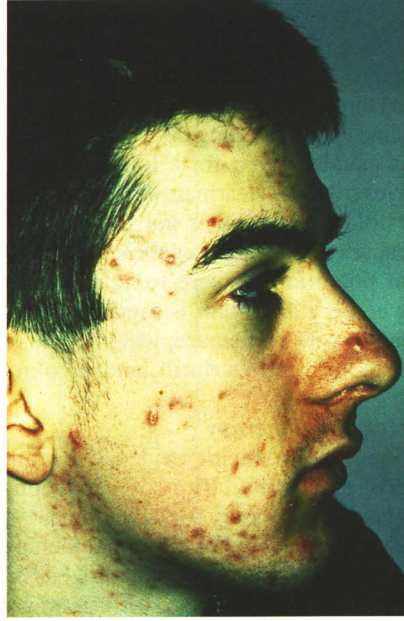
Retinoids, compounds chemically related to vitamin A normalise follicular hypercornification and loosen the comedones. They also have anti-inflammatory action. Retinoic acid (tretinoin) is the prototype retinoid. It is available in RSA as 0.05% cream and 0.025% gel. In the early stages of treatment with this agent skin irritation may occur. In some patients an eruption of pustules may appear within the first week of treatment. It reflects the elimination of previously invisible comedones. Patients should be informed that this is a favourable event.

Patients undergoing local treatment with retinoic acid should avoid prolonged sun exposure and no other topical treatment should simultaneously be

Table 1: International Acne Treatment Algorithm¹

Grade I (Mild)	Grade II-II (Moderate)	Grade IV (Severe)	Maintenance
Topical Retinoids	Topical Retinoids	Isotretinoin	Topical Retinoids
Benzoyl peroxide or topical antibiotic	Benzoyl peroxide or topical antibiotic	OR	Benzoyl peroxide or topical antibiotic
	Oral antibiotic	Topical retinoids, Oral antibiotics, Hormonal therapy	
	Hormonal therapy		

Figures 1,2,3: Mild, moderate and severe acne



used. The response is usually slow and several weeks are needed for a marked improvement. Topical isotretinoin (0,05% gel, Isotrex) seems equal to retinoic acid in mild-to-moderate non-inflammatory acne and is less irritant. Retinoic acid should be applied once daily at bedtime; isotretinoin may be applied twice daily.

Adapalene (0.1% gel and cream, Differin) has been shown to have more pronounced anti-inflammatory action than retinoic acid. It appears to be better tolerated than retinoic acid. Adapalene should be applied once daily at bedtime.

Tazarotene (0.05% gel, Zorak), the newest of topical retinoids developed for the treatment of psoriasis, is also effective in acne but irritates the skin. The previous three retinoids appear superior in the management of acne.

In patients with predominance of inflammatory lesions, benzoyl peroxide

and topical antibiotics are used. Benzoyl peroxide is used in both inflammatory lesions and comedones and has antimicrobial action. Propionibacterium acnes does not become resistant to it. Benzoyl peroxide is available in two concentrations (5% and 10%) in various formulations. Benzoyl peroxide tends to irritate and dry the skin, particularly in fair-skinned individuals. It is advisable to start with a 5% concentration and to increase it to 10% if the response is not satisfactory. As benzoyl peroxide is available over the counter many patients have already tried it before consulting a physician.


Topical antibiotics act by suppressing P. acnes. Topical erythromycin and clindamycin are used in 1% to 4% solutions and lotions. Resistance of P. acnes to erythromycin has been reported from several countries (especially in

those receiving oral erythromycin).³ Development of resistance can be lessened by concomitant use of benzoyl peroxide.

Preparations containing a combination of benzoyl peroxide and erythromycin (Benzamycin gel) and zinc acetate and erythromycin (Zineryt lotion) are available. Azelaic acid (15% cream, Skinoren) is of benefit in both inflammatory and comedonal acne. Azelaic acid works slowly and may irritate the skin.

MODERATE ACNE

In patients with moderate acne, topical treatment is aided by usage of systemic antibiotics and, in women, by hormonal therapy. For acne with a greater inflammatory component, it is prudent to also introduce benzoyl peroxide or topical antibiotics along with the topical retin-



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oids. Newer retinoids (e.g. adapalene) also have an anti-inflammatory action and are useful for treating papular pustular acne grades 1,2 and 3, according to the grading system of Plewig and Kligman.

Oral antibiotics

Antibiotics are the first choice for systemic oral therapy. The tetracyclines and erythromycin are most commonly used. Which tetracycline to choose? Doxycycline and minocycline are probably equally effective and both are effective in lower doses than tetracycline; 100-200 mg of doxycycline and minocycline daily versus 1-2 g daily of tetracycline. Doxycycline and minocycline absorption is less affected by dairy products than absorption of tetracycline. However, minocycline is not any longer considered very safe. Side effects are not common but when they occur, some are serious - hepatitis, acute eosinophilic pneumonia, lupus erythematosus, hepatorenal syndrome - all have been described. My choice is, at the moment, tetracycline and oxytetracycline 500 mg two to four times daily, taken between meals (with the starting dose most often 1.0 g daily).

Improvement in inflammatory lesions is usually noticed after 6 to 8 weeks and the dose may then be reduced. If there is no satisfactory effect within 4 to 6 months, another antibiotic may be tried or preferably isotretinoin prescribed. Six months is my limit to continue antibiotics. One has to have a time limit and not to linger on for many months.

Warn the patient about photosensitivity, particularly those on a dose above 1.0 g daily.

As there is growing evidence of resistance of P.acnes to erythromycin,

this antibiotic is now prescribed less frequently.

I use erythromycin only in patients who do not tolerate tetracyclines. In general, somewhat higher doses of erythromycin are required than tetracycline and the starting dose of 1.0 g daily is usually given for a longer period. Prescribe the stearinate salt rather than estolate as the latter not infrequently causes cholestatic hepatitis. Be aware of potentially severe toxic reactions when erythromycin is used concomitantly with carbamazepine, phenytoin, theophylline, warfarin, and digoxin.

Hormonal therapy

There is convincing evidence that androgenic stimulation of sebaceous glands is necessary for development of acne and the goal of hormonal therapy is to oppose the effect of androgens on the sebaceous glands. This can be accomplished by oestrogens and androgen receptor-blockers (cyproterone acetate)

Hormonal therapy can be effective in women with acne regardless of whether or not the serum androgens are abnormal. Hormonal therapy seems to work best in women whose acne started in adulthood, frequently flares premenstrually and consists of persistent inflammatory papules and nodules most commonly involving the lower face and neck. The combination of 2 mg cyproterone acetate and 35 ug ethinylloestradiol (Diane-35®) is an effective contraceptive and an appropriate choice for persistent inflammatory acne. Onset of action is slow and improvement may only be seen after three or four cycles. In recalcitrant cases, higher amounts of cyproterone acetate ranging from 10-50 mg per day may be given (for 10 to 15 days in the middle of each cycle). Duration of treatment depends on the

individual patient and treatment may be continued for several months. Side effects of hormonal therapy are common (menstrual abnormalities, breast tenderness and enlargement, fluid retention, mood swings, melasma).

Diane-35 is not the only oral contraceptive effective in moderate acne. Other low-dose oral contraceptives containing 20-30 ug of ethinylloestradiol and 50-200 ug of progestin-like agents have been found effective and safe.⁴ If oral antibiotics are used concomitantly with oral contraceptives the patient should be warned about the possible decreased efficacy of the oral contraceptive.


Severe acne

Isotretinoin (Roaccutane®) has revolutionised acne therapy. It is the only modality that affects all pathophysiological factors contributing to acne pathogenesis. It decreases sebum production and thus lowers the concentration of P. acnes, it inhibits comedogenesis and possesses anti-inflammatory action. Isotretinoin is the only drug that can cure acne, even the most severe nodulocystic type. It is a costly medication and has to be used correctly.

Who to treat with isotretinoin?

- Severe nodulocystic acne
- Moderate acne not responding after 4-5 months of oral antibiotics in adequate dose
- acne with marked scarring
- severe dysmorphophobia and depression resulting from acne

The standard dose is between 0.5 to 1.0 mg/kg/day. Doses higher than 1.0 mg/kg/day cause more adverse effects without real additional evidence of greater clearance.



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Being a lipid soluble compound, isotretinoin is better absorbed when administered with food.

At the moment, I usually do not start the treatment at doses higher than 0.5 mg/kg/day, increasing the dose if needed. Starting with this lower dose minimises and even often prevents flares that not infrequently accompany the inception of treatment.

The cumulative dose is of paramount importance, much more than the daily dose. The cumulative total dose of 120 to 150 mg/kg is required. The minimum of 120 mg/kg can be obtained by either giving 1.0 mg/kg/day for 4 months or a lower dose for a longer period of time.

I attempt to give every patient this 120 mg/kg minimum. Financial constraints do not always make this feasible.

Extensive clinical experience confirms that adherence to the adequate cumulative dose provides a near complete clearance after a single course of therapy and prevents relapses in the vast majority of patients.

There are small subsets of patients responding slower or having more frequent recurrences. Very young men with predominantly truncal lesions and women with hormonal dysfunction may require greater cumulative doses obtained by lengthening the treatment period. Repeated courses of isotretinoin can be instituted. There are no hard data on the long-term safety of multiple courses. However, long term sequelae were not observed even when patients had as many as five courses of treatment.⁵ Slow response is often observed in patients with macrocomedones.

Patients with macrocomedones are also prone to initial therapy flares. It is important to examine the skin prior to treatment for the presence of macrocomedones (macro - a comedo bigger than 1 mm in diameter, mainly an open comedo).

If macrocomedones are present, it is recommended to start with a low dose of 0.25 mg/kg/day and to increase the dose slowly. Macrocomedones can be removed with light cauterisation preceded by 90 to 120 minutes of topical anaesthetic. (EMLA). Side effects of isotretinoin, though numerous, are mostly trivial. Dryness of the face, lips, eyes and nares is experienced by all patients. In time these tend to lessen. Moisturisers should be used freely. Sunscreens are required throughout the treatment.

Teratogenicity of isotretinoin is well known and pregnancy must be avoided. A negative pregnancy test before prescribing isotretinoin is recommended. Sexually active women must use a reliable method of contraception during the treatment and for four weeks after its discontinuation.

There are three significant isotretinoin toxicities: triglyceride elevation, decreased night vision and pseudotumour cerebri. Mild elevation of triglycerides is common.

Patients showing marked rise in triglycerides at the 4 to 8 week visit should have triglyceride assessment done every month during their course of isotretinoin.

Decreased night vision does occur. Alert the patient to this symptom.

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Pseudotumour cerebri or benign intracranial hypertension may be caused not only by isotretinoin but also by tetracyclines. Concurrent use of tetracyclines and isotretinoin is not recommended.

Laboratory monitoring

The manufacturer advises frequent laboratory testing. Most physicians perform pretreatment baseline tests and another test at 4 to 8 weeks. If values are normal further tests are not done.

Which tests? The utility of lipid assessment is clear. The rationale behind liver function testing is not so obvious. Transient and mild elevation of liver enzymes occurs during isotretinoin intake while the more severe signs of liver toxicity are exceedingly rare. In South Africa, isotretinoin is not recommended for patients with porphyria variegata (not uncommon in teenagers of Afrikaner lineage) though little is known about the effect of retinoids on liver function in these patients.

Isotretinoids and depression

This is the topic of hectic recent debate. Depression is not rare in teenagers and the question arises whether it is related to isotretinoin. When significant depression occurs in patients on isotretinoin, the drug should be discontinued.

ACNE IN AFRICAN PATIENTS

Acne appears to be more or less equally prevalent among patients of African and European descent. However, the clinical presentation and course and, most im-

portantly, the long-term sequelae of acne can be different. In general, acne in Africans is milder, seldom with severe inflammatory, nodulocystic lesions, less often truncal.

Figure 4: Acne in an African patient. Mainly papular inflammatory lesions, postinflammatory hyperpigmentation

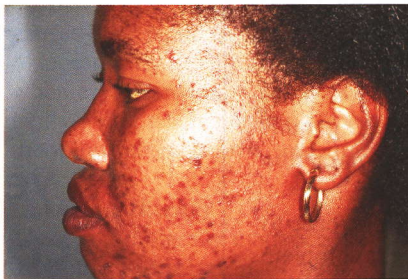


Figure 5: Acne in an African patient. Postinflammatory hyperpigmentation prevails



The most striking feature of acne in Africans is postinflammatory hyperpigmentation. These pigmentary changes often cause more concern than active acne lesions, and unlike European patients, Africans often seek dermatological care for this secondary problem. In general, the acne therapies effective in European patients are equally effec-

tive in African patients though few studies have been carried out in exclusively black populations.

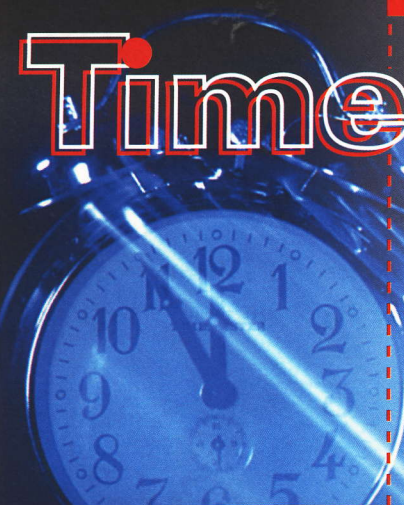
The ideal acne treatment for African patients should specifically target the inflammatory process resulting in hyperpigmentation. The recent study conducted in South Africa⁶ demonstrating that 0.1% adapalene gel was effective in reducing both the active lesions and acne associated hyperpigmentation requires confirmation on larger clinical material.

Figures 4 and 5 show the most common presentation of acne in African patients.

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