CLINICAL Dermatology

Everything you need to know about acne vulgaris

Acne can significantly affect the physical and psychological health of patients

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Acne is a common skin disorder affecting about 85% of teenagers, but can occur in most age groups and can persist into adulthood, with the prevalence of acne in adult females being about 12%.[2]

No mortality is associated with acne, but there is often significant physical and psychological morbidity, including permanent scarring, poor self-image, depression and anxiety.

Acne is a multifactorial inflammatory disease affecting the pilosebaceous units of the skin. Key pathogenic factors with important roles in acne development include:

I. follicular hyperkeratinisation (subsequent follicular plugging and clinical manifestation as comedones),
II. microbial colonisation with *Propionibacterium acnes*,
III. hyperseborrhoea (where there is a significantly greater number of lobules per gland compared with unaffected individuals), and
IV. complex inflammatory mechanisms involving innate and acquired immune systems.

Neuroendocrine regulatory mechanisms, diet, and genetic and non-genetic factors may also contribute to the multifactorial process of acne pathogenesis.

PREDISPOSING FACTORS

Genetics

The exact role of genetic predisposition in the multifactorial pathogenesis of acne remains unknown. The number, size and activity of sebaceous glands are inherited. The concordance rate for the prevalence and severity of acne among identical twins is extremely high.

The tendency to develop substantial acne (including the nodulocystic variant) runs in families, and an association between moderate to severe acne and a family history of acne has been observed in studies.[3]

Genome-wide association studies and other methods demonstrate genes encoding components of the tumour growth factor-β pathway, other inflammatory mediators and regulators of androgen metabolism may be linked to acne.[4]

Diet

Emerging evidence suggests that high glycaemic index diets may be associated with acne, potentially through stimulation of the IGF-1 receptors resulting in sebogenesis and follicular hyperkeratinisation.

In 2007, a randomised controlled trial with 23 Australian males 15 to 25 years of age examined the impact of a low glycaemic diet on acne.[5] Subjects randomised to follow a low glycaemic load diet had significant improvement in acne severity, a significant reduction in weight and body mass index (BMI), a significant decrease in free androgen index and improved insulin sensitivity at the end of 12 weeks.

Several observational studies in various ethnic groups have found that milk intake, especially skim milk (possibly related to the presence of 5α-pregnanedione, which is a precursor of 5α-DHT in milk and to an increase in IGF-1), may be positively associated with acne prevalence and severity.

Acne exacerbation with the use of whey protein supplements for body building has been reported also.

ASSESSMENT AND CLASSIFICATION

Methods of measuring the severity of acne continue to be a challenge. To date, there is no standardised acne assessment or classification system. Assessment methods for acne severity include simple grading based on clinical examination, lesion counting and the use of complicated instruments including photography, fluorescent photography, polarised light photography, video microscopy and measurement of sebum production.

The two commonly used measures are grading and lesion counting.

Grading is a subjective method, involving determination of acne severity based on observing the dominant lesions, evaluating the presence or absence of inflammation and estimating the extent of involvement.

Lesion counting involves recording the number of each type of acne lesion and determining the overall severity.

Grading is subjective, simple and quick but less accurate, and grading methods are used in clinical settings; lesion counting is objective, more accurate but time consuming and is used in clinical trials. Examples of commonly used acne grading systems include the Leeds technique[6] and the global acne grading system.[7]

ENDOCRINOLOGIC TESTING

Endocrinologic evaluation is indicated only in selected cases, as most acne patients will have normal hormone levels. Testing is indicated when patients present with clinical features or a history of hyperandrogenism.

In prepubertal children, these features may include acne, early onset body odour, axillary or pubic hair, accelerated growth, advanced bone age and genital maturation.

Growth charts and a hand film for bone age are good screening tools before specific hormonal testing.

In postpubertal females, infrequent menses, hirsutism, androgenetic alopecia, infertility, polycystic ovaries, clitoromegaly and truncal obesity warrant further hormonal testing.

TREATMENT
Topical therapies

Topical therapies are the main treatment for mild to moderate acne. Commonly used topical acne therapies including benzyl peroxide, antibiotics, retinoids and combination therapies.

Benzyl peroxide is an antibacterial agent that kills *P acnes* through the release of free oxygen radicals, and is mildly comedolytic. No resistance to this agent has been reported. The addition of benzyl peroxide to antibiotic therapy may improve results and reduce resistance development.

Benzyl peroxide is available as topical washes, foams, creams, or gels, and can be used as leave-on or wash-off agents. Treatment strengths vary from 2.5% to 10%. Benzyl peroxide therapy can be limited by concentration-dependent irritation, staining and bleaching of fabric, and, in rare cases, contact allergy. Lower concentrations (2.5%-5%), water-based and wash-off agents may be better tolerated in patients with more sensitive skin.

Topical antibiotics for acne accumulate in the follicle and may work through anti-inflammatory mechanisms and via antibacterial effects. The efficacy of these agents is enhanced when used in combination with benzyl peroxide and this also decreases development of resistant bacterial strains.

Clindamycin 1% lotion is currently the preferred topical antibiotic for acne. Topical erythromycin in 2% concentration (currently available only via compounding pharmacies) is also available but has reduced efficacy in comparison with clindamycin because of resistance of cutaneous Staphylococci and *P acnes*. Tolerance of these agents is usually excellent.

Topical retinoids are vitamin A derivatives. They are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedone lesion and are anti-inflammatory.

Topical retinoids include tretinoin (0.025%-0.1% in cream and gel), adapalene (0.1% in cream and gel) and tazarotene (0.05% cream). Topical retinoids exert their therapeutic effects by binding to the retinoic acid receptors (RAR). Retinoic acid receptors have three isoforms: RAR-alpha, RAR-beta and RAR-gamma. Each topical retinoid binds to a different set of retinoic acid receptors – tretinoin to alpha, beta and gamma; tazarotene and adapalene, selectively, to beta and gamma; and the new preparation trifarotene (see section below for more information) selectively to RAR-gamma – hence conferring differences in efficacy, activity and tolerability.

Topical retinoids enhance any topical acne regime and enable maintenance of clearance after discontinuation of oral therapy. However, their use may be limited by side effects, including dryness, peeling, erythema and irritation, and these can be mitigated by reduced application frequency. Some formulations of tretinoin are not photostable and should be applied in the evening. Topical retinoids are associated with an increased risk of photosensitivity; concurrent daily sunscreen can be used to reduce the risk of sunburn.

> Topical and systemic retinoids are contraindicated in pregnancy due to teratogenicity.

New topical retinoid treatment

Trifarotene 0.005% cream was approved by the TGA for treatment of acne vulgaris of the face and/or the trunk in patients from 12 years of age and older. Trifarotene selectively targets RAR-gamma, which is the most common RAR found in the skin and is the first topical treatment studied and proven to treat both facial and truncal acne. [8]

Topical and systemic retinoids are contraindicated in pregnancy due to teratogenicity.

Other topical treatments

Azelaic acid 20% is mildly effective as a comedolytic, antibacterial and anti-inflammatory agent. The agent has been used in patients with sensitive skin or of Fitzpatrick skin types IV or greater because of the lightening effect of the product on dyspigmentation. Azelaic acid is category B in pregnancy.

Nicotinamide (or niacinamide) is the water-soluble, amide isotype of vitamin B3. Topical nicotinamide has anti-inflammatory action and reduces sebum production — both properties are important in acne control. Clinical studies have reported that nicotinamide gel was comparable in efficacy to both topical 4% erythromycin[9] and 1% clindamycin[10] in reduction of acne and seborrhoea.

Oral treatments

Moderate to severe inflammatory acne is often treated with oral tetracycline derivates, especially doxycycline and minocycline, and less often macrolides such as erythromycin. A primary mechanism of action of these medicates is *P. acnes* growth suppression, thereby reducing bacteria-mediated inflammation. These antibiotics also possess intrinsic anti-inflammatory properties.

Hormonal therapy is an established second-line treatment for female patients with acne and can be effective, irrespective of whether or not the serum androgen levels are abnormal.

Combination oral contraceptive pills (COCs) containing both oestrogen and progesterone components reduce both inflammatory and comedonal lesions in acne. Four COCs are approved by the FDA for acne treatment including ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone acetate/ferrous fumarate, ethinyl estradiol/drospirenone and ethinyl estradiol/drospirenone/levomefolate. The mechanism of action of COCs in acne treatment is based on their antiandrogenic properties.

Spironolactone functions as both androgen receptor blocker and an inhibitor of 5α-reductase. It has been shown to reduce sebum production and improve acne in doses of 50-100mg twice daily. Side effects are dose-related and include menstrual period irregularity, breast tenderness, headache and fatigue. Hyperkalaemia is rare. As an antiandrogen, it carries a risk of feminisation of a male fetus if a pregnant woman takes this medication. Side effects can be minimised if treatment is initiated at a low dose of 25 to 50mg daily. Effective maintenance doses range from 25 to 200mg a day. A clinical response may take up to three months.

Oral isotretinoin was initially FDA approved for patients with severe, nodulocystic acne refractory to treatment, including oral antibiotics.

Over time, other forms of acne, including acne that is unresponsive to other therapy (including oral antibiotics) and or acne resulting in scarring, have been shown to benefit from oral isotretinoin treatment. Isotretinoin is highly effective in acne treatment because it combats all four key pathogenic factors responsible for acne.

Isotretinoin should be taken with a fatty meal to increase gastrointestinal absorption. Often, a lower dose is started during the first month of treatment to prevent an initial acne flare and allow the patient to adjust to dose-dependent side effects.

While the more traditional dose of 0.5 to 1mg/kg per day for four months to a cumulative dose of 120-150mg/kg per day has been used for a long time, review of literature (11, 12) suggests a lower daily dose of 10-20mg/day for up to 12 months may be used in acne management as the lower daily dose would avoid most of the adverse effects of standard-dose isotretinoin, including isotretinoin-induced flare of acne and dryness.

However, tetratogenicity remains a concern, irrespective the dose.

Subsets of patients who are less likely to respond to isotretinoin and/or more likely to require multiple or a longer course of treatment include adolescents under 16 years of age who have nodulocystic acne, and patients with endocrine abnormalities.

Surgical treatment

Comedo extraction can work in conjunction with topical comedolytic agents to help improve therapeutic responsiveness and the cosmetic appearance of acne. This can be performed with a comedo extractor or nicking the surface of a closed comedo with an 18-gauge needle. Comedo extraction should not be performed on inflamed comedones or pustules because of the risk of scarring. Gentle electrocautery and electrofulguration may also be an effective treatment for comedones.

Intralesional injection of corticosteroid (triamcinolone acetonide 2-5mg/ml) can provide quick therapeutic improvement for deep, inflamed acne nodules and cysts. However, larger cystic lesions may require incision and drainage prior to injection. The risks of corticosteroid injections include hypopigmentation (especially in darker-skin individuals), skin atrophy, telangiectasias and yellow-white dermal deposits of the medication.

Photodynamic therapy using topical 5-aminolevulinic acid with different light sources have also been used to treat acne.

INDICATIONS FOR REFERRAL

These include:

- Moderate to severe acne (such as nodulocystic/widespread acne) or scarring or fulminant (acute robust onset) acne
- When oral isotretinoin is being considered
- When there is lack of satisfactory response to previous treatment after a reasonable amount of time (usually three months)
- Patients with significant, associated psychological distress.

These patients should be referred to dermatologists for further assessment.

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