



UPDATE ON THE MANAGEMENT OF ACNE

- 👉 Acne, now recognised as a chronic skin disease, is the most common skin condition of adolescence
- 👉 There are several interrelated components to its development which should be considered, in addition to clinical severity, when deciding on treatment
- 👉 Most cases involve the use of topical agents with or without systemic drugs; combination therapy is more effective than monotherapy
- 👉 Patient education is vital as maintenance therapy may be needed for months or years after initial response in order to prevent relapse

INTRODUCTION

Acne (acne vulgaris) is the most common skin condition of adolescence.¹ It is estimated that up to 90% of teenagers may experience acne at some stage, most of which is mild in nature; however up to 20% may develop moderate to severe acne, potentially leading to scarring.²⁻⁴ Although perceived as a teenage self-limiting disease, **symptoms may occur in early childhood or the disease may persist into adulthood, with up to 3% of males and 5% of females aged 40 to 49 years of age reporting at least mild acne;**^{2,4} therefore acne is now regarded as a chronic condition.⁵ In addition, the development of persistent acne has been identified as a specific problem in adult women (>25 years).⁶ Acne may result in physical symptoms such as soreness, itching and pain but its **main effects are on quality of life.**⁴ Psychosocial distress is very common in adolescent patients affected by acne, not directly correlated with the clinical severity of the condition.⁷ In addition, **acne has been shown to be associated with an increased risk of anxiety, depression and suicidal ideation in a significant proportion of patients.**⁸ Acne is predominantly managed in primary care. This bulletin, which updates a previous bulletin, will outline its contemporary management, based on current awareness of the pathophysiology of acneiform lesions.^{1,5}

PATHOPHYSIOLOGY OF ACNE

Acne is thought to be a multifactorial inflammatory process of the pilosebaceous follicles (known as units) of the skin.^{9,10} Four factors are said to play a key role in the development of acne lesions: (1) **excess sebum production** (an early event in lesion initiation), (2) **hyper-keratinisation** of the follicular epithelium (resulting in follicular obstruction), (3) **colonisation of the pilosebaceous duct by *Propionibacterium (P) acnes*** and (4) activation of the innate immunity of the skin leading to the **release of inflammatory mediators.**^{5,9} Acne lesions can remain subclinical (known as microcomedones) or evolve into clinical lesions (due to impaction and distension with/without infection of the pilosebaceous unit); these lesions include open and closed comedones (known as blackheads and whiteheads respectively), papules, pustules and nodules (also known as cysts).⁹ However, recent research has shown that inflammatory markers are present even in the microcomedones; the involvement of inflammation from the very early phases of the process has implications for management of acne.^{1,11}

The **causes of acne** are still not clearly defined but are thought to be multifactorial. **Genetic factors:** a **positive family history** has been shown to double the risk of developing severe acne and recent research has identified potential genes that may be involved.^{4,8,12} **Increased androgen levels** (seen normally during puberty or in conditions such as polycystic ovary syndrome or 21-hydroxylase deficiency) can lead to increased sebum production and follicular epithelium abnormalities.² **Environmental factors:** The relationship between diet and the development of acne is still not established; recent studies suggest a potential association between (1) **dairy intake** and (2) a **high glycaemic index (GI) diet** and the development of acne but further studies are needed to confirm these findings.^{8,12} Conflicting results have been reported on the role of **chocolate** in the development of acne.¹² **Smoking** has been reported to increase the severity of acne.⁴ Certain **medicines** (including anabolic steroids, the anti-cancer drug gefitinib, ciclosporin, perioral corticosteroids and some anti-epileptic drugs) may cause acneiform eruptions.⁴ Studies have shown that there are distinct **subtypes of *P acnes*** which are highly associated with moderate to severe acne lesions, and which are different to those found in healthy skin;⁵ however, not all acne patients will have these subtypes.¹³ There is **no evidence** to support an association between **poor facial hygiene** and acne.^{2,3}

CLINICAL PRESENTATION AND DIAGNOSIS

Presentation: Acne may present as a spectrum of lesions ranging from non-inflammatory open and closed comedones to inflammatory papules, pustules and nodules.^{4,10} Conglobate acne, the most severe form of acne seen almost exclusively in males, presents with many comedones, marked by suppuration, cysts, sinuses, and scarring.¹⁴ The distribution of acne lesions corresponds to the highest density of pilosebaceous units (i.e. face, neck, upper chest, shoulder and back) with the disease most commonly affecting the face (99% of cases) followed by the back (60%) and chest (15%).^{2,15}

Classification: Acne is usually described as mild, moderate or severe; however, there is no universally agreed classification / grading of acne.¹⁰ Table 1 outlines European consensus-based schemes for classifying and grading acne; these are useful in determining the optimum treatment pathway and in monitoring response, according to disease severity.^{11,16}

Table 1: Classification and grading scales for acne vulgaris^{11,16}

EADV Classification	Global Evaluation Acne (GEA) grading scale	
Predominant comedonal facial acne [~mild]	0	Clear, no lesions
Mild to moderate papulopustular acne [~moderate]	1	Almost clear / almost no lesions
Severe papulopustular acne / moderate nodular acne [~severe]	2 (mild)	<50% of face involved; few comedones, papules, pustules
Severe nodular acne / conglobate acne [~very severe]	3 (moderate)	>50% of face involved; many comedones, papules, pustules (and up to one nodule)
	4 (severe)	Entire face involved, covered with many papules, pustules, comedones (rare nodules)
	5 (very severe)	Highly inflammatory acne covering the face with presence of nodules

EADV=European Academy of Dermatology and Venereology; GEA=Global Acne Severity

Diagnosis is based on the classical clinical presentation of acne lesions on the face and to a lesser extent on the back and chest.¹⁷ **Differential diagnoses** include: (1) **rosacea**, which usually presents in older patients and the facial eruption does not include comedones (rarely presents with lesions on the trunk); the presence of facial flushing, induced by heat, alcohol or spicy food is a useful indicator of rosacea, (2) **drug-induced** acneiform lesions (usually present as monomorphic lesions) and (3) **folliculitis** in the beard area (due to *Staph. aureus* infection) or the trunk regions (due to infection with *Pityrosporum spp.*).^{10,15,18} **Laboratory tests** are not normally warranted. Although androgens are known to be involved in the pathogenesis of acne, most patients have normal hormone levels; therefore **hormone testing** is only indicated if patients have clinical features suggestive of hyper-androgenism (e.g. evidence of axillary or pubic hair and genital maturation in prepubertal children; hirsutism, androgenetic alopecia, infertility, polycystic ovary syndrome in postpubertal females).¹⁰ **Microbiologic testing** is only undertaken if there is a suspicion of gram-negative folliculitis.¹⁰

MANAGEMENT OF ACNE

The goals of treatment are to (1) manage active disease according to clinical severity, (2) maintain remission and (3) prevent scarring of the skin.¹⁹ **Patients should be involved in their management programme.** Self-identity develops during adolescence and the visible lesions of acne may interfere with the formation process of the self and personal identity.⁷ Therefore, each patient's perception of disease severity (and his/her expectations about treatment outcomes) as well as the clinical severity and extent of disease must be taken into account when deciding on the treatment programme.¹⁷ **Education** is important to **maximise adherence** to therapy: patients should be informed that (1) acne is a chronic disease which will require therapy for several months or even years, (2) it usually takes 2 to 3 months in order to show maximal benefit of therapy and (3) the initial treatment regimen may need to be modified if intolerance or suboptimal response occurs.¹⁴

PHARMACOLOGICAL MANAGEMENT: TOPICAL THERAPY

Topical therapy is recommended as first choice for **mild to moderate acne**.²⁰ Treatment **choice** may be determined by the **extent and severity of disease, site of involvement, and patient age and preference**.^{10,21} Table 2 outlines the currently available topical therapies.

Table 2: Topical therapies used in the management of acne^{2,4,10,23-31}

Class	Mode of Action	Undesirable effects include*
Retinoids tretinoin adapalene	Anti-inflammatory; comedolytic; anti-comedogenic	Skin irritation, dryness, burning sensation, erythema, and contact dermatitis; may reduce with ↓ frequency of administration. Photosensitivity. C/I during pregnancy. Adequate contraception needed in WOCP.
Benzoyl peroxide (gel / cream / lotion)	Anti-microbial; anti-inflammatory and comedolytic (onset of effect by 5 days)	Skin irritation (local erythema, peeling), pruritus, and dryness; may reduce with ↓ frequency of administration. Staining / bleaching of clothing or skin.
Antibiotics clindamycin erythromycin	Anti-microbial; anti-inflammatory (only to be used in combination with other topical agents)	Skin irritation, urticaria, and risk of resistance with prolonged continuous M/T usage. GI upset and rare reports of pseudo-membranous colitis with prolonged usage (clindamycin only).
Azelaic acid	Anti-microbial; anti-inflammatory; comedolytic	Application site dryness, pruritus, rash – usually regress with continuation of treatment.
Salicylic acid	Anti-inflammatory; comedolytic	Skin irritation, dryness; may reduce with ↓ frequency of administration.
Nicotinamide	Anti-inflammatory	Skin irritation, dryness; may reduce with ↓ frequency of administration.

*Full prescribing information is available in the Summary of Product Characteristics at www.hpra.ie
C/I=contraindicated; GI=gastrointestinal; M/T=monotherapy; WOCP=women of childbearing potential

Retinoids are the **mainstay of topical therapy for acne because of their wide-ranging effects**, especially their activity against the precursor microcomedone lesion (Table 2).^{10,15} **Benzoyl peroxide** (BPO) is effective in patients with inflamed lesions; skin irritation is problematic but may be alleviated by changing the preparation or reducing the frequency of administration.^{17,31} **Azelaic acid** has been reported to have similar efficacy to BPO but it is less irritant;^{21,32} it is not associated with photosensitivity and may be useful for facial comedonal acne.^{10,31} **Topical antibiotics** used for acne (see Table 2) accumulate in the follicle and have anti-inflammatory as well as anti-microbial properties. **They should be used in combination with other topical therapies to increase efficacy and reduce resistance**.^{10,33} Limited efficacy data are available for **nicotinamide** and **salicylic acid**;^{2,4,10} however they may be useful when other topical agents are not tolerated.²

Practical aspects of topical therapy

Choice of therapy: For predominant comedonal acne, **monotherapy** with a retinoid (or BPO or azelaic acid) may be used as a first-line treatment.¹⁷ Monotherapy is also useful as maintenance therapy once papulopustular acne has achieved remission.¹⁵ **Combination therapy** is preferred for **mild to moderate predominant papulopustular acne**; this has been shown to increase efficacy, improve the safety profile and reduce the risk of developing bacterial resistance,

compared with monotherapy.^{11,21} Optimal combinations include a retinoid with either BPO or topical antibiotic or azelaic acid, or BPO with a topical antibiotic.

Patients should be advised to **apply the topical agent(s) to all the areas where the lesions have presented** and not just onto the lesions themselves; apparently “normal” follicles may be microcomedones which may develop into clinical lesions if infected with *P. acnes*.²¹ Patients should be advised of the importance of **adhering to the recommended treatment schedule**, which may last for several years.²¹

Local tolerability issues: As topical therapies may be irritating to skin, it is recommended to **gradually titrate the dose** (e.g. start using it once or twice weekly, gradually increasing to once or twice daily).²⁰ In addition, the **choice of preparation (and its vehicle) should take into account the patient’s skin type**: those with dry or sensitive skin may prefer creams or lotions, (less drying), whereas those with oily skin may prefer a gel (less greasy).^{11,22}

A new treatment plan should be introduced if there is insufficient clinical benefit within 4 to 8 weeks. If there is inadequate response to topical therapy (despite optimal dosage and good adherence), **oral medication** (with or without topical therapy) may be required, irrespective of the grade of acne being treated.^{10,11}

PHARMACOLOGICAL MANAGEMENT: SYSTEMIC THERAPY

Systemic (oral) therapy is indicated for the management of (1) moderate to severe acne, (2) acne which has failed to respond to optimal therapy with topical agents and (3) acne which is causing psychological difficulties for the patient, irrespective of its severity.³⁴ Table 3 outlines the currently available oral therapies.

Table 3: Oral therapies licensed for use in the management of acne ^{31,34-40}

Class	Mode of Action	Undesirable effects include*
ANTIBIOTICS: Tetracyclines lymecycline minocycline doxycycline Erythromycin	Anti-microbial; anti-inflammatory	Tetracyclines: Absorption may be affected by food, antacids, milk, calcium (not minocycline). GI upset. Rare ↑ LFTs, skin reactions, skin pigmentation. Only for use in those >12 years old. C/I during pregnancy and lactation. Doxycycline causes photosensitivity. Very rare reports of SLE with minocycline. DDI with oral retinoids (↑ risk of benign intracranial hypertension) Erythromycin: GI upset ++. <i>P. acnes</i> develops resistance quickly
Hormonal therapy oestrogen and cyproterone acetate	Reduction in sebum excretion; inhibition of comedogenesis.	GI upset. Weight gain; ↑ risk of VTE especially in first year of use - C/I in those with a history of, or multiple risk factors for, VTE. Headache / exacerbation of migraine. 6-monthly checks on blood pressure and body weight are recommended.
Retinoid Isotretinoin [use is under the supervision of a physician with expertise in the use of systemic retinoids]	Suppression of sebaceous gland activity; anti-inflammatory	Teratogenic; C/I during pregnancy. Adequate contraception needed in WOCP and for one month after D/C. Risk of potentially severe psychiatric reactions – patients should be monitored for depression during treatment. ↑LFTs and ↑ plasma lipids (should be monitored during treatment); ↓ bone marrow activity; allergic reactions; severe dryness of skin, eyes and other mucosal surfaces; acute flare-up of disease; photosensitivity. DDI with tetracyclines (↑ risk of benign intracranial hypertension)

*Full prescribing information is available in the Summary of Product Characteristics at www.hpra.ie

C/I=contraindicated; D/C=discontinuation; DDI=drug-drug interaction; GI=gastrointestinal; LFTs=liver function tests; SLE= systemic lupus erythematosus; VTE=venous thromboembolism; WOCP=women of childbearing potential

Oral antibiotics

Oral antibiotics work by targeting *P. acnes* and inhibiting its growth; in addition they have anti-inflammatory effects.¹⁹ They have been shown to be effective in the management of moderate to severe acne.¹⁰ They are **used in combination with topical therapy** (but not with topical antibiotics) to optimise efficacy and reduce the risk of developing bacterial resistance.^{2,22} The **tetracycline antibiotics are considered first-line therapy**, since they have notable anti-inflammatory as well as anti-microbial effects.¹⁰ A recent review found no reliable evidence to support superior efficacy for any member of this class;⁴¹ therefore the final choice should take into account the different safety profiles within the class, (Table 3) and whether the preparation is administered once or twice daily.³⁵⁻³⁷ **Erythromycin** is an alternative oral therapy; *P. acnes* resistance may develop more quickly which reduces its efficacy.³¹ **If there is no improvement with oral antibiotic therapy after 6 to 8 weeks, despite adherence to therapy, the regimen should be changed to another antibiotic** (either within the same class or to a different class).^{2,11,17} Oral antibiotics should be continued for a **maximum of 4 to 6 months** and they should not be used as maintenance therapy.^{11,17} **Trimethoprim** may be used to treat acne resistant to other antibiotics (unlicensed indication, under specialist supervision);³¹ **adverse effects** include gastrointestinal upset, photosensitivity and depressed haematopoiesis (monitoring required with longer-term use).^{10,42}

Anti-androgen hormonal therapy

Androgens are known to play a role in the pathophysiology of acne.⁴³ Androgen-related acne in women may present on its own or in association with other clinical features of hyper-androgenism, such as hirsutism or irregular menses. In addition, the majority of adult women with acne experience worsening of the lesions during the premenstrual period.⁶ Cyproterone is a progestin with strong anti-androgenic effects;⁶ the combined oral contraceptive (COC) **ethinylestradiol / cyproterone acetate** (Dianette®) is licensed for use in eligible women for the management of moderate to severe acne (related to androgen-sensitivity) which has not responded to topical and / or oral antibiotics.^{39,43} **Benefit should occur within 3 to 4 cycles** of treatment.²⁰ It is recommended that treatment be withdrawn 3 to 4 cycles after resolution of the acne; this preparation should not be used solely as a COC.³⁹ **Other COCs**, especially those containing the third or fourth generation progestins (e.g. norgestimate, drospirenone) have anti-androgenic properties and may be beneficial in the management of acne, although not specifically licensed for such an indication.^{10,44} Women should be evaluated for suitability prior to starting any COC therapy and they should undergo regular monitoring while on therapy (see Table 3). **Progesterone only contraceptives often worsen acne** and should be avoided in women with acne.⁴

Isotretinoin

Isotretinoin targets all the pathogenic mechanisms of acne and therefore is the most effective anti-acne treatment.^{19,45} However, because of its safety profile (see Table 3) its use is reserved for the **management of severe forms of acne (such as nodular or conglobate, or acne at risk of permanent scarring) which is resistant to other treatments**; its prescription and usage are under specialist supervision.⁴⁰ The dose (0.5 – 1.0mg/kg/day) should be titrated to the individual response (in terms of efficacy and safety - see Table 3); **usually a treatment course of 16 to 24 weeks is sufficient to achieve remission** in up to 85% of cases. It has been shown that no substantial additional benefit is to be expected beyond a cumulative dose of 120-150mg/kg per treatment course.^{10,11,40} An acute disease flare up (resulting in an increased number of inflammatory lesions) may occur 3 to 4 weeks into the treatment programme; this usually resolves spontaneously but oral prednisolone may be required in some cases.^{19,45} Relapse may occur in up to one third of cases (thought to be dose-related), often within the first year after completion of therapy.¹⁹ A further course of isotretinoin or another systemic therapy should be used according to the disease severity.¹⁹

Safety profile: Isotretinoin is a vitamin A analogue and is **teratogenic**.^{46,47} Women of childbearing potential can only be prescribed isotretinoin in accordance with the **Pregnancy Prevention Programme (PPP)** as outlined in the Summary of Product Characteristics;⁴⁰ this requires (1) negative pregnancy tests before and during treatment, and (2) the use of effective contraception (preferably two forms) during treatment, and for at least one month after discontinuation.^{40,46} A recent EU safety review of oral retinoids recommended an update of the educational materials for the PPP to facilitate discussions with female patients prior to initiating therapy.⁴⁷ The EU review also confirmed that **all patients should be monitored for signs of depression while on treatment** and referred for appropriate treatment if necessary; special attention should be paid to patients with a history of depression.⁴⁷

PHARMACOLOGICAL MANAGEMENT: MAINTENANCE THERAPY

Acne lesions typically recur for years, therefore acne is now regarded as a chronic relapsing disease.^{1,5} It is recommended that **patients should receive maintenance therapy** once remission has been achieved.¹⁵ Topical monotherapy with a retinoid is recommended because of its anti-comedogenic effect.^{15,19} Azelaic acid (or BPO if an anti-microbial effect is needed) are useful alternatives. Acute disease flare-ups should be managed according to the type and severity of the acne lesions; repeat courses of the regimen(s) used to achieve remission may be used again.³⁴

ACNE SCARRING

Acne scarring is caused by disruption of the skin structure during the disease process and/or overproduction of collagen following the production of inflammatory cytokines as a result of the immune response.¹ One of the aims of early intervention with appropriate effective treatment for acne is to prevent permanent scarring. In addition to providing advice on how to use their medicines correctly, **patients should be educated** to (1) **avoid picking at spots**, which may damage the skin, (2) **avoid vigorous skin washing** which may worsen the acne and (3) **use cosmetics / toiletries / sunscreen that do not clog pores** (non-comedogenic).⁴⁸ While acne scars may clear spontaneously with time, some become permanent without treatment.¹ A recent review of interventions for acne scars (including laser therapy, chemical peeling, skin microneedling and injectable fillers) was unable to recommend any intervention for first-line use due to a lack of high-quality clinical evidence.⁴⁹

OTHER THERAPIES FOR ACNE

Although light therapy has been used to treat acne in patients where pharmacological therapy may not be suitable, few studies have compared lasers and light therapies with conventional acne treatments, with no evaluation of their long-term benefit in acne management.⁵⁰ A recent review assessed the efficacy of herbal medicine (including Chinese medicine), acupuncture, wet-cupping therapy, low-glycaemic-load diet, tea tree oil gel, and purified bee venom (PBV) for acne.⁵¹ Some improvement was reported with use of tea tree oil gel and cosmetics containing PBV, however the studies were of short duration only; there was no evidence to support the use of the other complementary therapies in the review.

SUMMARY: PRACTICE POINTS

- Early diagnosis and management of acne lessens the risk of long-term sequelae such as scarring
- Choice of treatment regimen should take into account the (1) severity of the disease, (2) patients' perceptions of their disease and (3) their expectations about treatment outcome
- Patient education and ongoing support are needed to ensure adherence to therapy which may last several years
- Topical retinoid is the mainstay of treatment for mild to moderate comedonal acne
- Dual topical therapy (e.g. retinoid plus BPO or antibiotic) increases efficacy and reduces the risk of resistance in inflammatory lesions
- Topical therapy should be changed if the disease is not responding by 4 to 8 weeks, despite adherence to therapy
- Oral therapy (with or without topical therapy) is recommended for severe / conglobate acne, or where topical therapy has failed despite adherence to therapy; oral antibiotics should always be combined with topical therapy
- Once remission has been achieved, patients should receive maintenance therapy to prevent relapse of disease
- Treatment flare-ups should be managed according to the type and severity of acne lesions
- Specialist referral is recommended if isotretinoin therapy is required or for patients whose acne is causing severe psychological distress, irrespective of the type of acne
- The British Association of Dermatologists has a useful patient leaflet on acne, which is available at: www.bad.org.uk/for-the-public/patient-information-leaflets

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List of references available on request. Date of preparation: April 2018

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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