Managing acne vulgaris effectively

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The management of acne is a gratifying experience. Available treatments are effective, relatively nontoxic and generally safe. However, there is no quick fix. Antibiotics, hormone therapies and topical therapies are maintenance treatments. Isotretinoin can induce remission, as can some of the newer physical modalities of lights, lasers and radiofrequency devices. Effective management of acne often requires using a combination of treatments that act on different parts of the pathogenic process of acne development.

The pathogenesis of acne is thought to be an interplay between a number of factors including hyperkeratinisation with occlusion of the follicular orifice; colonisation by pathogenic *Propionobacterium acnes* and inflammation; excess androgenic stimulation; and sebum hypersecretion.

Although no treatment affects only one of these processes exclusively, it is useful to group treatment by the target most affected. Combination therapy is often chosen in an attempt to provide additive therapeutic efficacy, taking from agents exerting their effects on different pathogenic factors. Choice of therapy often depends on the patient's age and pattern of the acne (*Table 1*).

Reducing hyperkeratinisation of the hair follicle

Early or mild acne is often comedonal or papulopustular with little inflammation. In this subgroup, the treating practitioner should choose agents that will unblock and sterilise the follicle.

Physical treatments

Manual extraction of impacted comedones by the treating practitioner or a beauty therapist once or twice at monthly intervals may be added to hasten resolution. Pharmacies also carry a range of self administered acrylate glue based material strips that may be used by the patient at home (this is not the same as picking at the spots by the patient, which carries the risk of scarring).

Keratolytic agents

Keratolytic agents are the most effective topical medications for comedonal and early acne targeting the abnormal occlusion of the follicular orifice. Agents include: retinoids, azelaic acid, and the alpha and beta-hydroxy acids (AHAs and BHAs).

Topical retinoids

Tretinoin (or all trans retinoic acid) is topical vitamin A acid. In Australia tretinoin sells under the trade names Retin A, Stieva A, and Retrieve. This is probably the most potent of the available keratolytic agents. Topical isotretinoin (Isotrex) is also available but is probably not as effective. Adapalene (Differin) has recently been introduced to the market and is thought to be less irritant. Azarotene (Zorac) has also just been released in Australia.

Tretinoin acts to normalise the turnover of follicular lining epithelial cells[1] causing expulsion of comedones and inhibiting further comedone formation.[2] Three aspects of tretinoin have limited its widespread use: skin irritation, sun sensitivity, and initial flaring of acne.

Topical retinoids produce skin dryness or dermatitis which patients find unpleasant. This can be minimised by starting the treatment slowly and building up over a few weeks, either by increasing the time tretinoin is on the skin before washing it off, or by using it every second night initially until the skin can be treated nightly. Another method is to start with a low concentration (0.025%) initially and increasing to 0.05% as and when tolerated. Simultaneous use of other irritating chemicals should be avoided.

Sun sensitivity from retinoids is really a photo-degradation of the tretinoin and the photoproducts induce the sensitivity. Night usage and the use of a sunscreen usually avoids this problem.

Approximately 3 weeks after starting topical retinoid therapy there is a breakout of acne and a 'clearing out' of follicles.[3] There is then a further delay of 2 months before the retinoids exert their maximal effect.[4]

Adapalene is a synthetic naphthoic acid derivative and has both comedolytic and anti-inflammatory activities.[5] It is probably equipotent to tretinoin in anti-acne activity.[5,6]

Azelaic acid

Azelaic acid is a naturally occurring dicarboxylic acid and is not related to other acne medications. Azelaic acid helps to normalise follicular hyperkeratinisation[2] and may also have a direct anti-inflammatory effect through inhibition of hydroxy and superoxide radical production by neutrophils. It also has antimicrobial effects, being bacteriostatic against *P. acnes*.[7] It is only available as a 15% gel (Finacea). It is reasonably tolerated clinically and may have similar efficacy to other topical medications.[8,9] Local itching and burning sensations are occasionally observed.

Alpha- and B-hydroxy acids

Alpha hydroxyacids occur naturally in sugar cane, fruits, and milk products. Most commonly glycolic, lactic, citric and gluconic acids are used. Alpha hydroxyacids cause stratum corneum desquamation[10] and have action as a comedolytic aiding the treatment of comedonal acne.[11] Examples of these agents include Elucent®, Glyderm®, and MD formulations®. They are only mildly effective as a home topical treatment and probably have more efficacy as an in office peeling agent.[7] Beta hydroxyacids (salicylic acid) are comedolytic agents with a long history of dermatological use in acne which seem to be making a resurgence both in topical applications (eg. Acnederm®, Clearasil Acne Treatment/Facewash®, Salact®) and office procedures.

Reducing *P. acnes*

A change in the severity of acne occurs when the noninflammatory comedone develops into an inflammatory papule or pustule. This usually signifies the presence of *P. acnes*. Traditional treatments in the inflammatory phase are topical and systemic antibiotics acting as both antimicrobial and anti-inflammatory agents.

Benzoyl peroxide

Benzoyl peroxide is a potent bactericidal drug available as an over-the-counter preparation. Trade examples include Panoxyl®, Benoxyl®, BenzacAC®, and Brevoxyl®. This preparation is starting to appear in cleansers and combination therapies with topical antibiotics in an effort to both increase efficacy and limit antibiotic resistance.[12] Concentrations of 2.5–10.0% may reduce comedones, but its primary role seems to be its ability to sterilise the follicle by combating *P. acnes* therefore effectively reducing acne.[13] The metabolic by-product benzoic acid is harmless, however the parent compound commonly causes dry skin and occasionally allergy. It inactivates topical retinoic acid when used concurrently and may cause skin bleaching.

Topical antibiotics

The topical antibiotics clindamycin and erythromycin are available as topical hydroalcoholic solutions (Clindatech®) and hydrophilic gels (Eryacne®). These agents reduce numbers of *P. acnes*[14] and may also be anti-inflammatory agents by inhibiting neutrophil chemotaxis. Topical erythromycin and clindamycin appear equivalent in efficacy, but probably mixtures of these agents with benzoyl peroxide are better than either alone[15] and may help in decreasing the incidence of antibiotic resistance. Recently a combined agent with clindamycin and benzoyl peroxide has become available in Australia (Duac). Most often therapies are combined in an attempt to approach the problem from more than one vantage point, so a topical antibiotic or benzoyl peroxide is used in the morning and a keratolytic agent applied at night

Oral antibiotics

Oral therapy is indicated for moderate to severe and widespread forms of acne, particularly those patients who are at risk of scarring. Effective systemic therapies for acne include: tetracyclines (including its relatives minocycline and doxycycline), erythromycin and trimethoprim alone or in combination with sulfamethoxazole. Full dose antibiotic treatment should be given until the acne is under control and then may be pulled back to a lower maintenance dose. Each oral medication has known side effects. All oral antibiotics predispose to candida infections, particularly vaginitis. Tetracyclines, especially doxycycline (but less so minocycline) induce phototoxicity. Minocycline produces a dose related 'vertigo-like'

Table 1. Acne patterns, demographics and treatment

Typical age	Usual patient acne subtype	Likely treatment	Issues
Peripubertal, teenage, young adult	Comedonal disease	Comedolytics (adapalene, retinoic acid, AHAs and BHAs), benzoyl peroxide and azelaic acid, light or laser treatments	Young age, compliance with probable long term treatment, avoidance of comedogenic products
Teenage, young adult	Facial and truncal papulopustular disease	Topical therapies (antibiotics, retinoids, benzoyl peroxide), long term antibiotics, hormone therapy (OCP, antiandrogens), blue light and photodynamic therapy	Relative ineffectiveness of topical therapy Long term nature of therapy (alternative may be light/laser based therapies)
Older teenager	Nodulocystic disease	Long term antibiotics, isotretinoin	Unpredictable adverse reactions to antibiotics, predictable adverse reactions to isotretinoin
Women	Acne tarda papulopustular occasionally nodulocystic along jawline and neck	Topical antibiotics, hormone therapy, light and laser treatments	Hormone therapy in child bearing age group or women in their 30s

dizziness which patients seem to acclimatise to over time as well as serum sickness-like reactions, drug induced lupus, and drug induced hepatitis. Although tetracycline needs an empty stomach for absorption, the opposite is true for doxycycline and minocycline. Erythromycin often causes gastrointestinal distress and the use of trimethoprim-sulfamethoxazole may be associated with drug eruptions and Stephens-Johnson syndrome. Long term use of antibiotics may induce hepatotoxicity,[16] therefore periodic monitoring of blood chemistry is advisable.

Reducing excess androgen production

Oral contraceptives have been particularly useful in the treatment of acne since the advent of combination contraception where the progestin is actively anti-androgenic. Cyproterone acetate is the most common agent added to ethinyloestradiol (Diane®, Brenda®, Estelle®). In these pills, the active oral contraceptive tablets contain 35 µg of ethinyloestradiol and 2 mg of cyproterone acetate. Additional cyproterone acetate (10–50 mg) may be added, usually on each of the first 10 active oral contraceptive days each month. Other useful oral contraceptives in the control of acne include desogestrel in combination with ethinyloestradiol,[17,18] (Marvelon®), and drosperinone with ethinyloestradiol (Yasmin®). Similar comments pertain to contraceptives containing norgestimate/ethinyloestradiol.[19] An alternative drug for treating hormonal acne in women is spironolactone, which can be combined with oral contraceptive therapy. Although data is not strong, it is probably a reasonable drug for acne in women protected from pregnancy.[20,21] Other anti-androgenic therapies that may prove useful include flutamide, finasteride, and gonadotropin releasing hormone agonists.[22–24]

Reducing sebum hypersecretion

Isotretinoin

Isotretinoin is the treatment of choice for recalcitrant nodulocystic acne. Isotretinoin rapidly limits ongoing acne activity and therefore the possibility of scarring. It suppresses sebaceous gland production of sebum to pre-pubertal levels.[25] As the sebum is decreased, so is the ability to sustain *P. acnes*, therefore their numbers are significantly reduced. It also decreases intrafollicular keratinisation by promoting shedding of these lining keratinocytes. This agent induces long term remission in about 40% of patients, another 40% will get more minor acne not requiring a further course of isotretinoin, and the remaining 20% will need a further course. This is based on giving the patient about 1 mg/kg of their body weight per day until they have reached a total amount of drug equivalent to 100 mg/kg of body weight.[26] Currently most dermatologists will use slightly higher than this aiming at 120–150 mg/kg total dose.

Undesired effects from isotretinoin are seen in most patients but generally subside within 1 month of ceasing therapy. Skin dryness, mucous membranes, and dry cracked lips (retinoid cheilitis) are seen in over 90% of cases at therapeutic doses. Patches of a discoid type of eczema, so-called retinoid dermatitis, occur commonly, typically on the dorsal aspects of the upper limb. Moisturisers or low strength topical corticosteroid ointments are usually sufficient for treatment. Dry eyes and blepharoconjuctivitis are common (making contact lens wearing difficult) and commonly require artificial tears. Drying out of the anterior nares may cause epistaxis. Skin fragility and increased sun sensitivity are frequently reported. Myalgias and arthralgias are seen in about one in 6 patients and seem increased with increased exercise. Hair shedding is seen in 10% of patients, but is usually only temporary. Flaring or worsening of acne is quite common in the first few weeks of therapy. Using oral antibiotics such as sulfamethoxazole-trimethoprim or erythromycin or cephalosporin with or without concurrent oral corticosteroids for the first 1–2 months of treatment with a gradual increase in the isotretinoin dose usually allows successful introduction in difficult cases with very inflammatory disease. A painful, severe exacerbation of cystic acne with exuberant granulation tissue and scarring (acne fulminans) may rarely occur.[27]

Psychological depression and suicide in patients taking isotretinoin has recently been suggested to be a greater problem than previously recognised, however this awaits definitive assessment.[28,29] This has to be balanced against the increase in wellbeing and self esteem seen after successful acne resolution.

Some drugs are contraindicated for concomitant use with isotretinoin. Tetracyclines and oral vitamin A should be avoided as they induce an increased risk of pseudotumor cerebri, a rare side effect of isotretinoin.[30]

Teratogenicity is isotretinoin's Achilles heel. It requires continued vigilance, strict monitoring, careful patient selection, and adequate contraceptive counselling. Isotretinoin is not mutagenic and pregnancy is safe 1 month after cessation. Patients should not donate blood during isotretinoin therapy due to its teratogenicity.

Elevation of triglycerides with increases of about 50% within 2–3 months is common, however cholesterol is less affected.[31] Isotretinoin has been linked with premature closure of the epiphyses of long bones in laboratory animals.[32] For this reason, some physicians prefer to reserve its use for patients past their growth spurt.

Light and laser treatment

Recently, blue and longer wave visible light have been found to be useful in the treatment of acne by stimulating the production of natural porphyrins in *P. acnes* and the sebaceous glands by inducing unstable and destructive compounds in target cells.[33] This effect may be augmented by the use of exogenous applied porphyrins.[34] Many different laser and light systems have been suggested to be useful in the treatment of acne,[35–37] even after as little as a single treatment.

The second method involves a general dermal heating inducing a secondary destruction or injury of the sebaceous glands. Many technologies including lasers such as the 1320 nm, 1450 nm and 1540 nm diode lasers, as well as radiofrequency devices, are now available. All these machines protect the epidermis by cooling while producing general upper dermal heating inducing a semiselective injury to the sebaceous glands in this region. These treatments appear to be a useful adjunct to other modes of acne therapy in patients who:

- have failed medical management
- prefer to avoid long term drug treatment, or
- have concerns about, or experience significant side effects of isotretinoin and other medications.

Conclusion

The natural history and epidemiology of acne vulgaris usually relates to adolescence with a period of finite nuisance sometimes requiring

no treatment or topical therapies only. However, quite often this period is severe, resulting in life long scarring or prolonged disease. Sometimes acne may appear later in life when therapeutic options are somewhat more limited. We require therapies that are safe, effective and that offer long term benefit. At present we have somewhat limited options for treatment after topical therapy has ceased to be effective or if the acne is widespread. These include systemic antibiotics; hormone therapy; isotretinoin in certain circumstances; and most recently and possibly most excitingly, lasers, lights and radiofrequency devices that may be ushering a useful new alternative therapy.

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