Dermatology

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Acne

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Clinical features

The clinical features of acne are a cluster of signs related to distended, inflamed or scarred pilosebaceous units. The distended units include both closed and open comedones, whiteheads and blackheads, which have expanded orifices containing melanotic keratin. The inflamed lesions are pustules, papules, nodules and cysts, but post-inflammatory lesions also contribute importantly to the appearance of acne, especially when there is hyperpigmentation. Scarring can be superficial or deep (ice-pick) atrophic scars, and hypertrophic scars are common on the upper trunk. In acne conglobata, there are extensive nodular, cystic and suppurative lesions.

The overall appearance of acne in an individual is due to the combination of these various lesions (Fig 1). Acne is most common on the face, the back and sometimes the chest. Conditions to be distinguished include rosacea in an older age group, characterised by diffuse facial erythema and teleangiectasia with papulopustules but no comedones. Pityrosporum yeasts can produce an acneiform folliculitis on the back, for which itch, and again the absence of comedones, are diagnostic clues.

Prevalence and severity

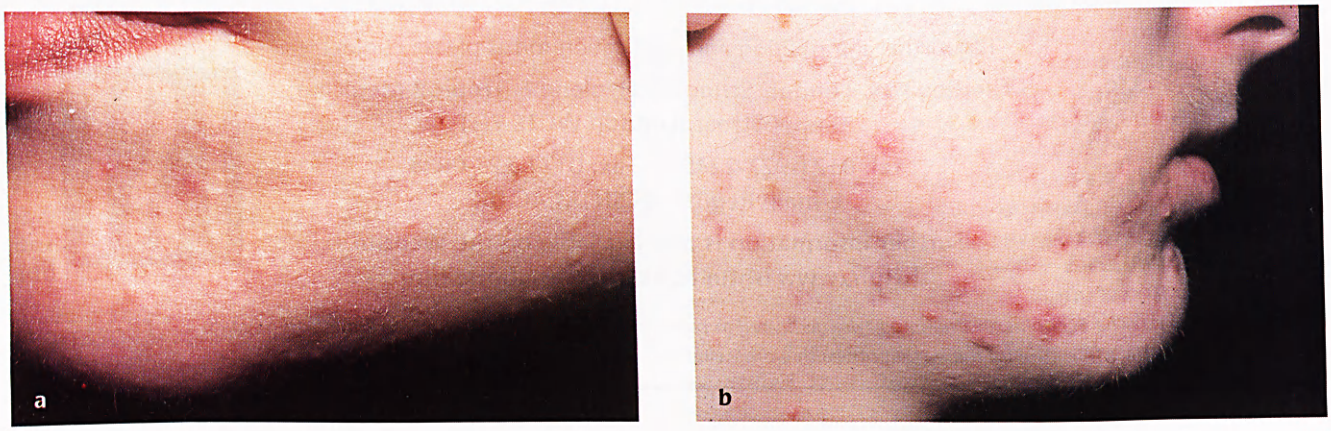
A degree of acne is almost universal in adolescence. Clinical acne occurs in 35–40% of teenagers[1], but its prevalence may be falling with adequate treatment. The worst cases of acne are usually in men. A few patients, mainly women, still have mild chronic acne in their 30s and 40s[2], and there is an infantile form, more common in boys (Fig 2).

Severity varies enormously; it can be assessed either by individual lesion counts by area, or by global scores by experienced observers[3]. These measurements are useful in clinical trials, but of questionable relevance to the sufferer. Acne, a disease in a sensitive site at a sensitive age, is a disorder where subjectivity matters. Methods of assessing the consequent disability have been developed[4].

Complications

Scarring, physical and psychological, are the most severe consequences of the lesions of acne. Acne is common in unemployed young people, probably as a consequence of their feelings of unattractiveness and lack of confidence[5]. Explosive exacerba-

Figure 1. The typical clinical presentation of acne: a mixture of comedones, inflammatory pustules, papules and post-inflammatory lesions: **(a)** predominantly comedones; **(b)** predominantly inflammatory lesions.



tion of acne (acne fulminans) may be accompanied by systemic features, fever and arthropathy. The most extreme variant of this process has recently been given the poetic acronym SAPHO: synovitis, acne, pustulosis, hyperostosis and osteomyelitis[6].

Pathogenesis

The principal pathogenic factors in acne are increased sebum excretion, hyperkeratosis of the sebaceous duct, and overgrowth of *Propionibacterium acnes*[7]. Adolescent acne begins at puberty with the dramatic increase in sebaceous gland activity. Severity correlates with the sebum excretion rate[8], but acne improves with age despite continuing high sebum excretion. Hyperkeratosis of the pilosebaceous ducts, in part under hormonal influence, probably leads to stasis and bacterial overgrowth, but bacterial products may contribute. The pathogenic relationship between these factors in triggering inflammation has not been fully unravelled. The development of individual inflammatory lesions may involve a variety of innate and acquired immunological mechanisms[9].

Microbiology

P. acnes is the commonest and most significant organism found in the lesions of acne. It is a normal skin surface commensal whose pathogenic potential may reside in its ability to hydrolyse sebum triglycerides to free fatty acids, or to induce pro-inflammatory cytokines under certain conditions[9]. However, Gram-negative infection may occur in patients on long-term antibiotic treatment for acne, causing sudden deterioration.

Genetic influences

A family history of acne is more common in patients than controls, and there is a higher concordance both of acne and of sebum excretion rates in identical than in non-identical twins[10], but the nature of the implied genetic factors is obscure. Acne is seen in disorders which produce hyperandrogenism, and acne conglobata may be found in XYY males[11]. Severe acne may be associated with familial hidradenitis suppurativa[12]. Apert's syndrome (acrocephalosyndactyly type I), which includes acne of unusual extent, has recently been found to be due to mutations in fibroblast growth factor receptor type 2[13]. The relevance of these syndromes to everyday acne is uncertain.

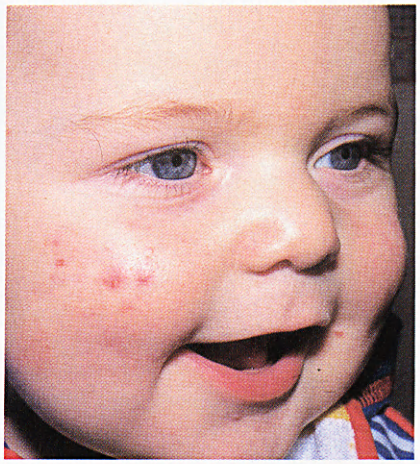


Figure 2. Infantile acne.

Hormonal influences

The pubertal onset of acne in both sexes is mainly due to androgens, and tumour-derived or exogenous androgens can trigger acne. Men with acne have normal plasma testosterone but, as a group, women with acne have slightly higher levels of circulating free testosterone than those without. Acne, without other evidence of hyperandrogenism, is rarely due to virilising tumours, and is not always found in androgenic syndromes such as polycystic ovary. One possible determinant of variation in pilosebaceous response to androgens is the activity of follicular 5-alpha-reductase, which converts testosterone into dihydrotestosterone[14]. There may be a premenstrual flare in acne severity.

Chemicals and drugs

Comedogenic chemicals may be found in mineral oils, cosmetics and pomades. Some chlorinated hydrocarbons can provoke chloracne, a

Key Points

- The clinical signs of acne are a mixture of dilated pilosebaceous units and inflammatory lesions
- Mild acne is almost universal in adolescence, but the disease may persist into middle age. Severe acne can produce extensive scarring
- The development of acne depends on the pubertal increase in sebum excretion and ductal hypercornification, but products of bacteria, notably *Propionibacterium acnes*, and host inflammatory responses also play a role in pathogenesis of the lesions
- Topical antibacterial and keratolytic agents, including retinoids, are effective in many cases. With oral or topical antibiotics, they are the mainstay of treatment of moderate acne
- Antibiotic resistance in *P. acnes* is an emerging problem
- Oral isotretinoin is a potent suppressor of sebum excretion, and an invaluable agent in the management of severe acne. Its side effects include embryopathy. In the UK, its prescription for acne is restricted to consultant dermatologists

chronic syndrome in which extensive comedones are accompanied by a range of systemic features[15]. Among the drugs reported to exacerbate acne, lithium is interesting because it also exacerbates psoriasis and other squamous disorders[16]. Oral corticosteroids, including inhaled steroids given for asthma, are associated with a superficial papular and pustular acneiform rash.

Management

Simple measures

Diet, including chocolate, is irrelevant to acne[17]. Avoidance of factors such as comedogenic make-up is important. Acne usually improves in the sun, but ultraviolet phototherapy is not reliable in reproducing this effect.

Topical agents

Most prescribed topical treatments for acne are either antimicrobial or keratolytic. Benzyl peroxide, a bleach, is antibacterial and is widely used for mild acne. Retinoids such as tretinoin (all-trans retinoic acid), isotretinoin (13-cis retinoic acid), or the new retinoid analogue adapalene[18], act on ductal hyperkeratosis, as do salicylic acid and azaleic acid. Topical nicotinamide appears to be effective through an anti-inflammatory mechanism[19]. Most of these agents are irritant, and individual tolerance needs to be established for optimum benefit. Topical antibiotics, for example, tetracycline, clindamycin and erythromycin, are effective in mild to moderate acne. Erythromycin has been combined with zinc or benzyl peroxide with the aim of increasing efficacy.

Systemic therapy

Oral antibiotics, taken in a course of six or more months, are the mainstay of management of moderate to severe acne, and may be combined with topical agents. Tetracyclines (1 g/day) are cheapest, but there can be poor compliance with correct timing before meals and twice-daily dosage in the prime acne age group. Once-daily tetracyclines, such as lymecycline, doxycycline or minocycline, are more expensive but reduce these problems. With minocycline, the rare occurrence of a reversible lupus-like arthropathy or of hepatitis has recently been highlighted[20]. Erythromycin is a valuable alternative, and other antibiotics such as co-trimoxazole, trimethoprim or even clofazimine have been used. Antibiotic resistance in *P. acnes* is increasing, but resistance to minocycline seems to be least common[21].

In women, anti-androgen therapy can be considered. Cyproterone acetate (2 mg) with ethinyl oestradiol (35 µg) is licensed for acne in the UK; it is packaged and functions as a contraceptive pill (Dianette). Oral corticosteroids, in combination with antibiotics, may reduce scarring in acne fulminans.

Oral retinoids

The only oral retinoid currently licensed for acne is isotretinoin (13-cis retinoic acid). This drug has a profound effect in shrinking sebaceous glands and reducing sebum excretion

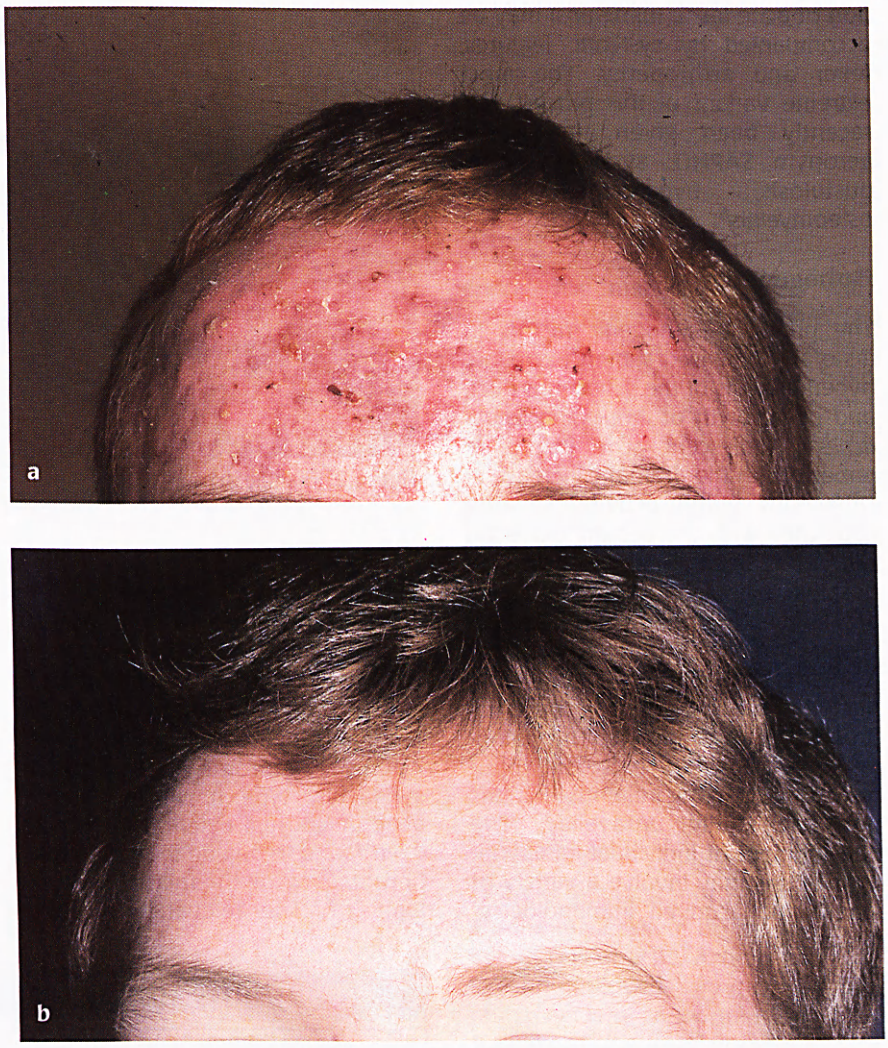


Figure 3. Nodulocystic acne **(a)** before and **(b)** 12 months after a 16-week course of oral isotretinoin.

which is sustained beyond the treatment period; it also acts on ductal hyperkeratosis, and may be anti-inflammatory. It is highly effective in acne (Fig 3), but in the UK can be prescribed only for severe acne and by consultant dermatologists. In practice, the indications include chronicity, failure of adequate antibiotic therapy (including Gram-negative folliculitis) and dysmorphophobia, as well as nodulocystic acne[22]. Most patients receive 1 mg/kg/day, but lower doses may suffice in some cases (for example, in older women with less severe lesions)[22]. Treatment is usually 16 weeks, after which 87% of patients obtain remission. The most significant adverse effect is embryopathy, and women of child-bearing potential must observe adequate contraception during and for a month after treatment. Exacerbation of acne, sometimes severe, can occur early in treatment and may require oral corticosteroids. Most patients tolerate the universal xerosis well; other side effects, such as myalgia, headache, altered serum triglycerides and liver function rarely cause problems. The cost of this drug seems high (in the UK, £370 for a course in a 65 kg person) compared with antibiotics, but in severe chronic acne the prolonged remission produces a saving[23] – let alone the satisfaction of effective treatment and reduction of antibiotic resistance. Unfortunately, UK prescription arrangements mean that hospitals in the public sector bear all the drug costs while the savings are made in the community.

Cysts and scars

Cysts and hypertrophic (keloidal) scars can be treated by intralesional steroids or cryotherapy, but results for keloids are often disappointing. Ice-pick scars can be excised or injected with collagen, with mixed results. Dermabrasion produces worthwhile improvement in the most severe acne scarring. Recently, ultrashort pulse carbon dioxide lasers have been introduced as a less bloody alternative to dermabrasion.

Future prospects

Effective non-antibiotic treatments for acne may become increasingly important if bacterial resistance continues to rise. Drugs under development include new retinoid analogues, and the potential of topically active agents, inhibitors of 5-alpha-reductase type I, is attracting interest[14]. Elucidation of mechanisms of inflammation in acne[9] suggests that anti-inflammatory agents may in future offer a useful third avenue for reduction both of acne severity and of scar formation.

References

1 Burton JL, Cunliffe WJ, Stafford I, Shuster S. The prevalence of acne vulgaris in adolescence. *Br J Dermatol* 1971;**85**: 119–26.
2 Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. *Br Med J* 1979;**278**:109–10.
3 Burke BM, Cunliffe WJ. The assessment of acne vulgaris: the Leeds technique. *Br J Dermatol* 1984;**111**:83–92.
4 Motley RJ, Finlay AY. Practical use of disability index in the routine management of acne. *Clin Exp Dermatol* 1992;**17**:1–3.
5 Cunliffe WJ. Unemployment and acne. *Br J Dermatol* 1986;**115**:379–83.
6 Benhamou CL, Chamont AM, Kahn MF. Synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome (SAPHO) – a new syndrome among the spondyloarthropathies. *Clin Exp Rheumatol* 1988;**6**:109–12.
7 Leyden JJ. New understandings of the pathogenesis of acne. *J Am Acad Dermatol* 1995;**32**:S15–S25.
8 Burton JL, Shuster S. The relationship between seborrhoea and acne vulgaris. *Br J Dermatol* 1971;**84**:600–l.
9 Webster G. Inflammation in acne vulgaris. *J Am Acad Dermatol* 1995; **33**:247–53.
10 Walton S, Wyatt EH, Cunliffe WJ. Genetic control of sebum excretion and acne – a twin study. *Br J Dermatol* 1988; **118**:393–6.
11 Voorhees JJ, Wilkins JW Jr, Hayes E, Harrell ER. Nodulocystic acne as a phenotypic feature of the XYY genotype. *Arch Dermatol* 1972;**105**:913–9.
12 Fitzsimmons JS, Guilbert PR. A family study of hidradenitis suppurativa. *J Med Genet* 1985;**22**:367–73.
13 Wilkie AOM, Slaney SF, Oldridge M, Poole MD, *et al.* Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. *Nat Genet* 1995;**9**:165–72.
14 Chen W, Zouboulis CC, Orfanos CE. The 5-alpha-reductase system and its inhibitors. Recent development and its perspective in treating androgen-dependent skin disorders. *Dermatology* 1996;**193**:177–84.
15 Crow KD. Chloracne and its potential clinical implications. *Clin Exp Dermatol* 1981;**6**:243–57.
16 Gupta AK, Knowles SR, Gupta MA, Jaunkalns R, Shear NH. Lithium therapy associated with hidradenitis suppurativa: case report and review of the literature. *J Am Acad Dermatol* 1995; **32**:382–6.
17 Fulton JE, Plewig C, Kligman AM. Effect of chocolate on acne vulgaris. *JAMA* 1969;**210**:2071–4.
18 Shalita A, Weiss JS, Chalker DK, Ellis CN, *et al.* A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris. *J Am Acad Dermatol* 1996; **34**:482–5.
19 Griffiths CEM. Nicotinamide 4% gel for the treatment of inflammatory acne vulgaris. *J Dermatol Treat* 1995;**6**: S8–10.
20 Moss C, Ferner RE. Minocycline for acne. *Br Med J* 1996;**312**:138.
21 Eady EA, Jones CE, Tipper JL, Cove JH, *et al.* Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *Br Med J* 1993; **306**:555–6.
22 Layton AM, Cunliffe WJ. Guidelines for optimal use of isotretinoin in acne. *J Am Acad Dermatol* 1992;**27**:S2–7.
23 Cunliffe WJ, Gray JA, Macdonald-Hull, Hughes BR, *et al.* Cost effectiveness of isotretinoin. *J Dermatol Treat* 1991;**1**: 285–8.

Further reading

1. Cunliffe WJ. *Acne.* London: Martin Dunitz, 1989.
2. Bergfeld WF, Odom RB (eds). New perspectives on acne. *J Am Acad Dermatol* 1995;**32**:S1–56.