Guide to the management of acne in primary care

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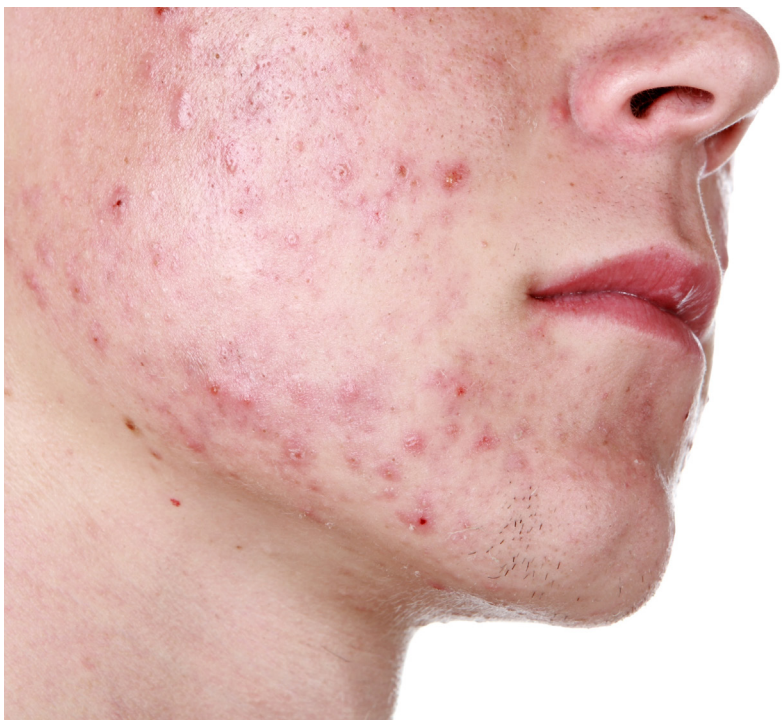
Acne is a common skin condition that can have profound physical and psychological impacts. This article outlines its clinical presentation and recommended management in primary care and discusses when referral to secondary care is necessary.



Acne vulgaris is a multifactorial, chronic skin condition characterised by dysregulation of the pilosebaceous unit. It typically affects the face, chest and back; sites of dense sebaceous gland concentration. Acne can be classified as inflammatory, comprising erythematous papules, pustules, nodules and cysts; or comedonal, in which there are blackheads (open follicles with darkly oxidised keratin) and whiteheads (closed follicles presenting as small white papules). Additional clinical features include seborrhoea, post-inflammatory hyperpigmentation and scarring.[1]

Far from only a cosmetic concern, studies have demonstrated that having acne is associated with an increased probability of developing anxiety, depression and suicidal ideation.[2]

Traditionally considered a disorder of adolescence, it has a prevalence of up to 85% in those aged 12–24 years old, though it can develop at any age, including in the neonatal period.[3] During the adolescent years, there is equal prevalence between genders, but females are disproportionately affected as older adults.[4] Acne is more common overall in African American ethnicities, and they are also more likely to develop secondary changes such as dyspigmentation and keloid scarring.[5]

Aetiology

The pathophysiology of the development of acne is underpinned by four key processes (see Table 1). There is also a genetic predisposition with offspring almost three times more likely to develop acne if there is a positive parental family history.[6]

The role of lifestyle factors is debated but a recent systematic review reported the pro-acnegenic effect of diets containing foods with a high glycaemic index and dairy products, though this is potentiated by gender and ethnicity.[7] Other potential risk factors include obesity, smoking and abnormal gut microbiota, though evidence from different sources is conflicting.[8]

Diagnosis

The diagnosis of acne is based on the clinical presentation and history. The assessment of the severity of acne is subjective

Follicular hyperkeratinisation	• Abnormal shedding of skin cells leading to their accumulation in follicles, contributing to microcomedone formation
Excess sebum production	• Thought to be in part due to increased sensitivity to circulating androgens
Colonisation with *Cutibacterium acnes*	• Cleaves lipids within sebum into free fatty acids
Inflammation	• In part due to free fatty acids • Increased expression of proinflammatory mediators

Table 1. Pathophysiological processes of acne

but the following criteria have been recommended by NICE:[9]
- Mild acne – mainly open and closed comedones
- Moderate acne – widespread comedonal and inflammatory lesions
- Severe acne – as for moderate but with nodules, cysts and possibly scarring.

Investigations may be warranted to assess for associated conditions such as polycystic ovary syndrome (PCOS), should there be clinical suspicion.

Management

The aim of treatment for acne vulgaris is to reduce the frequency and severity of exacerbations as well as improve the overall appearance of the skin and minimise scarring. The pharmacological management of acne can be approached using the stepwise manner illustrated in Figure 1.

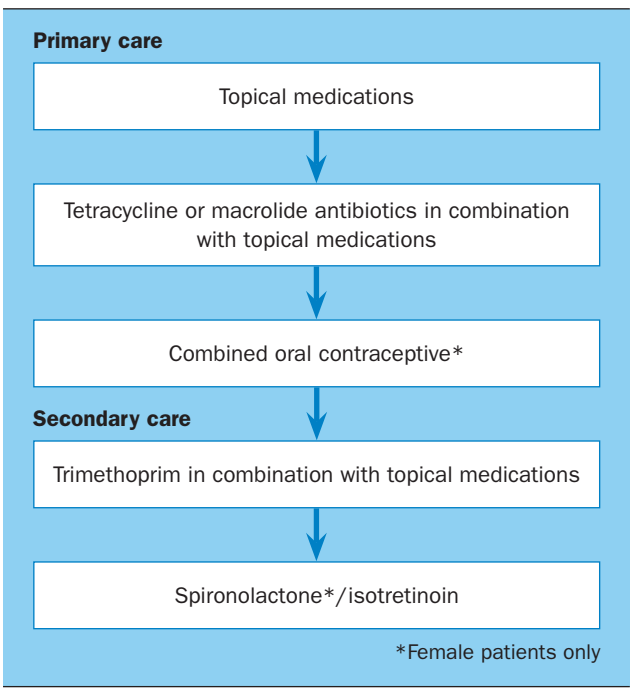


Figure 1. Stepwise treatment approach for management of acne

It is important for the clinician to dispel any myths the patient may have about the causes of acne, such as its relationship with poor hygiene and diet. Patients should be encouraged to remove make-up at the end of each day, and to cleanse affected areas twice a day with a foaming cleanser followed by a non-comedogenic moisturiser. Sunscreen should be encouraged for daytime use as it can improve the appearance of post-inflammatory hyperpigmentation. Patients may have questions about the rise of 'cosmeceuticals' in managing their acne. There is emerging evidence for the benefit of niacinamide and for alpha-hydroxy acids such as glycolic acid.[10]

Topical medications

Topical products are either used as monotherapy in mild acne or in combination with oral treatment in the management of moderate to severe acne. The agents most commonly prescribed include topical benzoyl peroxide, azelaic acid, antibiotics and retinoids. In patients who are pregnant, breastfeeding or considering pregnancy, topical benzoyl peroxide, azelaic acid and topical antibiotics are considered to be safe.[11]

Benzoyl peroxide

Benzoyl peroxide is available in a variety of strengths and formulations. It is bactericidal and lowers the concentration of *Cutibacterium acnes* on the skin surface. It commonly causes skin irritation, so a gradual uptitration in frequency is recommended. Patients should be warned about the bleaching effect it can have on clothing and bedlinen but can be reassured that it has no lightening effect on the skin. Benzoyl peroxide is generally used in combination with oral antibiotics to reduce antibiotic resistance. It has a modest effect in treating inflammatory lesions and is more effective when combined with other medications.[12]

Azelaic acid

Azelaic acid can be prescribed at as a 15% gel (Finacea) or 20% cream (Skinoren). Lower strengths are available over the counter. It is applied to the entire area twice daily with efficacy being reported from six weeks. It can reduce inflammatory lesion count by up to 70% in moderate acne.[13] Other than mild skin irritation, it is generally very well tolerated.

Topical antibiotics

The most commonly prescribed topical antibiotics for acne are erythromycin and clindamycin. They are considered more effective in treating inflammatory acne than comedonal acne. They have a bacteriostatic effect on *C. acnes* as well as an anti-inflammatory effect due to inhibition of complement pathways and neutrophil chemotaxis.[14] Side-effects are minimal and are generally limited to skin irritation. They should always be combined with topical benzoyl peroxide or retinoid to minimise antibiotic resistance.

Topical retinoids

In the UK, the most commonly prescribed topical retinoids are Differin (adapalene), which is available as a 0.1% cream or gel,

and tretinoin. They are effective in the treatment of both comedonal and inflammatory acne, but their efficacy is further enhanced when they are combined with a topical antibiotic or benzoyl peroxide.[15] Trifarotene cream (Aklief) is a new topical retinoid with rigorous clinical trial data to support its use in facial and truncal acne, and is the first treatment to be approved for acne in 20 years.[16] Retinoids may induce greater skin irritation than other topical treatments and are also photosensitising and contraindicated in pregnancy and breastfeeding.

Fixed-combination topical agents

Fixed-combination topical agents are recommended as first-line treatment for acne and include: topical adapalene with benzoyl peroxide gel (*eg* Epiduo), topical tretinoin with clindamycin gel (*eg* Treclin) and topical benzoyl peroxide with clindamycin gel (*eg* Duac). In patients who experience skin irritation, advise short contact (wash off after an hour) or alternate day application initially with gradual progression to standard application.[17]

Oral medications

Oral antibiotics

Topical or oral antibiotics should not be used as monotherapy or in combination with each other. Tetracycline antibiotics are the first-line oral agent of choice in treating acne. They disrupt bacterial protein synthesis and exert a bacteriostatic effect on *C. acnes*. Lymecycline 408mg once daily or doxycycline 100mg once daily for a minimum of three months can be prescribed initially. If the response is insufficient, the dosing frequency can be doubled but this is off-licence use. The side-effects of tetracyclines are mainly gastrointestinal (with oesophagitis particularly associated with doxycycline) and increased photosensitivity. Tetracyclines should not be prescribed in conjunction with oral retinoids because of the risk of raised intracranial pressure.[18] Tetracyclines have usually been avoided in patients under the age of eight years due to the risk of dental staining and hypoplasia, but large review studies suggest that they can be safely prescribed for younger children.[19]

Erythromycin, a macrolide antibiotic, can be prescribed as an alternative oral agent at a dose of 500mg twice daily. Typically, patients are prescribed a three-month initial course and if beneficial, it can be maintained for up to six months. There is an increasing problem with resistance to erythromycin and as a result its efficacy is becoming limited in some areas.[20]

Trimethoprim is an alternative antibiotic that can be prescribed if others have not reached the desired efficacy. It is licensed for use in acne at a dosage of 300mg twice daily. Initially, the prescription is for three months but this can be continued for up to six months if effective. It is bactericidal and reduces sebum production. It is effective in approximately two-thirds of patients who have not responded to tetracyclines.[21] It is contraindicated in pregnancy due to teratogenic effects. It can rarely cause agranulocytosis, so patients should be warned to stop the medication if they develop a fever or sore throat. There have been reports of patients developing severe cutaneous adverse reactions (*eg* toxic epidermal necrolysis and drug reactions with eosinophilia and systemic symptoms).[22] Patients should therefore be counselled to discontinue the drug should any rash develop and seek medical attention if it is severe or associated with mucositis. We recommend monitoring full blood count (FBC), renal function and liver function tests (LFTs) at baseline and after two to six weeks of therapy because trimethoprim can adversely affect renal and liver function.[23] Patients with reduced renal function, diabetes and those prescribed concomitant medications that can increase risk of hyperkalaemia should have ongoing monitoring.[24]

- Xerosis
- Photosensitivity
- Headaches
- Acne flare
- Myalgia
- Hepatitis
- Hypertriglyceridaemia
- Hair loss
- Depression
- Sexual dysfunction
- Impaired night vision
- Suicidality
- Benign intracranial hypertension

Table 2. Potential side-effects of isotretinoin by frequency[32]

Hormonal therapies

Combined oral contraceptives (COCs) contain both an oestrogen and a progestogen. They reduce circulating free androgen levels, which reduces inflammatory and non-inflammatory acne lesions.[25,26] According to NICE guidelines, third- and fourth-generation COCs are generally preferred. Co-cyprindiol (Dianette) or other ethinylestradiol/cyproterone acetate-containing products can be considered where other treatments

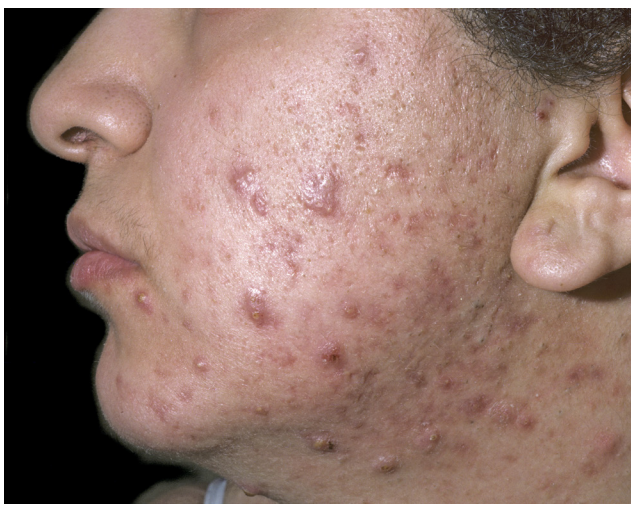


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Figure 2. Nodulocystic acne is a severe form of inflammatory acne characterised by painful nodules and cysts that typically lead to scarring. Patients presenting with this type of acne are among those who should be referred to secondary care for treatment

have failed but require a discussion of the benefits *versus* risks with patients.[9]

It is important to recognise that progesterone-only formulations have androgenic properties, which can exacerbate acne. Physicians should therefore avoid prescribing progesterone-only contraceptives in patients with concomitant acne.[26] This is not limited to oral formulations; a recent large review reported that hormonal intrauterine systems (IUS) are also associated with the worsening of acne.[27]

Spironolactone is an aldosterone antagonist commonly prescribed for hypertension and its diuretic properties. It can also be prescribed in females for acne because of its anti-androgenic properties. Patients should be started at a dose of 50mg once daily, titrated to a maximum of 200mg once daily according to response and adverse effects. Results can be impressive with an average 78% reduction in acne lesions reported.[28] Spironolactone is contraindicated in pregnancy due to the risk of feminisation of the male fetus *in utero*. It is generally well tolerated; common side-effects include breast tenderness and menstrual irregularities. It should not be co-prescribed with any other agent that has the potential to cause hyperkalaemia. Renal function and potassium levels should be checked at baseline, but ongoing monitoring is only required if other risk factors for hyperkalaemia are present (*eg* in patients over 45 years old).[29]

Oral retinoids

Isotretinoin (commonly prescribed as the brand Roaccutane) is an oral retinoid whose effects include normalisation of keratinisation and inhibition of sebaceous gland function in addition to its anti-inflammatory properties. In the UK, isotretinoin can only be prescribed by consultant dermatologist-led teams. It is titrated to a dose of 0.5–1mg/kg daily with an overall target cumulative dose of 120–150mg/kg. Patients need to be carefully counselled about the potential side-effects (see Table 2).

The Medicines and Healthcare products Regulatory Agency (MHRA) has introduced new safety measures and additional oversight for patients prescribed isotretinoin with particular emphasis on the risk of sexual and psychiatric side-effects.[30] Patients must complete objective assessments of their mental health before and during treatment with isotretinoin. It is important for primary care physicians to report any previous or current mental health concerns in patients referred for consideration of isotretinoin and work together with secondary care teams to access mental health support where required.

Women of childbearing potential (WOCBP) should be made aware of the teratogenic risks of isotretinoin before starting treatment and must be enrolled onto the Pregnancy Prevention Programme. Pregnancy must be excluded before starting treatment. Patients who use the contraceptive implant or who have a coil (IUD) or IUS can have repeat prescriptions every 12 weeks once stable on isotretinoin. Patients using a hormonal contraceptive pill or contraceptive injection need to agree to also use a barrier method (*eg* condom) and repeat isotretinoin prescriptions can only be renewed for 30 days. Contraception

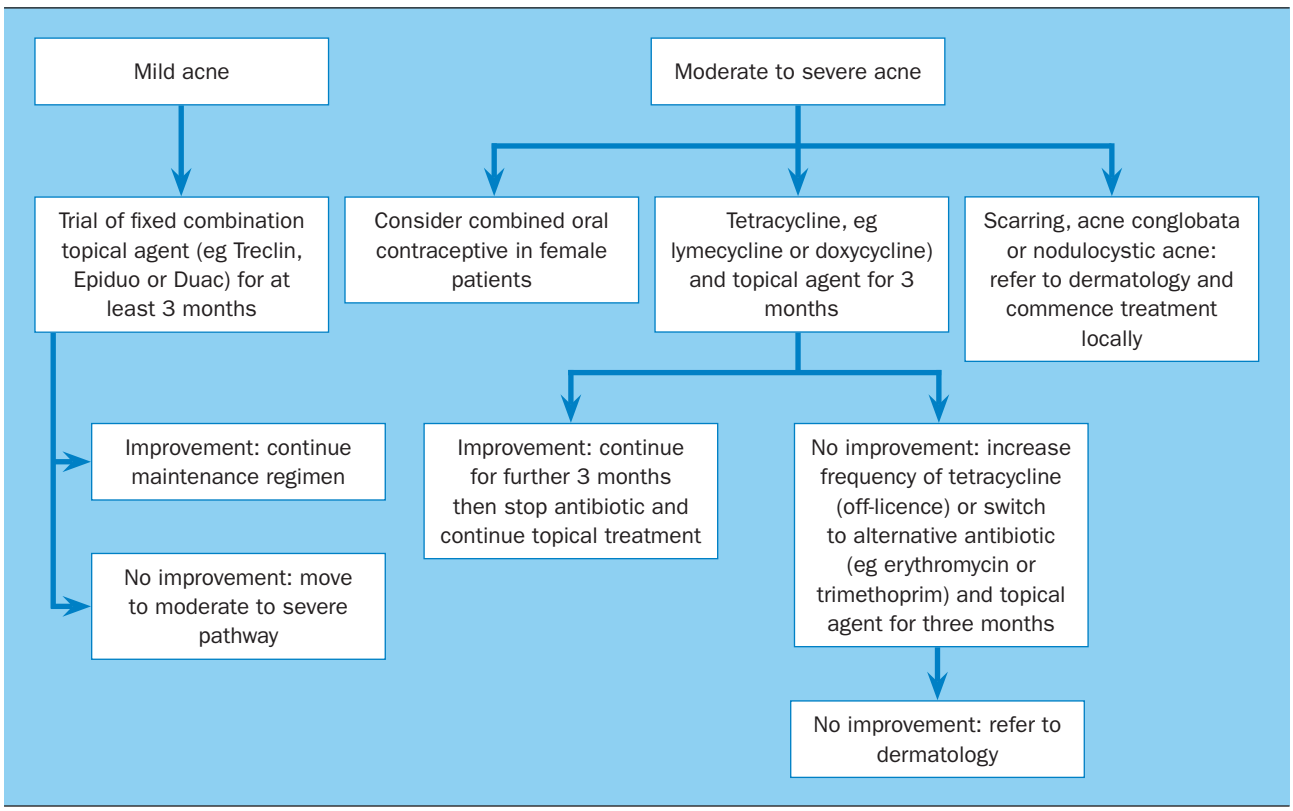

Figure 3. Pathway for the management of acne in primary care

should start one month before isotretinoin, continue throughout and for at least one month after stopping isotretinoin. In rare circumstances, WOCBP may opt out of the Pregnancy Prevention Programme (*eg* hysterectomy or same-sex relationships).

Blood monitoring (FBC, renal function, LFTs, lipid profile and random glucose) is requested at baseline and repeated after four weeks of treatment and three monthly thereafter. Tetracycline antibiotics are contraindicated alongside isotretinoin because of the increased risk of idiopathic intracranial hypertension. There is evidence that skin fragility may persist for six months following completion of isotretinoin treatment. Patients should be counselled to avoid procedures such as laser treatment and waxing as these may cause excessive skin trauma.[31]

Referral to secondary care

NICE guidance recommends patients should be referred to a dermatologist in the following scenarios:[9]

- If there is evidence of scarring (generally distinguished from post-inflammatory hyperpigmentation by the presence of textural change)
- Mild to moderate acne that has not responded to two completed courses of treatment
- Moderate to severe acne that has not responded to previous treatment (including an oral antibiotic)
- Acne conglobata or nodulocystic acne (see Figure 2)
- Acne of any severity contributing to persistent psychological distress.

A new acne primary care referral proforma has been created by the British Association of Dermatologists, taking into account the new recommendations from the Commission of Human Medicines, and should be used by primary care healthcare professionals to refer patients to secondary care.[33]

Relapses

If acne recurs or the patient reports an exacerbation following previous successful treatment, then consider restarting the same therapy or an alternative option, as outlined in Figure 3. Acne can return after isotretinoin and primary care physicians should try first-line agents, even if they were not effective before isotretinoin treatment. Referral for further courses of isotretinoin can be considered for patients with severe acne and those who do not respond to treatment.

Conclusion

Acne is a common cutaneous disorder that affects a large proportion of the population and has profound physical and psychological impacts. Successful management of acne requires a holistic approach, taking into consideration the severity of clinical presentation and patient factors and preferences.

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Declaration of interests

VY has received honoraria and participated in advisory boards for Abbvie, Leo Pharma, Novartis and UCB.

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