Acne vulgaris

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Acne is a chronic inflammatory disease of the pilosebaceous unit resulting from androgen-induced increased sebum production, altered keratinisation, inflammation, and bacterial colonisation of hair follicles on the face, neck, chest, and back by *Propionibacterium acnes*. Although early colonisation with *P acnes* and family history might have important roles in the disease, exactly what triggers acne and how treatment affects the course of the disease remain unclear. Other factors such as diet have been implicated, but not proven. Facial scarring due to acne affects up to 20% of teenagers. Acne can persist into adulthood, with detrimental effects on self-esteem. There is no ideal treatment for acne, although a suitable regimen for reducing lesions can be found for most patients. Good quality evidence on comparative effectiveness of common topical and systemic acne therapies is scarce. Topical therapies including benzoyl peroxide, retinoids, and antibiotics when used in combination usually improve control of mild to moderate acne. Treatment with combined oral contraceptives can help women with acne. Patients with more severe inflammatory acne usually need oral antibiotics combined with topical benzoyl peroxide to decrease antibiotic-resistant organisms. Oral isotretinoin is the most effective therapy and is used early in severe disease, although its use is limited by teratogenicity and other side-effects. Availability, adverse effects, and cost, limit the use of photodynamic therapy. New research is needed into the therapeutic comparative effectiveness and safety of the many products available, and to better understand the natural history, subtypes, and triggers of acne.

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Introduction

Acne is a disease of the pilosebaceous unit—hair follicles in the skin that are associated with an oil gland (figure 1).[2] The clinical features of acne include seborrhoea (excess grease), non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and various degrees of scarring. The distribution of acne corresponds to the highest density of pilosebaceous units (face, neck, upper chest, shoulders, and back). Nodules and cysts comprise severe nodulocystic acne. This Seminar summarises information relating to the clinical aspects of common acne (acne vulgaris). Acne classification, scarring, acne rosacea, chloracne, acne associated with polycystic ovary syndrome, infantile acne, acne inversa, and drug-induced acne have been reviewed elsewhere.[3–10]

Prevalence and natural history

Some degree of acne affects almost all people aged 15 to 17 years,[11–13] and is moderate to severe in about 15–20%.[8,12,14] Prevalence estimates are difficult to compare because definitions of acne and acne severity have differed so much between studies, and because estimates are confounded by the availability and use of acne treatments.[15] Surveys of self-reported acne have proven unreliable.[16] Although perceived as a teenage disease, acne often persists into adulthood.[17,18] One population study in Germany found that 64% of those aged 20 to 29 years and 43% of those aged 30 to 39 years had visible acne.[19] Another study of more than 2000 adults showed that 3% of men and 5% of women still had definite mild acne at the age of 40 to 49 years.[20]

Acne typically starts in early puberty with increased facial grease production, and mid-facial comedones[8] followed by inflammatory lesions. Early-onset acne (before the age of 12 years) is usually more comedonal than inflammatory, possibly because such individuals have not yet begun to produce enough sebum to support large numbers of *Proprionibacterium acnes*.[21] One prospective study of 133 children aged 5·5 to 12 years, followed up for an average of 2·5 years, found asynchronous facial sebum production initially, with increasing numbers of glands switching on sebum production over time.[22] Subsequent expansion of the propionibacterial skin flora (in the nares and then facial skin) occurred earlier in children who developed acne than in children of the same age and pubertal status who did not, suggesting that postponement of sebum production or expansion of propionibacterial skin flora until after puberty could prevent acne or minimise disease severity. Predictors of acne severity include early onset of comedonal acne,[8] and increasing number of family members with acne history.[14] Factors that can cause acne to flare include the menstrual cycle, picking, and emotional stress.[23,24] Beliefs about external factors affecting acne vary according to ethnic group.[25] Acne vulgaris is a chronic disease that often persists for many years.[26] There is little research about what factors might predict whether acne will last into adulthood.[27] We could not find any good quality cohort studies summarising the natural history of acne. Sequential prevalence surveys of different populations showing a gradual decrease in

Search strategy and selection criteria

Our main sources of evidence included all systematic reviews on acne published since 1999 which have been mapped by NHS Evidence—skin disorders annual evidence updates,[1] supplemented by specific searches on Medline for articles published between January, 2003, and Jan 16, 2011, using the search terms "acne", "comedones", "vulgaris", and "aetiology", "causes", "natural history", "pathophysiology", "treatment", "management", and "guidelines". We also scrutinised citation lists from retrieved articles.

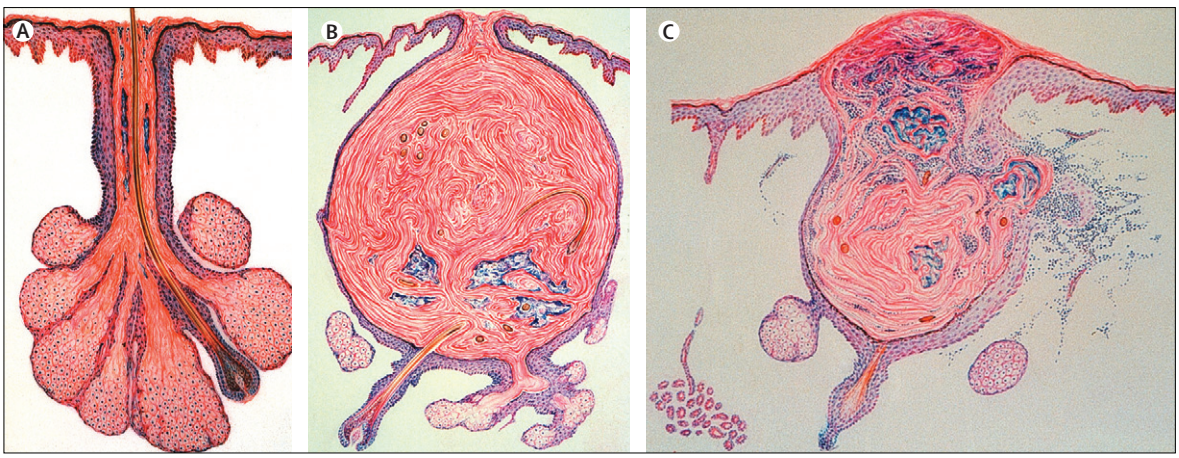

Figure 1: **Normal sebaceous follicle (A) and comedo (B), and inflammatory acne lesion with rupture of follicular wall and secondary inflammation (C)**
Reproduced, with permission, from reference 2.

acne prevalence after the age of 20 years weakly underpin our current understanding of the natural history of acne. Mild inflammatory acne declines or disappears in a large proportion of those with acne in their teens. Cytokines that induce comedogenic changes at the follicular infundibulum might also inhibit lipid secretion from the sebaceous gland, resulting in remission of individual lesions.[28] However, seborrhoea persists throughout adult life, long after inflammatory lesions have resolved.[29] Adult acne related to circulating androgens goes by several names, including post-adolescent or late-onset acne, and occurs most commonly in women beyond the age of 25 years.[30]

Cause

Risk factors and genes associated with acne prognosis and treatment are unclear.[31,32] Twin studies have pointed to the importance of genetic factors for more severe scarring acne.[33] A positive family history of acne doubled the risk of significant acne in a study of 1002 Iranian 16-year-olds,[14] and the heritability of acne was 78% in first-degree relatives of those with acne in a large study of Chinese undergraduates.[34] Acne appears earlier in girls, but more boys are affected during the mid-teenage years.[35] Acne can occur at a younger age and be more comedonal in black children than in white children, probably from earlier onset of puberty.[36] A study of 1394 Ghanaian schoolchildren found that acne was less common in rural locations, but the reasons for this are unclear.[37]

Although earlier observational studies suggested an inverse association between smoking and acne,[38] subsequent studies have shown that severe acne increases with smoking.[19,39] Increased insulin resistance and high serum dehydroepiandrosterone might explain the presence of acne in polycystic ovary syndrome.[40,41] Occlusion of the skin surface with greasy products (pomade acne),[42] clothing, and sweating can worsen acne. Drugs such as anti-epileptics typically produce a monomorphic acne, and acneiform eruptions have been associated with anti-cancer drugs such as gefitinib.[10] The use of anabolic steroids for increasing muscle bulk might be underestimated, and can give rise to severe forms of acne.[43] Tropical acne can occur in military personnel assigned to hot, humid conditions.[44] Dioxin exposure can result in severe comedonal acne (chloracne), but it is not associated with common acne.

Diet, sunlight, and skin hygiene have all been implicated in acne,[45] but little evidence supports or refutes such beliefs.[46] One systematic review suggested that dairy products (especially milk) increase acne risk, but all the included observational studies had significant shortcomings.[47]

Previous studies of giving young people large quantities of chocolate to try and provoke acne were too small and too short to claim no effect.[48] The apparent absence of acne in native non-Westernised people in Papua New Guinea and Paraguay[49] has led to the proposal that high glycaemic loads in Western diet could have a role in acne, perhaps through hyperinsulinaemia leading to increased androgens, increased insulin-like growth-factor 1, and altered retinoid signalling.[50,51] A randomised controlled trial showing that a low glycaemic load diet might improve acne provides preliminary support for this theory.[52] Although acne has been associated with increasing body mass,[53] no evidence suggests that putting people on restrictive diets reduces acne.

Disease mechanisms

Four processes have a pivotal role in the formation of acne lesions: inflammatory mediators released into the skin; alteration of the keratinisation process leading to comedones; increased and altered sebum production under androgen control (or increased androgen receptor sensitivity); and follicular colonisation by *P acnes*.[27] The exact sequence of events and how they and other factors interact remains unclear.

Immune-mediated inflammatory processes might involve CD4+ lymphocytes and macrophages that stimulate the pilosebaceous vasculature precede follicular hyperkeratinisation.[54] Defective terminal keratinocyte differentiation leads to comedo formation under the influence of androgens and qualitative changes in the sebum lipids that induce interleukin 1 (IL1) secretion.[55] Sebaceous glands are an important part of the innate immune system, producing a variety of antimicrobial peptides, neuropeptides, and antibacterial lipids such as sapienic acid. Each sebaceous gland functions like an independent endocrine organ influenced by corticotropin-releasing hormone, which might mediate the link between stress and acne exacerbations.[56] Vitamin D also regulates sebum production, and insulin-like growth-factor 1 might increase sebum through sterol-response-element-binding proteins.[57] Oxidised lipids such as squalene can stimulate keratinocyte proliferation and other inflammatory responses mediated by the proinflammatory leukotriene B4.[58] Matrix metallo-proteinases in sebum have an important role in inflammation, cell proliferation, degradation of the dermal matrix, and treatment responsiveness.[59]

Sebaceous follicles containing a microcomedone provide an anaerobic and lipid-rich environment in which *P acnes* flourishes.[60] Lipogenesis is directly augmented by *P acnes*.[61] Colonisation of facial follicles with *P acnes* follows the asynchronous initiation of sebum production,[22] which might explain why treatment with isotretinoin treatment too early can need to be followed up with subsequent courses, as new previously *P acnes*-naive follicles become colonised and inflamed. Unique *P acnes* strains with different bacterial resistance profiles colonise different pilosebaceous units and induce inflammation by the activation of toll-like receptors in keratinocytes and macrophages.[62] In-vitro work suggests that *P acnes* could behave like a biofilm within follicles, leading to decreased response to antimicrobial agents.[63] *P acnes* resistance to commonly used oral antibiotics for acne affects treatment response, suggesting that direct antimicrobial effects might be important in addition to the anti-inflammatory actions of antibiotics.[64]

How does acne affect people?

Acne results in physical symptoms such as soreness, itching, and pain, but its main effects are on quality of life. Psychological morbidity is not a trivial problem,[65] and it is compounded by multiple factors: acne affects highly visible skin—a vital organ of social display; popular culture and societal pressures dictate blemishless skin; acne can be dismissed by health-care professionals as a trivial self-limiting condition; and acne peaks in teenage years, a time crucial for building confidence and self-esteem.

Case-control and cross-sectional studies assessing the effect of acne on psychological health found a range of abnormalities including depression, suicidal ideation, anxiety, psychosomatic symptoms, shame, embarrassment, and social inhibition,[66] which improve with effective treatment.[67] Anger inversely correlates with quality of life in acne and satisfaction with acne treatment.[68] Patients might not volunteer depressive symptoms and need prompting during consultation. UK teenagers with acne twice as often scored in the borderline or abnormal range on an age-appropriate validated questionnaire of emotional wellbeing than did those who did not have acne, and had higher levels of behavioural difficulties.[69] The presence of acne was associated with unemployment in a case-control study of young men and women.[70] One community study of 14–17-year-old Australian students reported no association between acne and subsequent psychological or psychiatric morbidity, a surprising finding perhaps explained by effective treatments or personality traits.[71]

Acne severity and degree of psychological impairment do not necessarily correspond—mild disease in one person can cause high degrees of psychological disability, whereas another with more severe disease can seem less bothered by their acne.[12] Most studies assessing psychological morbidity in acne have been cross-sectional, and therefore unable to establish causal direction. Few studies report the direct and indirect costs of acne.[72,73]

How can acne be managed?

Skin hygiene

There is no good evidence that acne is caused or cured by washing.[46] Antibacterial skin cleansers might benefit mild acne, and acidic cleansing bars are probably better than standard alkaline soaps. However, excessive washing and scrubbing removes oil from the skin surface, drying it and stimulating more oil production. Antibacterial skin cleansers provide no additional benefit to patients already using other, potentially irritating topical treatments.[46]

Counselling and support

Spending time dispelling myths and explaining that most treatments will not cure is worthwhile and might improve adherence.[74] Because acne treatments work by preventing new lesions rather than treating existing ones, an initial response might not appear for some weeks. Most effective treatments can require months to work.[75] Health-care providers should assess loss of self-esteem, lack of confidence, and symptoms of depression including suicidal thoughts. Acne's emotional effect might not be immediately evident or volunteered, but even mild acne can cause significant distress. Patients should also be told that online acne information, including from some support groups, varies in quality and can reflect sponsor bias, and clinicians have a role in guiding them to trustworthy resources.

Treatment guidelines

The many over-the-counter and prescription treatments for acne allow for a large number of potential combination treatments. A comprehensive systematic review

	Sebum excretion	Keratinisation	Follicular *Proprionibacterium acnes*	Inflammation
Benzoyl peroxide	–	(+)	+++	(+)
Retinoids	–	++	(+)	+
Clindamycin	–	(+)	++	–
Antiandrogens	++	+	–	–
Azelaic acid	–	++	++	+
Tetracyclines	–	–	++	+
Erythromycin	–	–	++	–
Isotretinoin	+++	++	(++)	++

+++=very strong effect. ++=strong effect. +=moderate effect. (+)=indirect/weak effect. –=no effect.

Table: **Targets of acne treatments**

in 1999 identified 274 trials of 140 treatments in 250 combinations.[76] Most were placebo-controlled studies of me-too products, and the authors found no basis from controlled trials to judge the efficacy of any treatment in relation to others, nor in the sequence of therapy. The table shows how different treatment medications target different aspects of acne pathology. The large number of products and product combinations, and the scarcity of comparative studies, has led to disparate guidelines with few recommendations being evidence-based. Recent acne guidelines include those from the Global Alliance to Improve Outcomes in Acne,[77] the American Academy of Dermatology/American Academy of Dermatology Association,[78] and the European expert group on oral antibiotics in acne.[79] Because of the paucity of evidence, these guidelines rely on the opinions of experts, many of whom declare significant potential conflicts of interest. Practical advice on how to manage acne based on a systematic search of evidence by an independent team is available in an online UK Clinical Knowledge Summary.[75] All of these guidelines illustrate similar approaches on which initial therapies should be based—ie, acne severity and whether the acne is predominantly non-inflammatory or inflammatory. We propose an algorithm for treating acne in figure 2 on the basis of our interpretation of the clinical evidence. This interpretation differs slightly from the Global Alliance recommendations by suggesting slightly more initial use of topical benzoyl peroxide than topical retinoids on the grounds of cost and on a longer track record of efficacy and safety. Assessment of treatment response in such a polymorphic condition can be difficult and should include an assessment of reduction of inflammatory and non-inflammatory lesions in relation to baseline photographs, plus an assessment of psychological wellbeing.

Topical treatments

Topical agents when used alone or in combination effectively treat mild acne consisting of open and closed comedones with a few inflammatory lesions.[77] The many treatment options offer different modes of action. Although all are more effective than placebo, establishing the most appropriate strategy for initial and maintenance treatment requires further research.[77,80] Topical treatments only work where applied. Because topical therapies reduce new lesion development they require application to the whole affected areas, rather than individual spots. Most cause initial skin irritation, and some people stop using them because of this. The irritation can be minimised by starting with lower strength preparations and gradually increasing frequency or dose. Where irritation persists, a change in formulation from alcoholic solutions to washes or gels to more moisturising creams or lotions might help.

Benzoyl peroxide

Benzoyl peroxide is a safe and effective[81] over-the-counter preparation that has several mechanisms of action, and should be applied to all the affected area.[82] Single-agent benzoyl peroxide works as well as oral antibiotics or a topical antibiotic combination that included benzoyl peroxide for people with mild-to-moderate facial acne.[64] It has greater activity than topical (iso)tretinoin against inflammatory lesions;[83,84] the results of two further underpowered trials were equivocal.[85,86] Further studies are needed, especially as combination therapy might be better.[86] Benzoyl peroxide causes initial local irritation. Patients need to be counselled to expect irritation but discontinue treatment if it becomes severe. Irritation will decrease in most cases, especially if patients start applying it every other day and then increase the frequency. Low strength (2·5% or 5%) benzoyl peroxide is recommended, since it is less irritating and there is no clear evidence that stronger preparations are more effective.[87]

Topical retinoids

Treatment with tretinoin, adapalene, and isotretinoin require medical prescriptions. Tazarotene is not licensed in the UK for acne. All retinoids are contraindicated in pregnancy, and women of childbearing age must use effective contraception. Topical retinoids act on abnormal keratinisation and are also anti-inflammatory, so they work for both comedonal and inflammatory acne. Many placebo-controlled or non-inferiority studies citing better tolerability exist, but few trials guide practice. More trials comparing retinoids against each other and against other therapies are needed. Randomised controlled trials (RCTs) have shown that higher-strength preparations might have greater activity than lower-strength ones, but at the expense of more irritation. All topical retinoids induce local reactions, and should be discontinued if severe. They do not seem to cause temporary worsening of acne lesions,[88] but can increase the sensitivity of skin to ultraviolet light.

Topical antibiotics

How topical antibiotics improve acne has not been clearly defined, but they seem to act directly on *P acnes* and reduce inflammation. Topical antibiotics have less

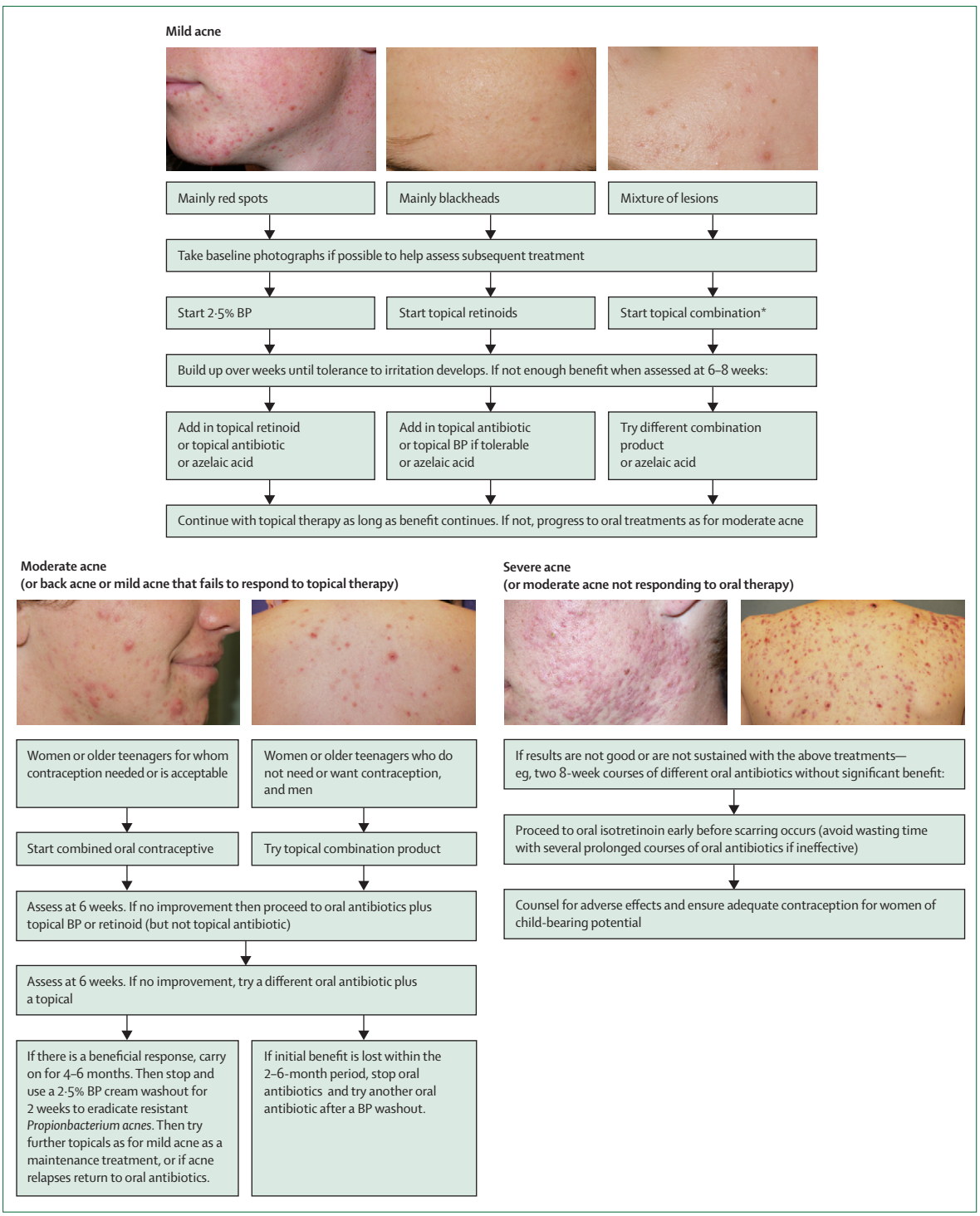

Figure 2: **Suggested algorithm for treatment of mild, moderate, and severe acne based on our appraisal of current clinical evidence and uncertainties**
Figures reproduced with permission from DermNet NZ. BP=benzoyl peroxide. *Topical combination could be benzoyl peroxide plus topical antibiotic, or topical benzoyl peroxide plus topical retinoid.

activity than other agents against non-inflamed lesions. For more severe acne, topical antibiotics are usually combined with other products such as topical retinoids or benzoyl peroxide. Patients with back acne might respond better to oral antibiotic therapy because of the difficulties of applying treatments to large areas that are

difficult to reach. Topical antibiotics include clindamycin, erythromycin, and tetracycline. Topical antibiotics are also available in combination with benzoyl peroxide and zinc acetate. Alcohol-based preparations are more drying, and therefore more suitable for oilier skins. The efficacy of erythromycin might be declining because of bacterial resistance.[89]

Other topical therapies

Salicylic acid is an exfoliant and is a component of many over-the-counter preparations. No studies support routine use of salicylic acid in preference to other topical therapies. The American Guidelines state that data from peer-reviewed literature regarding the efficacy of sulphur, resorcinol, sodium sulfacetamide, aluminium chloride, and zinc are limited.[78] Similarly there is no reliable evidence to support the use of nicotinamide or combination triethyl citrate and ethyl linoleate.[90] Despite recent interest in topical dapsone[91] and taurine bromamine,[92] neither is licensed in the UK, and current comparative evidence does not support a change in practice. A new vehicle, emollient foam, containing sodium sulfacetaminde 10% and sulphur 5% is now available for acne treatment in the USA.[93] Azelaic acid has both antimicrobial and anti-comedonal properties but can cause hypopigmentation, and darker-skinned patients should therefore be monitored for signs. Anecdotal reports have suggested that azelaic acid might reduce post-inflammatory hyperpigmentation, which is possibly attributable to its activity on abnormal melanocytes. The American Guidelines note that its clinical use, compared to other agents, has limited efficacy according to experts.[78]

Combination topicals

There is accumulating information that combinations of topical treatments with different mechanisms of action work better than single agents.[94] Few combinations have been tested properly against the relevant monotherapy. The trials tend to be methodologically flawed by factors such as suboptimal dose or frequency of monotherapy.[82] Compliance can be increased with once-daily combination products because of their convenience and faster speed of onset,[95,96] although individual generic preparations used concomitantly might be more cost-effective.[64] Benzoyl peroxide inactivates tretinoin, and the two agents should not therefore be applied simultaneously; if used in combination one should be applied in the morning and one at night.

Oral treatments

Oral antibiotics

Oral antibiotics are usually reserved for more severe acne, acne predominantly on the trunk, acne unresponsive to topical therapy, and in patients at greater risk of scarring. Although antibiotics have shown effectiveness in terms of reducing the number of inflammatory lesions, none clear acne completely. Most patients seek acne clearance rather than reduction in lesion counts. There is no conclusive evidence that one antibiotic is more effective than another (including first and second generation tetracyclines) or that oral antibiotics are more effective than topical preparations for mild-to-moderate facial acne.[64] There is no evidence that higher doses are more effective than lower doses or that controlled-release preparations are necessary.[64,76,82,97]

The choice of antibiotic should therefore be based on the patient's preference, the side-effect profile, and cost. The tetracyclines (tetracycline, oxytetracycline, doxycycline, or lymecycline) are the preferred options; minocycline has significant adverse effects.[98] Co-trimoxazole should be avoided because the sulfamethoxazole component has significant side-effects. Quinolones are not recommended in adolescents due to arthropathy risks and because oral ciprofloxacin shows rapid selectivity that promotes resistance.[99] Aminoglycosides and chloramphenicol have very limited effects[79] and oral clindamycin, although effective, has the potential for significant adverse effects such as pseudomembranous colitis. There is increasing resistance to the macrolides (erythromycin and azithromycin) and trimethoprim that is causing worldwide concern.

The use of antibiotics for acne has been questioned owing to resistance concerns, especially since they are used for long periods at low doses.[100] Concomitant benzoyl peroxide can reduce problems with bacterial resistance,[101] whereas concomitant treatment with different oral and topical antibiotics should be avoided. Data from a large well-reported RCT indicated that 6–8 weeks is an appropriate time to assess response.[64] If an individual does not respond to antibiotics or stops responding, there is no evidence that increasing the frequency or dose is helpful. Such strategies increase selective pressure without increasing efficacy.[82] Antibiotics should be stopped if no further improvement is evident. Antibiotics should not be routinely used for maintenance because alternatives exist with similar efficacy and preventative action.[79,82] Benzoyl peroxide protects against resistance by eliminating resistant bacteria: the Global Alliance to Improve Outcomes in acne (2003) recommends that if antibiotics must be used for longer than 2 months, benzoyl peroxide should be used for a minimum of 5–7 days between antibiotic courses to reduce resistant organisms from the skin.[77]

Oral contraceptives

Combined oral contraceptives (COCs) contain an oestrogen (ethinylestradiol) and a progestogen. COCs are frequently prescribed for women with acne because oestrogen suppresses sebaceous gland activity and decreases the formation of ovarian and adrenal androgens. Progestogen-only contraceptives often worsen acne and should be avoided in women who have no contraindications to oestrogen-containing

preparations.[102] Progestogens bind to both progesterone and androgen receptors and their androgenic effects are dependent on the type and dose of progestogen. Third-generation progestogens such as desogestrel, norgestimate, and gestodene bind more selectively to the progesterone receptor than do the second-generation progestogens (eg, levonorgestrel and norethisterone), but at the cost of an increased risk of thromboembolism.

The Global Alliance Guidelines state that hormonal therapy is an excellent choice for women who need oral contraception and that it should be used as a component for combination therapy in women with or without endocrine abnormalities.[77] Hormonal therapy should be used early in women with moderate-to-severe acne, or in those with seborrhoea, acne, hirsutism, and alopecia symptoms. A Cochrane review found few important differences between different combined oral contraceptive types in their effectiveness for treating acne, and how they compare with alternative acne treatments is not clear.[102] Although preparations containing cyproterone acetate have been traditionally used for acne treatment, there is little evidence to show its superiority over other progestins. The same applies to the antiandrogen actions of spironolactone.[103]

Oral isotretinoin

When given for around 20 weeks, oral isotretinoin is the most effective medication resulting in clinical cure in around 85% of cases.[76,94,104] Relapse rates are around 21% and are dose-dependent, the best responses being seen with daily doses of 1 mg/kg per day or a total of 150 mg/kg over the treatment duration. Isotretinoin is usually reserved for severe nodulocystic scarring acne or acne resistant to other therapies (figure 3). Research is needed to investigate whether isotretinoin could be beneficial if used sooner for moderate cases. Isotretinoin causes cheilitis, dry skin, nose bleeds, secondary infection, temporary worsening of lesions, photosensitivity, and increased serum lipids, but these are rarely severe enough to cause treatment withdrawal.[105] Other less common side-effects might include an increased risk of ulcerative colitis.[106] Due to teratogenicity, isotretinoin should be given with adequate contraception for women of childbearing age. Strict regulation in the USA has decreased legal isotretinoin prescriptions and increased illegal buying over the internet.[107] A possible link between isotretinoin and depression is discussed later.

Complementary and alternative medications (CAMs)

The use of CAMs for acne is widespread. A systematic review of CAM treatments for acne in 2006 identified 15 RCTs covering diverse approaches such as *Aloe vera*, pyridoxine, fruit-derived acids, kampo (Japanese herbal medicine), and ayurvedic herbal treatments.[108] Although mechanisms of potential benefit for some of the CAM therapies were biologically plausible, the included studies were generally of poor quality and inconclusive. Another systematic review found some benefit for acupuncture with moxibustion, but the quality of included studies was limited.[109] A systematic review of four RCTs of tea-tree oil in 2000 did not find conclusive evidence of benefit,[110] although a recent well-reported study of 60 people in Iran with mild-to-moderate acne showed a modest reduction in lesion count and few local adverse effects when compared with placebo, suggesting that larger trials might be worthwhile.[111] CAM cannot be recommended for acne treatment because it is not supported by good evidence—CAMs might work, but the key studies have not been done, or when done, they have been inconclusive or reported poorly. CAM therapy for acne is a research gap that needs to be addressed given the high degree public interest and spending on CAM approaches.

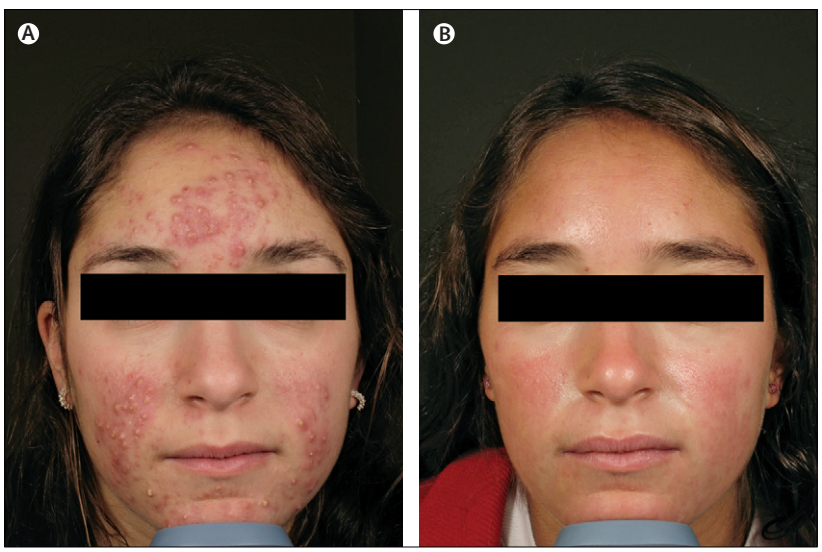

Figure 3: **Before (A) and after (B) view of a woman with severe acne treated with a course of isotretinoin**
Reproduced with permission from Amy Derick; full patient consent was received.

Special clinical problems

The depth and extent of acne scarring varies and can be improved by multiple procedures including subcision, punch excision, laser resurfacing, dermabrasion, and chemical peels.[27,112] Increasingly acne scarring is being treated with fractionated laser treatments—a technique that produces thousands of microthermal areas of dermal ablation separated by areas of untreated skin, with fewer side-effects and a quicker healing period than ablative lasers.[113]

Whereas open comedones can often be extracted with minimal skin trauma, cysts and closed comedones provide more challenging targets for acne surgery. Closed comedones can be nicked with a bevelled needle before expression with a comedone extractor, and large closed comedones can be treated with electrocautery or laser.[114,115] Injection of intralesional steroid (0·1 mL of 5 mg/mL

triamcinolone acetonide) into cysts often rapidly improves their appearance without extrusion.[116]

Body dysmorphic disorder (dysmorphophobia) is defined as significant psychosomatic distress caused by imagined or minor defects in one's appearance. Roughly 14% of patients with acne have sufficient distress related to their facial appearance to be diagnosed with dysmorphophobia.[117] It is notoriously difficult to treat, but aggressive treatment of residual acne and cognitive behavioural therapy can help.[118,119]

Severe acne with fever remains an important entity to recognise and treat early to prevent extreme scarring and patient suffering.[120,121]

With the exception of avoidance of tetracyclines, isotretinoin, and hormonal treatments, management of prepubertal acne is similar to adult acne management and is reviewed elsewhere.[8,122]

Trying to persuade teenagers to persist for many months or years with potentially irritating topical treatments that only prevent a proportion of new lesions occurring is a challenge. Many teenagers are more preoccupied by dealing with large spots as they appear, prompting a range of home remedies, such as toothpaste, publicised on social internet sites such as YouTube. The use of social internet sites as a means of targeting treatments for acne is potentially interesting.[123] It is possible that digital photography will be increasingly used by physicians to manage concordance of acne patients from home.[124]

Areas of controversy and uncertainty

Retinoid safety

Topical retinoids, a first-line acne therapy in the USA, have been associated with increased deaths in older male veteran patients in a randomised controlled trial of actinic keratosis.[125] Although this finding has been ascribed to chance, informing all topical retinoid users of these results might be warranted until further data are obtained.[126] A branded form of oral isotretinoin (Accutane) was introduced in the USA in 1982 and has been used by more than 13 million patients, but has now lost more than 95% of the market share and is being discontinued by its manufacturer Roche Pharmaceuticals.[127] The business decision is based on the high cost of defending the drug maker from personal injury lawsuits—initially suits alleged that Accutane was associated with depression and suicide. More recently at least 500 suits have been filed alleging that Accutane causes inflammatory bowel disease.[127] These disputed associations remain ripe areas for future research.[128]

A systematic review of isotretinoin use and depression and suicidal behaviour published in 2005 did not find any evidence to support the notion that depression worsened after treatment, and some studies showed that depression scores improved on treatment, although all nine included studies had limitations.[129] It is still possible that a rare idiosyncratic psychological reaction to isotretinoin does occur,[130] especially since there are plausible biological mechanisms by which retinoids might induce psychopathology.[128] The picture is a complex one as depression and suicidal ideation occur with severe acne in the absence of isotretinoin treatment.[131]

A retrospective cohort study in Sweden found that attempted suicide was increased in those taking isotretinoin, although an increased risk was also present before treatment. An increased risk of attempted suicide was present 6 months after isotretinoin, which suggests that patients should be monitored for suicidal behaviour after treatment has ended.[132] The generic form of isotretinoin continues to be available.

Lasers, light sources, and photodynamic therapy

Two systematic reviews of 16 and 25 trials, respectively,[133,134] assessed various forms of light sources including photodynamic therapy, infrared lasers, broad-spectrum light sources, pulsed dye lasers, intense pulsed light, and potassium titanyl phosphate laser. Both reviews concluded that optical treatments can improve inflammatory acne in the short-term, with the most consistent outcomes for photodynamic therapy. Pain, redness, swelling, and increased pigmentation were common adverse effects. Although several forms of light therapies can improve acne initially,[135] longer-term outcomes and comparisons with conventional acne therapies are needed.

Antibiotic resistance and other experimental therapies

Concerns regarding the rise of antibiotic resistance have increased the urgency for developing effective non-antibiotic therapies. Although two trials of subantimicrobial dosing (ie, the prescription of low doses that are anti-inflammatory but not antimicrobial) have shown efficacy for lower doses,[136,137] the studies are too small to make reliable estimates of bacterial resistance that could be promoted by the lower doses used. Relatively inexpensive hand-held home lasers and heating devices have been developed. Randomised controlled equivalency trials of these new devices using patient-centred metrics are urgently needed. In the more distant future, vaccination with killed *P acnes* and sialidase-based vaccines holds some promise.[138]

Natural history

Longitudinal studies that document the natural history of acne are needed, especially with a view to identifying risk factors for persistent disease. It is unknown whether early treatment (eg, at prepubertal years) can alter the natural history of *P acnes* colonisation and subsequent inflammatory acne.

So many treatments of unknown comparative efficacy

Treatment decisions for patients with acne and doctors are compounded by the profusion of available treatments, most of which have been introduced through

Panel: Important developments in understanding acne and its treatment

- Acne is a chronic disease that can persist into adulthood
- Acne causes significant psychological morbidity
- Immune-mediated inflammatory changes precede follicular hyperkeratinisation and *Propionibacterium acnes* colonisation
- The possible association between acne and diet remains uncertain
- Comparative effectiveness research could help reduce the plethora of current theraputic options for initiation and maintenance treatment
- Prolonged use of oral antibiotics might contribute to bacterial resistance in the community
- Oral isotretinoin results in significant clearing of acne, but it is limited by teratogenicity and other side-effects

placebo-controlled trials. Despite occasional exceptions,[64] the absence of trials with active comparators is a significant handicap to shared clinical decision making. Clinical trials of the cost-effectiveness of different strategies for initial treatment and maintenance therapy of acne are needed. Almost half of recently published acne trials contain serious flaws that could be overcome by better reporting.[139] The lack of agreement on suitable outcome measures also hampers secondary research.[140] Treatment uncertainties for acne are summarised in the UK Database of Uncertainties about the Effects of Treatments.[141] Comparative-effectiveness research on acne therapy has been targeted as a top 100 priority in the USA by the Institute of Medicine. The panel summarises key developments in understanding acne.

Contributors

All authors contributed to searching published works and took part in writing the first and subsequent drafts.

Conflicts of interest

We declare that we have no conflicts of interest.

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