Acne vulgaris

Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit affecting almost all adolescents to some degree, being moderate to severe in 15–20% (Ghodsi et al, 2009; Williams et al, 2012). As such, it is a mainstay of dermatological practice and patients with acne will be encountered regularly by clinicians. Understanding the underlying pathophysiology, the range of treatments and their side effects will help the attending physician to choose the most appropriate therapy for an acne sufferer.

Pathogenesis

Acne vulgaris results from interaction between four aetiological factors: seborrhoea (increased sebum production by the pilosebaceous unit, which is partly driven by androgens), hyperkeratinization of follicular ducts (consequently follicular pore plugging, clinically manifest as comedones), bacterial colonization with *Propionibacterium acnes*, and inflammation. Treatment is directed towards one or more of these underlying causes and will be explored in greater detail in this article (James, 2005; Williams et al, 2012) as outlined in *Table 1*.

Risk factors

Acne is multifactorial with both genetic and environmental factors playing their part. Molecular genetics studies have implicated genes involved in the innate immune response, steroid hormone metabolism and associated receptors in the pathogenesis of acne (Szabo and Kemeny, 2011), but our understanding of the interaction of mechanistic pathways remains incomplete. In some patients, family history of severe acne can be a risk factor.

There is no conclusive evidence that acne is associated with poor hygiene, lack of exercise, sunlight or high consumption of chocolate or dairy produce, factors often cited by patients as possible causes of their acne (Williams et al, 2012). Some drugs can elicit acneiform eruptions (which lack comedones), notably corticosteroids (resulting in monomorphic inflammatory lesions, affecting predominantly the trunk), anticonvulsants, lithium, iodides, and newer chemotherapeutic agents such as epidermal growth factor receptor inhibitors (e.g. erlotinib, in which precipitation of the acneiform eruption is associated with favourable response of primary tumour) (Layton, 2005; DeWitt et al, 2007).

Clinical presentation and assessment

Clinical findings include pathognomonic open and closed comedones ('non-inflammatory' lesions), papules, pustules, nodules and cysts ('inflammatory lesions'), often on the background of seborrhoea. Following acne lesions, scarring may ensue, which may be atrophic, hypertrophic or 'icepick' in configuration. Post-inflammatory hyperpigmentation is a complication often observed in dark-skinned individuals. The most commonly affected areas are the face (99%), back (60%) and chest (15%) (Archer et al, 2012), corresponding to the sebaceous gland-rich sites of the body.

While some patients with acne can experience pain, itch and soreness, the more notable consequences are those of psychosocial morbidity, which can be associated with anxiety, low mood, eroded self-esteem, suicidal ideation and depression. Clinician-graded severity of acne may not necessarily represent the degree of psychosocial impact.

Assessment of patients with acne should include the disease duration, subjective severity, effect upon quality of life, previous treatments, duration of treatment, how topical treatments were applied (all over the face, as it should be, or just on active lesions), their effectiveness and side-effects. Exploring patients' expectations of therapy is an important part of the consultation. To guide treatment options, all patients should be asked about previous psychiatric morbidity and current medications being taken, and women should be asked about plans for family and current contraceptive measures being used as some treatments for acne can interfere with these. Objective measurement of severity is aided by use of standardized scales such as the Leeds Acne Grading Scale (Burke and Cunliffe, 1984).

Identification of the predominant type of acne lesion is important in selecting the most appropriate initial treatment, whether 'anti-comedonal' or 'anti-inflammatory'. Therapy should take into account the severity and extent of the acne; for example, in a patient with widespread inflam-

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Table 1. Mechanism of action of topical and systemic acne therapies

Therapy		Reduced sebum production	Comedolytic	Antimicrobial	Anti-inflammatory
Topical	Benzoyl peroxide		+	+	
	Retinoids		+	+	+
	Antibiotics			+	+
	Azelaic acid/salicylic acid		+	+	
Systemic	Combined oral contraceptive	+	+		
	Antibiotics			+	+
	Isotretinoin	+	+	+	+

matory and pustular lesions, systemic treatment with antibiotics may be preferable to topical treatments.

Failure of initial therapy

Patient concordance with prescribed therapy is a significant determinant of success: apparent failure of a treatment modality often reflects poor concordance with prescribed therapy, with either incorrect application of topical treatments, insufficient duration of use or premature termination owing to side effects. Other apparent reasons for treatment failure include *P. acnes* antibiotic resistance and incorrect diagnoses (e.g. rosacea or acne variants) (Williams et al, 2012). Treatment plans must be agreed with the patient, anticipated side effects and the need for several months of treatment explained, together with the caveat that the acne may worsen before substantially improving. As disease activity may fluctuate, several courses of treatment may be required, so it is important to gain the patient's trust and commitment to therapy.

Topical therapies

Topical therapies are the mainstay of treatment of mild-to-moderate acne. Patients should be advised how to use their therapy, gradually building up from low to higher concentrations using increasing durations of application, from a few hours initially to overnight to up to twice daily.

Topical benzoyl peroxide has both keratolytic and antimicrobial properties, so can be applied to inflammatory and non-inflammatory lesions. The use of benzoyl peroxide reduces the risk of development of antibiotic-resistant strains of *P. acnes*, making it a useful adjunct to other agents. Tolerance is limited by local irritation and bleaching of both skin and clothes.

For predominantly comedonal (non-inflammatory) acne, topical retinoids (adapalene, isotretinoin, tretinoin) are of particular use, although they also have a role to play in inflammatory acne. Retinoids are vitamin A agonists whose mechanism of action includes both keratolytic and anti-inflammatory activity. Side effects include dryness of the skin and local irritation. Topical (and systemic) retinoids are contraindicated in pregnancy owing to their teratogenicity (see below).

Predominantly inflammatory acne warrants use of topical antibiotics (such as clindamycin or erythromycin) to reduce *P. acnes* colonization of the pilosebaceous unit and the ensuing inflammation. Effectiveness of such agents is improved and the chance of bacterial resistance is decreased by concurrent use of benzoyl peroxide or retinoids. Where retinoids cannot be tolerated, salicylic or azelaic acid can provide additional keratolytic action (Strauss et al, 2007).

Newer fixed-dose combination therapies, marrying two of the above classes of agents, allow more rapid resolution and greater efficacy than a single agent by aiming to treat the maximum number of underlying aetiological factors. A topical retinoid in combination with an antimicrobial agent (either benzoyl peroxide or topical antibiotic) are usually used as the first-line therapy for most patients with acne (Thiboutot et al, 2009).

Combined oral contraceptive

Where topical treatments have failed, systemic treatments are indicated. In women, a useful initial adjunct, where there are no contraindications, is the introduction of a combined (oestrogen-containing) oral contraceptive pill (e.g. Dianette or Microgynon). By increasing the levels of sex hormone-binding globulin, such agents reduce both total androgen and free testosterone plasma concentrations (Thiboutot et al, 2001) and can be useful in the presence or absence of hyperandrogenic states, such as polycystic ovarian syndrome (James, 2005).

It should be noted that progesterone-only contraceptive agents can exacerbate acne, owing to non-selective agonism of both progesterone and androgen receptors. Comprehensive endocrinological assessment is not necessary for the majority of female patients with acne. However, this may be indicated where there are clinical features of hyperandrogenism, such as recalcitrant acne, infrequent menses, hirsutism, infertility, acanthosis nigricans or truncal obesity (Strauss et al, 2007).

Systemic antibiotics

In moderate-to-severe acne, and in cases of back, shoulder and chest involvement and where topical therapies have failed, a protracted course of systemic antibiotics should be considered. Antibiotics have both antimicrobial and anti-inflammatory effects: agents commonly used include tetracyclines (tetracycline, oxytetracycline, lymecycline, doxycycline, and minocycline), macrolides (erythromycin, clarithromycin) and trimethoprim.

As there remains little conclusive evidence as to the superiority of any one antibiotic over others, choice of antibiotic is governed by patient preference, side-effect profile, likelihood of concordance and cost (Williams et al, 2012). Grading systems have shown that an improvement of around 10% per month can be expected. Response to regular use of an oral antibiotic should be gauged at least 8 weeks after instigation, before considering switching to an alternative agent. Typical treatment duration is 3–6 months but longer durations are justified in selected cases.

The burgeoning problem of increasing community antibiotic resistance may be avoided by concurrent use of topical benzoyl peroxide with systemic antibiotics and avoidance of concomitant topical antibiotic application, in addition to avoidance of antibiotic switching when an antibiotic has previously been efficacious.

Isotretinoin

In cases of severe acne, and where two or more protracted courses of systemic antibiotics together with other therapies have failed to control the disease, systemic isotretinoin can be considered by a dermatologist. It should also be considered in cases of severe cystic acne, acne fulminans and where there is evidence of scarring. Isotretinoin, a retinoid, is hugely effective in the treatment of acne, being the only therapy to effectively target all four aforementioned underlying mechanisms (Layton, 2009). Its use is limited by side effects, for which the patient must be counselled and documented consent obtained before starting treatment and which require regular monitoring throughout the course of treatment.

Foremost among these side effects is teratogenicity, with babies born to mothers who have taken isotretinoin at any time during their pregnancy being at high risk of craniofacial, nervous system and cardiovascular abnormalities (Goodfield et al, 2010). The British Association of Dermatologists' guidelines recommend

that all women of childbearing potential should be counselled of this risk and receive the patient information leaflet of the brand they are due to take (Goodfield et al, 2010). Two methods of contraception are advised 1 month before initiation, throughout treatment and 1 month after cessation of isotretinoin therapy, together with 4-weekly review, pregnancy testing and repeat prescription (known as the 'pregnancy prevention programme').

While no definitive evidence exists causally linking isotretinoin with depression (Marqueling and Zane, 2005), patients should also be informed of reports of low mood, anxiety, irritability and suicidal ideation among patients taking isotretinoin, particularly in patients with previous depressive episodes or bipolar disease. Where the prescribing physician has concerns about previous psychiatric morbidity, liaison with and the advice of psychiatrists can be useful before starting therapy. Patients and their families should be urged to report any changes in mood to their primary care physician for evaluation: isotretinoin-associated perturbations of mood resolve within days to weeks of stopping the treatment.

Other risks of therapy that should be monitored are the risks of hypertriglyceridaemia, liver dysfunction, dryness of lips (in almost all patients) and mucosal membranes, epistaxis, myalgia, arthralgia and impairment of night vision (of notable concern in pilots and heavy goods vehicle drivers).

Dosage usually starts at 0.5 mg/kg body weight and is increased as tolerated to 1 mg/kg body weight. The cumulative dose aimed for is 120–150 mg/kg body weight, typically over a 20-week timespan. Following such a course of systemic isotretinoin, 40% of patients feel that their acne has fully resolved, 40% require less intensive treatment and 20% may require a further course of isotretinoin (Williams et al, 2012).

When to refer

Patients who should be referred to dermatologists for comprehensive evaluation include those with severe acne, those with moderate acne and evidence of scarring, those who have shown an inadequate response to at least two 3-month courses of topical therapies and systemic antibiotics and those with severe, associated psychological distress.

Acne scarring

Scarring often ensues following all variants of acne and remains difficult to treat effectively. Treatment modalities available include scar revision, fillers, and a variety of resurfacing techniques including dermabrasion, chemical peels, carbon dioxide laser skin resurfacing, dermaroller, the details of which can be garnered elsewhere (Goodman, 2011).

Conclusions

Acne vulgaris remains one of the commonest dermatological pathologies, with high prevalence and profound psychosocial consequences. While recognized to have a familial propensity, its aetiology is multifactorial and remains largely unknown. Early recognition and active treatment avoids post-inflammatory scarring and hyperpigmentation, which remain difficult to treat. Further large randomized controlled trials comparing different topical and systemic agents are required to devise the optimal initial treatment algorithm, taking into account the burgeoning problem of antibiotic resistance. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Acne vulgaris is a common inflammatory dermatosis of multifactorial aetiology, typically first affecting patients during adolescence.
- There is no definitive evidence that acne is associated with diet.
- Topical and systemic treatments are targeted at one or more of the underlying causes: seborrhoea, comedogenesis, *Proprionibacterium acnes* colonization and inflammation.
- Recognition of predominantly inflammatory or comedonal lesions will aid initial selection of treatment.
- Patient understanding of therapies, their correct application, the need for prolonged duration of treatment and therefore concordance, often dictates success of treatment modalities.
- *P. acnes* antibiotic resistance is a burgeoning problem that can be abrogated through concomitant use of benzoyl peroxide.
- Isotretinoin is highly effective against acne vulgaris; caution must be taken in its use owing to its side-effect profile, most notably teratogenicity.
- There are a range of techniques used to reduce scarring following inflammatory acne, none of which are perfect. Prevention is better than cure.