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MANAGEMENT OF ACNE VULGARIS

-  Acne vulgaris, the commonest dermatological condition in primary care, may have a significant impact on a patient's quality of life
-  Mild acne should be treated topically, either with monotherapy or combination therapy
-  Moderate acne which fails to respond to topical therapy should be treated with oral antibiotics (e.g tetracyclines)
-  Patients with severe acne failing to respond to adequate treatment may be referred to a specialist for consideration of isotretinoin therapy

INTRODUCTION

Acne vulgaris is the commonest dermatological condition in primary care¹ affecting up to 85% of teenagers.^{2,3,4} The peak incidence of acne is at 17 years; most patients improve in their 20's, however up to 10% have acne after 25 years and some patients still experience acne in their 40's.^{5,6,7} It is estimated that up to 14% of people consult their GP with acne at some stage in their lives, while 0.3% will consult a dermatologist.⁵ Even though it is not a life threatening disease it can produce cutaneous and emotional scars, particularly in teenagers, which can last a lifetime.^{5,6,8} The psychological impact of acne has been recognised for many years¹ and the social, psychological and emotional impairment associated with it has been compared to that associated with epilepsy, asthma, diabetes and arthritis.² Acne has been associated with depression, social withdrawal, unemployment, anxiety and even suicide.^{5,6-10} **It is important to be aware that even patients with mild to moderate acne have a higher prevalence of suicidal ideation compared to patients with more chronic and disfiguring dermatological conditions.**^{1,6} This bulletin will outline the management of acne vulgaris in primary care.

PATHOPHYSIOLOGY OF ACNE VULGARIS

The pathogenesis of acne vulgaris is multifactorial and not completely understood.⁶ While genetic factors have an influence,^{10,11} it is widely accepted that acne vulgaris is an inflammatory disease of the pilosebaceous follicle.^{2,5,12} There are four main factors involved in the pathogenesis: 1) increased sensitivity of the sebaceous glands leading to excessive sebum production, 2) abnormal differentiation and hyperproliferation of the follicular epithelium in the sebaceous glands leading to the formation of microcomedones, 3) proliferation of *Propionibacterium acnes* within the microcomedones, and 4) subsequent perifollicular inflammation.^{12,13}

The increased production of sebum is stimulated by the increasing production of androgens,⁶ which explains why the first signs of acne commonly coincide with the onset of puberty.^{6,12} The blockage of sebum flow and progressive enlargement of microcomedones gives rise to clinically visible comedones, while the proliferation of *P. acnes* probably contributes to the development of inflammation which colonises the follicular duct and proliferates in teenagers with acne.² The microcomedone can evolve into a non-inflammatory comedo or become inflamed and present as a papule, pustule or nodule.⁴ The density of *P. acnes* on the skin however does not correlate well with the degree of inflammation or the severity of acne.¹⁴ There are a number of drugs, which are known to precipitate/exacerbate acneiform lesions, including corticosteroids, anticonvulsants and lithium.⁹ Some cosmetic ingredients have also been cited as causes of acne and include: lanolin, vegetable oils, butyl stearate and oleic acid.⁹

CLINICAL PRESENTATION

The **commonest clinical presentation** is increased oiliness (seborrhoea) and the development of non-inflammatory open and closed comedones (blackheads and whiteheads respectively). These may present alone or more commonly occur with pustules and erythematous papules on any site, but most commonly in areas where pilosebaceous glands are numerous, including the face, back and chest.^{2,4} Nodules, which also occur can be painful and unsightly, and associated with more scarring than superficial disease.⁵

Acne conglobata is characterised by widespread nodules with interconnecting channels containing haemorrhagic, purulent exudates.⁵ It is uncommon in adolescence and generally occurs in adulthood.⁹ When acne conglobata is associated with fever, arthritis and neutrophilia it is described as acne fulminans.⁵ **Acne fulminans** is rare occurring most commonly in adolescent males.⁹

No laboratory testing is routinely recommended for acne, however testing for hormonal abnormalities may be required in women also presenting with abnormal menses, hirsutism or acanthosis nigricans, suggestive of polycystic ovarian syndrome.¹³ Acne scarring can occur and be associated with either loss (ice pick or atrophic macular scars) or increase in collagen (hypertrophic or keloid).⁹

When assessing acne it is important to take an all-embracing approach and to examine carefully for both the clinical and psychological effects of the disease process.¹ While there are many grading systems for assessing the severity of the disease, there is no universal consensus on the best way to do this.¹⁵ Grading systems can be useful for recording the progress of the disease and for making treatment decisions.^{5,16} Table 1 (overleaf) gives one example of a system for classifying acne vulgaris.

Table 1: Classification of acne¹⁷

Severity	Description
Mild	Predominantly open and closed comedones with or without sparse inflammatory lesions.
Moderate	Widespread comedones, more numerous inflammatory lesions. Minor pitting or scarring lesions.
Severe	Extensive inflammatory lesions which may include nodules, more significant pitting or scarring lesions.

MANAGEMENT OF ACNE VULGARIS

The primary goals of acne management are to alleviate clinical symptoms, prevent scarring and reduce psychological stress.¹⁶ The selection of acne therapy should depend on a comprehensive assessment of the disease, including a record of previous therapies and response to these treatments, as well as a careful physical examination.^{1,9,16} It is important to consider assessing the psychosocial disability produced by acne and there are a number of questionnaires that have been developed to help in this assessment including the Cardiff Acne Disability Index questionnaire, the Dermatology Life Quality Index questionnaire and the Leeds Assessment of the Psychological and Social Effects of Acne questionnaire.^{1,9}

Patients should be informed on how to use their treatment and of the potential side-effects.⁵ They should be advised that **improvement may take up to six weeks to occur as many patients believe acne can be cured quickly and may discontinue treatment prematurely due to a perceived lack of efficacy.**⁷ Physicians should be aware that the severity of the acne is often overestimated by the patient (in particular teenagers) and minimised by the doctor.⁸ Most patients with acne can be managed in primary care, but referral to a specialist is indicated in certain situations.

NON-PHARMACOLOGICAL MANAGEMENT

Patients should be reassured that acne is very common, will improve and is not a disease of poor hygiene. They should be advised that vigorous scrubbing may actually exacerbate the acne^{11,17} and to avoid “picking” which can lead to trauma, secondary infection and scarring. Women with acne should be advised to avoid the use of heavy make-up and use make-up that is labelled as “non-comedogenic”, “oil-free” or “acne-friendly”.¹² Even though *P. acnes* is killed by light, and acne improves after sun exposure, patients should be informed that the use of sun lamps should be avoided because of the risk of carcinogenesis.¹²

PHARMACOLOGICAL MANAGEMENT

The aims of pharmacotherapy are to: reduce the production of sebum, normalise the keratinisation, clear the existing microcomedones, reduce *P. acnes* colonisation, prevent the development of new microcomedones and subsequent comedones and inflammatory lesions and clear the existing inflammatory lesions.⁶ A combination of therapies is often required and each treatment needs to be continued for at least six weeks before changing or adding other treatments.⁵

TOPICAL THERAPY

Topical treatments include benzoyl peroxide (BPO), topical retinoids, azelaic acid and topical antibiotics, which are available in a variety of strengths and delivery systems.² Gels, washes and solutions are the most drying and are suited for oily skin whereas creams, lotions and ointments are preferable for patients with dry, easily irritated skin.² To date there is no effective topical therapy that will control all four pathogenic factors.¹³ Optimal topical therapy combines agents in order to impact on as many pathogenic processes as possible.¹

Benzoyl peroxide (BPO) is used as first-line treatment in mild acne vulgaris¹⁷ and has anti-microbial, anti-comedonal and anti-inflammatory effects.^{1,4,5,18} BPO can also be used concomitantly with topical retinoids and antibiotics, which improves efficacy and protects against antibiotic resistance. Improvement is usually noted 5 days after treatment is commenced.²

Adverse effects skin irritation is common and bleaching of clothes can occur.^{1,9,12} This problem is reduced when water-based preparations are used rather than alcohol based products² and by reducing the frequency of application.¹²

Topical retinoids can also be used as first-line treatment. They are the most effective topical preparations for inhibiting comedogenesis,^{2,3,8} and are ideal for targeting the microcomedone before it becomes inflamed.^{3,4} In addition they have moderate anti-inflammatory effects and also improve the penetration of other topical medications. They can be used alone in mild acne, in particular for those patients with comedones and also in combination with topical or oral antimicrobial agents for patients with more severe acne.^{2,4} **Topical retinoids however must not be combined with oral retinoids.** The first generation retinoids (tretinoin and isotretinoin) have weak anti-inflammatory effects when used topically, while the third generation adapalene has stronger anti-inflammatory effects.^{19,20} Retinoids reduce post-inflammatory hyperpigmentation, which can be a common problem in dark skin.^{4,13}

Adverse effects include irritation and initial acne flare, especially with tretinoin.^{9,16} Irritant dermatitis and flare can be reduced by beginning at lower concentrations and by using a cream rather than a gel.⁹ Local irritation is less of a problem with the third generation retinoids such as adapalene.^{19,20} Patients using topical retinoids should be advised to avoid exposure to ultraviolet light or strong sunlight.^{1,17,21-23} Even though significant systemic absorption of topical steroids has not been demonstrated,⁹ women should be warned of the potential (although low) risk of teratogenicity.^{17,19} **They are contraindicated in pregnancy, and women of childbearing potential must use effective contraception.**^{19,21-23}

Azelaic acid has similar properties to BPO^{9,18} and is useful in patients who cannot tolerate BPO.¹⁸ It inhibits the synthesis of keratinocytes, has anti-comedonal activity and can reduce post-inflammatory hyperpigmentation.^{13,24}

Adverse effects include skin irritation, which can be minimised by reducing the frequency of application or temporarily discontinuing treatment.^{3,5,9}

Salicylic acid has similar properties to BPO and azelaic acid and can also be used as an adjunct with other therapies.³ It can also cause irritation, erythema and peeling.³

Topical antibiotics such as erythromycin²⁵ and clindamycin²⁶ or tetracycline²⁷ are all similar in efficacy.¹⁷ They reduce the population of *P. acnes*, have a mild anti-comedonal effect and an anti-inflammatory effect^{3,4,9} Bacterial resistance is a concern with topical antibiotics (in addition to oral antibiotics)²⁸ and can be reduced when they are used in combination with BPO.^{14,18} Their use as monotherapy is restricted due to concerns regarding resistance.⁴

Adverse effects: skin irritation rarely occurs.^{3,18} Tetracycline is associated with photosensitisation and yellow skin discolouration.²⁷ In widespread long-term use of topical clindamycin isolated cases of pseudomembranous colitis have been reported.^{18,26}

Combination therapy – topical treatments can be used in combination, and are more effective than when either agent is used alone.^{4,9,18,29,30} Combination therapy also reduces the risk of bacterial resistance.^{3,4,29} Options for combination therapy include topical antibiotics combined with BPO or topical retinoids and topical retinoids combined with BPO.

ORAL THERAPY

Oral treatment options for primary care management include oral antibiotics and hormonal therapy.

Oral antibiotics

Oral antibiotics are indicated for moderate to severe disease in patients with inflammatory disease where topical combinations have failed or are not tolerated.^{2,4,9} They suppress the growth of *P. acnes* and reduce inflammatory mediators.^{9,14} While the different classes of antibiotics exert their antibacterial effects in different ways,¹⁴ no oral antibiotic has been shown to be more effective than others.^{4,5} Resistance to *P. acnes* is an increasing problem and research in Europe suggests that at least 50% of acne patients are colonised by erythromycin resistant strains of *P. acnes* and as many as 20% are colonised with tetracycline resistant strains.¹⁴

Duration of treatment – oral antibiotics should be used for up to three months and may be used for up to six months if a therapeutic effect is observed and other therapies are not tolerated.^{10,14,31} **Oral antibiotics can be combined with topical retinoids to increase efficacy.**^{14,31,32} If used for prolonged periods they should be **used in combination with BPO to reduce the likelihood of *P. acnes* resistance emerging.**^{14,31} They should not be used in combination with topical antibiotics, which may increase the risk of *P. acnes* resistance.^{14,31}

Lack of Response to oral antibiotics may be due to a number of factors including: inadequate duration of treatment (at least a month is needed), poor compliance or the development of resistance to the antibiotics.² Antibiotic resistance should be suspected in patients who do not have a response to treatment or who have a relapse during treatment, especially those who have been on multiple courses of oral and topical antibiotics or have a history of variable compliance.^{2,14}

Tetracyclines should be considered as first line.^{14,31,33} They can be classified as first generation (tetracycline and oxytetracycline) and second generation (doxycycline, lymecycline and minocycline).^{9,14} First generation need to be taken at least twice daily and their absorption is impaired by food and milk whereas second generation can be taken once or twice daily and their absorption is unaffected by food.¹⁴ There is insufficient evidence to support one tetracycline over another in terms of efficacy.³³ There is cross-resistance within the class, but no cross-resistance to other antibiotic classes.¹⁴ Tetracyclines are contraindicated in children and pregnancy.¹⁴ Women using the combined oral contraceptive should use additional contraception for the first 3 weeks when starting a course of tetracyclines.¹⁷

Adverse effects include nausea, vomiting, diarrhoea and oesophagitis.^{5,14} To reduce the risk of oesophagitis, tetracyclines should be taken with plenty of water sitting upright.^{34,35} Photosensitivity can also occur particularly with doxycycline.^{11,12,14} Tetracyclines should be used with caution in patients with hepatic impairment.³⁴⁻³⁶ Rare side-effects include hepatotoxicity, hypersensitivity, blood disorders and benign intracranial hypertension.⁵ In addition, minocycline is also associated with rare cases of auto-immune hepatotoxicity, systemic lupus erythematosus and hyperpigmentation.^{35,37} As the potential adverse effects of minocycline are more serious than doxycycline and lymecycline, recent evidence suggests that when a second generation tetracycline is required **doxycycline** or **lymecycline** should be used.^{31,33,37,38} The Summary of Product Characteristics (SPC) should be reviewed for full prescribing information (available on www.imb.ie and www.medicines.ie).

Erythromycin has become less useful due to the increasing microbial resistance,^{14,31} however it is the antibiotic of choice for acne in pregnancy.^{4,9,12} Oral **clindamycin** is rarely used for acne due to potential serious adverse effects.¹⁴ **Trimethoprim** (300mg BD) is also used by specialists for acne, which is resistant to other antibiotics (although it is not authorised for this indication).^{14,31,39}

Hormonal therapy

The hormonal combination of **ethinylestradiol and cyproterone acetate** (Dianette®) may be considered for female patients if antibiotic therapy is ineffective.^{40,41} Cyproterone acetate blocks the androgen receptor and reduces sebum production.⁹ In Ireland it is authorised for use in the management of severe acne and androgen-dependant acne.⁴² It is as effective as oral antibiotics⁴³ however may take 3 - 6 months to produce significant sebum suppression, resulting in slow therapeutic results.¹ It has a higher risk of thromboembolism than the low-dose combined oral contraceptive (COC)⁴¹ and is contraindicated in women with a personal or close family history of venous thromboembolism.^{9,42}

COCs are also used in primary care to moderate the hormonal influences of acne (even though they are not authorised for this indication).^{9,12} They are associated with both a reduction in acne lesion counts and acne severity, however their effect depends on the balance of oestrogen and progestogen and the anti-oestrogenic activity of the progestogen.^{2,44,45} COCs containing the newer generation progestogens with anti-oestrogen properties (including norgestimate, gestodene, desogestrel)⁴⁴ and the anti-androgen (drospirenone)^{44,45} have demonstrated efficacy in the treatment of acne. COCs containing the lower dose of oestrogen are preferred due to the lower risk of thromboembolism and women should be advised that preparations containing gestodene and desogestrel have been associated with an increased risk of thromboembolism.⁴⁶ COCs containing progesterone with high androgenic activity may worsen acne in susceptible women. Progestogen only contraceptives should be avoided as they may exacerbate acne.^{1,12}

As well as clearing acne lesions and preventing scarring, effective pharmacological treatment reduces the psychological impact of acne and improves self-esteem and quality of life. Table 2 summarises the pharmacological treatment options for a patient with acne vulgaris in primary care.

Table 2: Management of acne vulgaris in primary care¹⁷

Mild acne (usually treatment with one drug is sufficient)

- Start with topical treatments such as benzoyl peroxide (BPO) or topical retinoids
- Azelaic acid is an alternative if BPO or topical retinoids are not tolerated
- Topical antibiotics may be required (usually in combination with BPO) if inflammatory lesions are present

Moderate acne (usually benefits from combined treatment with two topical drugs)

- Topical antibiotic plus BPO is a first-line choice
- Topical retinoid plus BPO is also effective but may cause skin irritation
- Topical retinoid plus a topical antibiotic can be used for inflammatory and non-inflammatory lesions, but resistance can be a concern
- Azelaic acid can be used as an alternative if other products cause unacceptable skin irritation
- Treat with systemic antibiotics if topical treatment has failed or cannot be tolerated, there is moderate acne of the back or shoulders and there is a significant risk of scarring

Severe acne

- Prescribe an oral tetracycline as first-line treatment
- Erythromycin is an alternative for people who cannot take or tolerate tetracyclines and in pregnancy
- Topical therapy in combination with oral antibiotics should be considered
- Ethinylestradiol and cyproterone acetate may be considered in females where a hormonal cause is suspected

OTHER SYSTEMIC THERAPY FOR ACNE VULGARIS

Isotretinoin is a synthetic form of Vitamin A which has been used in the treatment of acne for >20 years and is the only acne treatment which impacts on the four main aetiological factors driving acne.^{1,9,10} **It should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne.**^{47,48} It is authorised for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.^{10,47}

It is estimated that up to 40% of patients remain free of acne after one course of treatment with isotretinoin, 40% have a recurrence of low severity which will respond to treatment that previously was resistant to treatment and 20% will require further treatment with isotretinoin.² Patients should be warned that it is common for acne to deteriorate in the first four weeks of treatment and that rarely a severe flare or even acne fulminans can occur.^{9,12}

The starting dose should be 0.5mg/kg per day and the dose should be adjusted according to response and adverse effects.⁹ Patients with multiple comedones or severe nodular acne are at increased risk of flaring,⁹ these patients should be started at a lower dose 0.25mg/kg per day and gradually increased over 4 - 6 weeks.

Adverse effects mucocutaneous problems including cracked lips, nose bleeds and dry skin are the most common side-effects and are dose dependent.^{5,9} Isotretinoin is also associated with raised liver transaminases and raised triglycerides.^{2,5,49} Adverse psychiatric events such as mood swings, depression and suicide have also been reported as possible adverse events of isotretinoin.^{5,9} While acne itself is often associated with anxiety and depression it appears that there may be a rare idiosyncratic reaction in some patients who develop depression on oral isotretinoin⁹ and patients should be counselled about mood changes and closely monitored during treatment.⁵

Isotretinoin is highly teratogenic and a **Pregnancy Prevention Programme** is required for all women of child-bearing potential where the use of isotretinoin is considered.^{2,9,10,47,48,50} **All doctors prescribing or monitoring isotretinoin therapy need to be fully aware of the Pregnancy Prevention Programme and ensure that the patient understands the need for and complies with the conditions for pregnancy prevention.**⁴⁸ The Pregnancy Prevention Programme states that the patient must understand the teratogenic risk associated with isotretinoin use, and is on one and preferably two forms of effective contraception including a barrier method for at least one month before start of treatment, throughout the treatment period and at least one month after cessation of treatment. The patient is also required to have medically supervised pregnancy tests performed in the first 3 days of the menstrual cycle prior to starting therapy, at follow-up visits at 28 day intervals, and five weeks after stopping treatment to exclude pregnancy.^{47,48} Prescriptions for oral isotretinoin are limited to 30 days' treatment for women of childbearing potential. **The prescriber must review the full details of the Pregnancy Prevention Programme, which is available in the SPC for isotretinoin.**⁴⁷

Baseline blood tests including fasting lipids and liver function should also be done prior to initiating therapy and repeated one month after starting treatment and 3 monthly thereafter.^{10,47}

SUMMARY

Acne remains a very common dermatological problem seen in primary care. Acne can have a significant impact on a patient's quality of life. It frequently affects young people at a time when they are undergoing maximum physical and social changes. The options for management of acne have expanded significantly. The increasing emergence of antibiotic-resistant *P. acnes* should be taken into account when prescribing topical antibiotics alone or oral antibiotics; which can be combined with other topical therapy to reduce resistance. Combining topical therapies, logical prescribing of systemic antibiotics along with topical treatments and/or the use of oral isotretinoin should ensure excellent efficacy and result in minimal psychological and physical scarring for acne patients.

List of references available on request. Date of preparation: April 2008

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 for specific information on a drug

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