INDIAN J DERMATOL VENEREOL LEPROL 1987; 53 : 146-154

CONTINUING MEDICAL EDUCATION

MANAGEMENT OF ACNE VULGARIS

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Acne vulgaris predominantly affects adolescents and occurs universally. The peak incidence has been found at 14 years in girls and at 16 years in boys,[1] the age at which most people would like to look their best. Proper management, therefore, is of paramount importance to minimise the psychological effects of acne and to protect the facial skin from permanent scars.

A number of factors are known to modify acne. A greater incidence of acne is found in caucasoids than in the Japanese indicating a racial predisposition.[2] Hecht[3] suggested that genetic predisposition may be important and this is frequently seen in our patients too. In India, there is a general tendency of acne patients to become worse in summer and rainy season. In female subjects, acne tends to become noticeably worse in the premenstrual phase. Emotional stress[4] has also been incriminated for exacerbations. The role of diet in modifying acne is however controversial. Various items of diet suggested to aggravate acne include carbohydrates, fats, chocolates, iodides.[5] The fact however, is that the sebaceous gland is a secretory rather than an excretory gland. The dietary fat or serum lipids are therefore not likely to effect the secretion of lipids by the sebaceous gland. Use of cosmetics is known to aggravate acne because of the presence of comedogenic agents like lanolin, petrolatum etc.[5a]

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Pathogenesis of acne

Acne vulgaris is a disease of the pilosebaceous units. The major factors believed to be responsible for the causation of acne are, (1) Enhanced sebum production, (2) Obstruction of the pilosebaceous canal, (3) Increased bacterial colonisation of the pilosebaceous follicles, and (4) Biochemical alterations in the skin surface lipids.

1. Enhanced sebum production : Studies of large populations have indicated a direct correlation between the rate of sebum excretion and acne.[6] There is ample evidence that the sebaceous gland activity, both in man and experimental animals is androgen mediated.[7] What however still remains controversial is whether it is an increased circulating androgen which is responsible for the increased sebum secretion[8] or it is a localised increase in the tissue-active androgen, 5 alpha-dihydrotestosterone which results in the increased sebum excretion rate.[9]

2. Obstruction of the pilosebaceous unit : Strauss and Kligman[10] demonstrated that most of the inflamed acne lesions have histological evidence of ductal hyperkeratinisation. Cunliffe and Blanc[11] on the other hand, found that many of the inflamed acne lesions had no histological evidence of hyperkeratinisation. Kligman[12] thought that obstruction of the pilosebaceous orifice occurs with keratin and begins in the infra-infundibulum. Dynamic studies have shown an increased rate of keratinisation in comedones as compared to the normal sebaceous follicles.[13] In addition, acne patients showed a decreased dehiscence of keratin.[14]

Factors responsible for these changes include intrinsic changes of the follicular epithelium about which little is known, and the comedogenic agents within the sebum itself of which squalene and certain free fatty acids are the most important.[12] Inflammatory changes follow either rupture of the pilosebaceous duct wall which liberates keratin and other irritant materials into the surrounding dermis, or the diffusion of lipids and bacterial products through the duct wall into the dermis. The type of clinical lesion will depend upon the level within the dermis, of the initial inflammatory reaction, and on the patient's cellular and humoral immune response.[12]

3. Bacterial colonisation of sebaceous follicles and biochemical alteration in the skin surface lipids. The free fatty acids present in the skin surface lipids are derived largely from the microbial lipolysis of the sebaceous gland triglycerides.[15] The organisms implicated include *Propionibacterium acnes*,[15] *Pityrosporum ovale*[16] and *Staphylococcus epidermidis*.[17] Though there is an increased number of these micro-organisms which may actually be secondary to the ductal hyperkeratinisation, more important are the various lipolytic bye-products produced by these organisms. The various acnegenic fractions which have been found to be increased in acne patients include squalene,[18] sebaleic acid,[19] wax and sterol esters.[18] In addition to the production of acnegenic bye-products from sebum, these organisms may induce inflammation by releasing their cytotoxins,[20] via activation of the complement pathways[21] and release of other exo-enzymes.

Treatment of acne vulgaris

A review of the management of acne can be unexpectedly complex, largely because of the multiplicity of treatments that have been tried and many of them empirically. Indeed the clinical cynic could well conclude that the confusing array of acne medicaments is merely a testimony to the general inadequacy of therapy. However, most dermatologists feel otherwise, and in most cases therapy is fairly gratifying. In this article an attempt will be made to relate therapy to the factors that are currently believed to be important in the pathogenesis of acne. It must be emphasised that the therapy needs to be individualised in every case, and the gains are often slow.

I. Treatment by reduction in sebum production

(a) Diet—There is a strong folk-lore surrounding the relationship of acne and diet. Of late the tendency of the practicing dermatologist is not to advise restriction of diet unless a particular patient is adamant about certain foods making his acne worse. It has been observed that restriction of certain food items does not make any significant difference in the management of acne.

(b) Estrogens and the contraceptive pill—Estrogens in adequate doses reduce sebum production in both males and females. This correlates with an improvement in acne.[22] Estrogens are known to inhibit androgen production;[22] these also act at the cellular level to suppress testosterone uptake and its subsequent metabolism to dihydrotestosterone.[23] These may also have a local anti-inflammatory effect.[22]

Estrogens are used either in the form of a contraceptive pill[22] (containing a non-androgenic progestin), or in combination with an anti-androgen. This form of therapy can be given only to the female patients particularly when other forms of therapy have failed. It is especially useful in women with a premenstrual aggravation of acne.[24] The risks of therapy are small except for the usual side effects of contraceptive pills but a few patients experience an initial aggravation of acne. The therapy needs to be continued for a minimum of 3-4 months before beneficial effects become apparent.[25]

Topical estrogens have also been found effective, but only in doses that are sufficient to produce systemic effects,[26] and hence have not been used extensively.

(c) **Anti-androgens** : The most logical treatment for acne seems to be the anti-androgens. These agents either inhibit the enzyme which converts testosterone to dihydrotestosterone or block uptake of androgen by the target cell.[27] These agents should be used only by female patients because in males, impotence and gynaecomastia are likely to occur. Cyproterone acetate has a peripheral action as well as an anti-gonadotrophic effect.[28] It is most frequently used along with ethinyl estradiol 50 μg given from day 5-25 of the menstrual cycle, in a dose of 100 mg daily from 5-14th day. This is called reversed sequential therapy and gives 80-90% results. Cimetidine acts peripherally and has to be used in a dose of 1.5 gm daily to be effective.[29] Spiranolactone decreases testosterone formation, increases conversion of testosterone to estradiol as well as decreases uptake of dihydrotestosterone by the cells. It is effective in a dose of 25-100 mg daily.[30] Contraception is essential in female patients.

Since anti-androgens act peripherally, it should be possible to devise a topical formulation which would act peripherally without systemic effects. However, despite several trials, so far no satisfactory agent has been found for topical use.[31]

(d) **Retinoids** : With the advent of retinoids, treatment of severe forms of acne has become less difficult. Isotretinoin effects the sebaceous glands predominantly. Its principle action is reduction in the sebum secretion[32] because of a reduction in the sebaceous gland size and an inhibition of cellular differentiation. It also reduces ductal hyperkeratinization and has anti-inflammatory and immunomodulatory effcets.

Because of their toxicity, the use of isotretinoin is restricted mainly to the nodulo-cystic variety and acne conglobata. Most studies have shown a 90-95% response within 16 weeks of therapy on a dose of 1 mg/kg/day for face lesions and 2 mg/kg/day for back lesions. The remissions may last as long as upto 38 months even after cessation of therapy. Patients who do not respond with the first course, may be given a second course after a gap of eight weeks.[33]

Toxicity of isotretinoin includes cheilitis (universal), exfoliation of the skin (60%), dryness of mucosae (30%) and mild alopecia (20%). More serious toxic effects are hepatotoxicity (10%)[34] and an elevation of serum triglycerides (70%).[35] Due to its teratogenic potential, contraception is mandatory in female subjects.[36] In view of their toxicity, retinoids need to be used judiciously with planned investigational studies in patients of acne not responding to other forms of treatment.

(e) **Corticosteroids** : There is very little place for the use of topical corticosteroids in the management of acne though inflammatory lesions often subside rapidly with topical corticosteroids. There may however, be an aggravation of acne following continued topical application of a potent fluorinated corticosteroid.[37]

Corticosteroids, systemically, in an initial dose of 20 mg prednisolone daily, have been reported to be beneficial in the severe forms of nodulo-cystic acne, when all other measures have failed.[38] This would need to be weaned off rapidly. Higher doses of corticosteroids are acnegenic. In female patients, a significant reduction in sebum secretion is seen following oral prednisolone in a dose of 20 mg per day. This reduction was interestingly not seen in males. It is, thus, possible to attribute some of the benefits of systemic corticosteroid therapy in acne, to a decrease in sebum production in females.[39] Other factors, like their anti-inflammatory effect must explain their favourable clinical response in males.

(f) **Miscellaneous modalities** : Two other compounds, 2-naphthol and poldine methyl

sulphate have been shown to reduce sebum production but have not found extensive use in acne because of their side effects.[54]

Superficial X-ray therapy and Grenz ray therapy frequently used in the past, are best abandoned for the management of acne,[40] especially with the availability of retinoids.

II. Treatment by reduction in obstruction of the pilosebaceous unit

For long, the physician has used peeling agents with a view to reduce the pilosebaceous obstruction.

(a) Ultraviolet light : In addition to its peeling effect, ultraviolet light induces a pigmentary camouflage, especially in the white skinned individuals. It also reduces the population of surface bacteria. It has been given over a 4-6 week course and found useful.[41]

(b) Sulphur : Despite recent evidence that elemental sulphur may in fact be harmful in acne,[42] sulphur continues to enjoy an important position in the management of acne. Sulphur has a keratolytic effect and a primary irritant effect causing peeling.[43] This effect is greatly enhanced by combination with salicylic acid.[43] Sulphur has been used in concentrations of 1-10% in various vehicles.

(c) Salicylic acid : Salicylic acid has a keratolytic, antiseptic and anti-inflammatory effect.[44] It has been used in a concentration of 1-4%, usually along with sulphur.

(d) Benzoyl peroxide : This is now a well established topical therapeutic agent in acne.[45] Benzoyl peroxide acts in various ways. By its oxidising potential, it reduces the bacterial count resulting in a decrease in the skin surface free fatty acid levels.[46] By acting as an oxidant on the disulphide bonds, it breaks the intercellular bridges resulting in dehiscence of keratin.[47] It also has a dermal primary irritant vascular response.[48] The action of benzoyl peroxide is enhanced by the addition of sulphur; this may be because benzoyl peroxide oxidises sulphur to pentathionic acid which is very effective.[49] It is used in concentrations of 5-10%. Incorporation into an alcoholic gel improves the delivery system and has been found effective even in severe acne.[50] It has been used along with sulphur as well as retinoic acid.

Benzoyl peroxide is generally tolerated well. Primary irritant reactions[45] and less frequently allergic sensitivity may decrease patient compliance. Rarely it causes bleaching of hair.[51]

(e) Vitamin A and retinoic acid therapy : Sporadic reports are available describing success with large doses of vitamin A for acne.[38] In addition to its well known effect on keratinisation, vitamin A may somehow modify either androgen production or its metabolism.[52]

Topical retinoic acid has been used in the therapy of acne for almost two decades. It affects both epidermal proliferation and differentiation. It increases the epithelial cell turnover in the pilosebaceous units and promotes dehiscence of keratin which would in normal circumstances lead to follicular obstruction.[53] It is used in concentrations of 0.025—0.1%, in a variety of vehicles. It has been found useful both in the non-inflammatory and the inflammatory lesions.[54] Retinoic acid usually produces a transient redness and scaling. The acne may appear to get worse initially and at least six weeks of therapy is necessary to judge improvement. Photoirritation is a rare side effect; pigmentation may be seen infrequently.

(f) Diuretic therapy : This form of therapy has been suggested for the management of premenstrual exacerbation but on the whole their use has been disappointing.[55]

III. Treatment by modification of skin microbes and surface lipid composition

There is no doubt that microbes and their enzymes are important in the pathogenesis of acne. A large number of chemotherapeutic agents have been used in the hope of modifying

either the skin microflora or by inhibiting the bacterial extracellular enzymes.

(a) Tetracyclines : Tetracyclines are known to be bacteriostatic for *P. acnes*[56] but the main effect of this group of drugs is on the extracellular lipases produced by *P. acnes*.[57] They also inhibit chemotaxis. It is now generally aecepted that long term, small dose therapy (250-500 mg daily) with one of the tetracyclines is one of the most effective methods of treating patients with moderately severe forms of acne.[58] This form of therapy is associated with very few side effects.[59] Dyspepsia, vaginal candidiasis, Gram negative folliculitis and diarrhoea are the known complications of long term tetracycline therapy. These should be avoided in patients with impaired renal function, and in pregnant women. Exacerbation of acne following tetracycline therapy has been observed in some patients[60] and is probably due to the eradication of normal flora in the pilosebaceous unit leading to an overgrowth of *Pityrosporum ovale*. The major risk of using subtherapeutic doses of tetracyclines over prolonged periods is the development of resistance of bacteria to the drug. Many dermatologists therefore, advise use of full therapeutic doses for short periods only. Other tetracyclines tried in acne vulgaris are doxycycline and minocycline with similar results.

Though topical tetracycline may be somewhat useful, topical erythromycin and clindamycin are considered superior.[61]

(b) Erythromycin : Erythromycin has been found effective in acne vulgaris.[38] Systemic erythromycin acts directly on *P. acnes*, and it has no effect on its lipases.[67] Gram negative folliculitis, intra-hepatic cholestasis and abdominal pain are main side effects of erythromycin therapy.[49]

Topically, erythromycin tends to affect both the metabolism as well as viability of *P. acnes*.[63] Erythromycin has been used topically in a concentration of 1-2% in a variety of vehicles. Inflammatory lesions respond better than non-inflammatory lesions.[62] Rappaport et al[64] have found topical erythromycin better than systemic low dosage tetracycline. Although development of resistant pathogenic organisms is a theoretical possibility with local antibiotic therapy, it does not seem to be a problem in actual practice.[65]

(c) Sulphonamides : Both sulphonamides and co-trimoxazole affect the viability of *P. acnes* with a resultant reduction in the free fatty acid levels in the skin surface.[66] These drugs have been found as effective as tetracyclines in the management of acne vulgaris.[67] Dapsone has also been tried successfully in the management of cystic acne.[68]

(d) Clindamycin : Lincomycin[69] and clindamycin[70] have been used systemically for the management of acne vulgaris. The clinical improvement is associated with a decrease in the skin surface fatty acids. The systemic use of these antibiotics may be associated with gastro-intestinal upsets and pseudomembranous colitis.

Clindamycin phosphate and hydrochloride topically have also been found very effective.[71] Used in a concentration of 1-2%, these agents reduce the skin surface free fatty acid levels mainly be inhibiting the *P. acnes* lipases. There use in India is limited because of non-availability.

(e) Ethyl lactate and sodium lactate : Lactic acid is released by the action of bacterial lipases and this inhibits further lipolysis of triglycerides due to lowering of the local pH.[72] Lactic acid in addition is an antibacterial agent and has an effect on the viability of *P. acnes* and other Gram positive and Gram negative bacteria. Moreover, it is a physiologic chemical (produced by the skin itself) and is, therefore, not likely to cause allergic or toxic effects. Local applications of 5% sodium lactate in a suitable vehicle have been reported to be effective in controlling

even inflammatory types of acne in 8-12 weeks. A thin layer of the solution applied as a cosmetic twice a day is adequate, though application of excessive amounts can lead to a reversible cauterizing effect on skin.[73]

(f) Azelaic acid : This saturated dicarboxylic acid has recently been used for therapy of acne. Preliminary observations indicate that it is a competitive inhibitor of oxidoreductases and also exerts a bacteriostatic effect on *P. acnes*. It inhibits the conversion of testosterone to 5 dihydrotestosterone. Used in a concentration of 15%, a significant improvement is seen in 4-8 weeks. Side effects include mild erythema and scaling.[74]

(g) Zinc : Topical zinc has been used for a considerable time for local therapy in the form of zinc sulphate. Role of oral zinc in the management of acne vulgaris has been controversial. Zinc, perhaps acts by stabilisation of the biological membranes and decreasing the activity of bacterial exoenzymes. Welmer et al[75] found oral zinc sulphate slightly effective in the management of pustular acne in a dose of 660 mg daily. There was a high incidence of gastrointestinal side effects.

(h) Others : Use of other antilipase agents like protamine sulphate is being studied.[76]

IV. Surgical measures in acne

Several surgical procedures are employed for the treatment of acne vulgaris.

(a) Comedone extraction : The extrusion of the follicular plug is of temporary benefit only. The open comedone can be removed by a comedone extractor, while the closed comedone requires puncturing before removal of the comedone can be achieved. Permanent eradication of the enlarged pore requires excision, but this invariably leaves a scar, and is, therefore, not recommended.

(b) Treatment of pustules and cysts : The pustules tend to heal rapidly if the contents are expressed, but this is generally not needed. Indolent cysts may sometimes require surgical opening followed by introduction of a saturated solution of trichloroacetic acid, which is to be rapidly diluted with alcohol. Some dermatologists recommend marsupilisation but the best results are found with the use of intralesional corticosteroids.

(c) Treatment of scarring : Scarring is common when the lesions are either comedones or cysts and may be either in the form of pits or hypertrophic scars.

Dermabrasion or planning has been found useful for broad-based flat pits. The response of 'ice pick' scars is less satisfactory. It is important to inform the patient that dermabrasion would at best reduce the scars, but it does not remove them completely. Since, there is a large element of psychic overlay inherent to this form of therapy, it is important to choose the patient carefully. As a rule, there is 50-70% improvement from planning, but often the patient is more satisfied than the surgeon. It should be avoided in patients with active lesions, as there may be a pustular exacerbation. One adequate planning gives better results than a number of inadequate procedures. Planning basically consists of removal of the superficial portion of the skin with a rapidly revolving brush. The entire face can be planned in 15-20 minutes, after application of a freezing agent like ethyl chloride or freon 114. The local dressing which is applied after the dermabrasion, is removed after 4-6 hours. There is mild bleeding and oozing for about 24 hours. The crust which forms is shed in 7-10 days when the patient can resume his work. The skin remains pink for 6-12 weeks, during which period the patient is asked to avoid sunshine and apply sunscreens to prevent hyperpigmentation.

Complications are infrequent and include haemorrhage, infection, erythema, milia formation and pigmentary changes. Sun sensitivity is common, especially in the immediate postoperative period.

Cosmetic chemosurgery using 30-50% trichloroacetic acid has been used for superficial acne scars with satisfactory results.

Cryosurgery is efficacious, both in active acne as well as in acne scars. The recent use of liquid nitrogen applied with a cryoroller has given good results. Application is followed by erythema, scaling and rarely blistering. The treatment is repeated at 1-4 weekly intervals till the desired results are obtained. The same technique is used with carbon dioxide. The simplest method is to use carbon dioxide snow mixed with acetone to form a slush. This is applied to the skin with a cotton applicator. Liquid nitrogen or nitrous oxide can be applied as a spray. Cryotherapy now forms the most efficacious method of treating acne scars.

Intradermal injections of collagen prepared from bovine sources, have been recently introduced to raise the depressed scars. Thirty days after an intradermal test for possible hypersensitivity, 0.5-2.0 ml of bovine collagen are injected at the site of each scar. Repeated treatments may be needed to obtain the best results. It is as yet too early to assess the efficacy of this method of treatment.

With the advent of the newer modalities of treatment, it is now easier to manage even patients with severe forms of acne and the distressing scars can be easily minimised.

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