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REVIEW

Dermatology: how to manage acne vulgaris

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Abstract

Background: Acne vulgaris is the most common skin disease that can lead to disfigurement and psychological distress. This article aims to provide a narrative updated review on the management of acne vulgaris.

Methods: A PubMed search was performed with Clinical Queries using the key term "acne". The search strategy included clinical trials, meta-analyses, randomized controlled trials, observational studies and reviews. The search was restricted to articles published in English.

Results: Treatments of acne include proper skin care, topical medications, oral medications and procedural therapies. Topical agents are the first-line treatment for mild-to-moderate acne and can be used as combination therapy for more severe acne. Systemic therapies are usually prescribed for the initial treatment of moderate-to-severe acne as well as for acne that is refractory to topical therapies.

Conclusion: Topical retinoids are the drugs of choice for the treatment and maintenance therapy of patients with mild-to-moderate acne vulgaris. Depending on the severity of the acne, topical retinoids may be used alone or in combination with benzoyl peroxide and topical or oral antibiotics. Oral antibiotics are an important therapy for inflammatory acne unresponsive to topical therapy. Neither topical nor oral antibiotics should be used as monotherapy. Oral contraceptives and/or spironolactone are useful for many women with acne. Oral isotretinoin is the drug of choice for severe, extensive, nodular acne vulgaris but is also often used in moderate cases where scarring is evident, acne-related psychosocial distress is significant or other treatment modalities have failed.

Keywords: acne, antibiotics, benzoyl peroxide, comedones, erythematous papules, oral contraceptives, pustules, retinoids, spironolactone.

Citation

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Introduction

Acne vulgaris is a common, chronic, inflammatory disorder of the pilosebaceous unit (comprising the hair follicle and sebaceous gland) caused primarily by increased sebum production, hyperkeratinization of the follicle, bacterial colonization and inflammation. The condition is characterized by chronic or recurrent development of comedones, erythematous papules and pustules most commonly on the face but may also involve the neck, trunk and proximal upper extremities. Although generally considered a benign, self-limited condition, acne vulgaris may cause severe psychological problems and disfiguring scars. This article provides an updated review on acne with a focus on the management of this condition.

Methods

A PubMed search was performed in July 2021 with Clinical Queries using the key term "acne". The search strategy included clinical trials, meta-analyses, randomized controlled trials, observational studies and reviews published within the past 10 years. The search was restricted to the English language. The information retrieved was used in the compilation of this article.

Epidemiology

The global prevalence of acne vulgaris in the general population is estimated at approximately 9.4%.[1] The condition typically begins at puberty when sex hormones begin to

be produced and occurs most frequently in adolescents and young adults, with progressive reduction in prevalence with increasing age thereafter.[2] Although uncommon, acne may occur in the neonatal period and develop *de novo* in adulthood.[3] The prevalence of acne in boys increases from 40% at age 12 years to 95% at age 16 years.[4,5] In girls, the prevalence increases similarly from 61% to 83%.[4,5] During adolescence, there is a male predominance, particularly with more severe forms of acne.[2,6] In contrast, during adulthood, the condition is more common in women than in men.[6] Mild acne is more common in Caucasians whereas severe acne tends to be more common in Asians and Africans.[7]

There is growing evidence that diet may contribute to the development of acne.[8–11] A 2021 systematic review of 53 studies (11 interventional clinical trials and 42 observational studies) showed that a high glycaemic-load diet, foods with a high glycaemic index, dairy products, chocolate and fatty food have a positive effect on the development of acne.[12] On the other hand, fatty acids, vegetables and fruit tend to protect against the development of acne.[12] Studies have also shown that vitamin D deficiency, high-dose vitamin B6 and vitamin B12 supplements and whey protein supplements may be associated with acne.[13,14] Other predisposing factors include genetic predisposition (family history of severe acne), obesity, oily/seborrheic skin, higher skin surface pH, emotional stress, repetitive mechanical trauma, exposure to excess sunlight, pre-menstruation, mechanical occlusion (e.g. headbands, shoulder pads, surgical masks, N95 respirators), topical application of greasy products or occlusive preparations, medications (e.g. anabolic steroids, hydantoin, benzodiazepines, ramipril, adalimumab, cyclosporin, isoniazid, lithium, iodides), congenital adrenal hyperplasia, adrenal tumours, polycystic ovarian syndrome and body dysmorphic disorders.[15–29]

Pathogenesis

Acne vulgaris is a chronic inflammatory process of the pilosebaceous unit. The condition usually occurs with the onset of puberty due to increased production of androgens by the adrenals and gonads and/or increased sensitivity of androgen receptors.[30,31] Obstruction of the pilosebaceous canal may result from follicular hyperkeratinization, hypertrophy of the sebaceous gland with increased production of sebum, and shedding of keratinocytes in clumps leading to the formation of a follicular plug, all of which are under the influence of androgens.[32–40] When the normal flow of sebum onto the skin surface is obstructed by follicular hyperkeratosis, a microcomedo is formed. As the sebum accumulates, the microcomedo enlarges into a visible comedo.[17]

In the pilosebaceous gland, triglycerides are hydrolysed into free fatty acids and glycerol by lipase produced by *Cutibacterium acnes*, formerly known as *Propionibacterium acnes*.[4,5,33,40] *C. acnes*, which increases dramatically at the time of puberty, is a key promoter of inflammation in acne.[4,5,33,40] The free fatty acids, once released into the skin through follicular breakdown, are cytotoxic and contribute to the inflammatory reaction.[5,40] Pro-inflammatory cytokines, such as IL-1, IL-8, IL-12 and defensins, are then produced by the recruited inflammatory cells, leading to the formation of inflammatory papules, pustules and, in severe cases, cysts and nodules.[3,6,41] Serum calprotectin, a biomarker of inflammation, is elevated in patients with acne.[42] Recent evidence suggests that *C. acnes* can activate components of the innate and adaptive immune systems and biofilms of *C. acnes* can promote follicular hyperkeratosis.[43,44]

Clinical manifestations

Acne vulgaris manifests most commonly in areas of the body that have abundant sebaceous glands, such as the face and, to a lesser extent, the trunk, where sebaceous follicles predominate.[5,39,40] At times, the neck and proximal upper extremities may also be affected.[5,40] The initial stage of the disease begins with the pathognomonic comedo, a clogged follicle, which may be either closed or open.[38,40] A closed comedo (colloquially known as whitehead) appears as a white or flesh-coloured, domed-shaped papule without a readily visible central pore and without any clinical signs of inflammation (Figure 1).[40] It is flask-shaped with the narrowest portion connected to the skin surface.[40] As the follicular opening is enlarged and eventually opened with continued distension as a result of keratin and sebum build-up, an open comedo (colloquially known as blackhead) is formed.[6] An open comedo typically presents as a flat or slightly raised black lesion with a central, dilated, follicular orifice containing a black keratotic plug, typically measuring 1–3 mm in diameter (Figure 2).[40,43] The black surface of the open comedo is oxidized melanin not oxidized fat or dirt.[40,43]

Blackheads do not generally become inflamed unless the pilosebaceous canal is disrupted by external forces, such as may occur by squeezing the lesion, thus patients should be advised to not 'play' with their lesions.[40] Whiteheads may either open up their pores resulting in blackheads or they may rupture.[40] With rupture of the obstructed follicle and release of free fatty acids into the surrounding tissue, an inflammatory reaction ensues, resulting in erythematous papules (Figure 3), pustules, papulopustules (Figure 4) and, occasionally, nodules and cysts depending on the location and amount of the tissue involved and the magnitude of the inflammatory response.[38,40] Nodules and cysts comprise severe nodulocystic acne (Figure 5).[31]

Several clinical variants exist. Acne conglobata (also known as conglobate acne), found predominately in young males, is a severe, destructive and highly inflammatory form of acne marked by the presence of grouped and polyporous comedones, nodulocystic lesions, burrowing, interconnecting deep-seated abscesses, and draining sinus tracts with purulent, foul-smelling discharge (Figure 6).[5,40,45–47] The condition

Figure 1. Numerous closed comedones on the forehead of a 16-year-old girl.

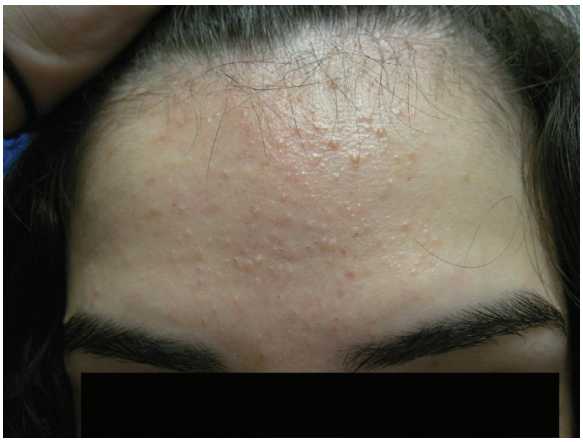


Figure 2. Multiple open comedones on the face of a 17-year-old boy.

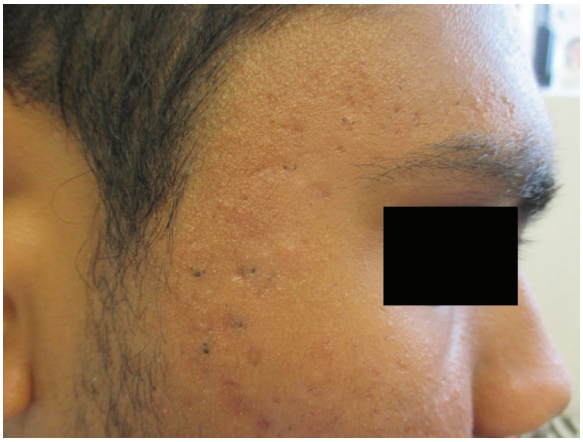


Figure 3. Multiple inflammatory papules on the cheek.

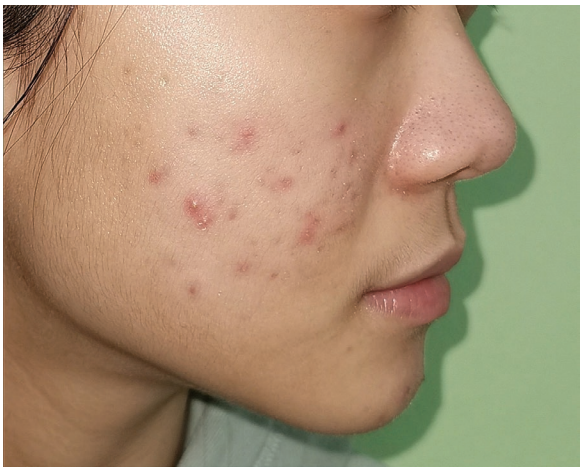


Figure 4. Closed and open comedones, inflammatory papules and pustules over the forehead of a 13-year-old boy.

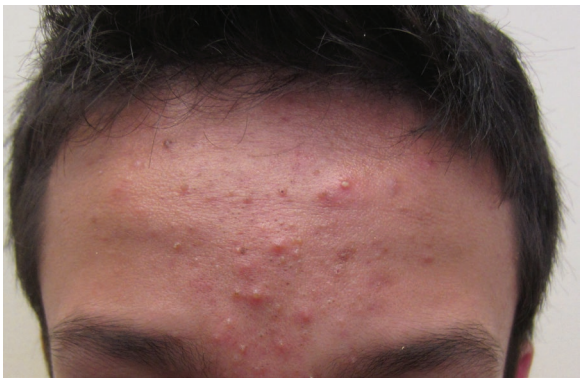


Figure 5. Nodulocystic acne on the face.

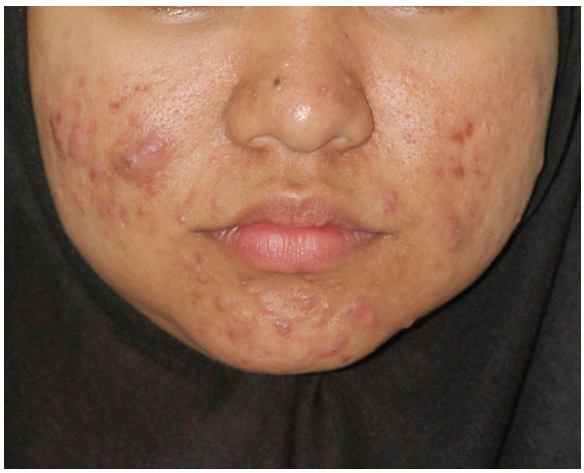
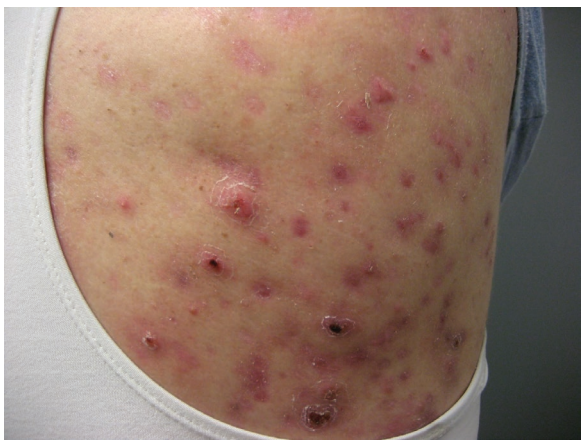


Figure 6. Acne conglobata presenting as grouped comedones, nodulocystic lesions, abscesses and draining sinus tracts on the back.



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may lead to significant scarring.[48] Acne conglobata is more commonly found on the posterior back and chest but may extend to the buttocks.[5,40,45,47] Less commonly, the lesion can appear on the face, proximal arms, shoulders, abdomen and scalp.[45]

Acne fulminans (also known as acne maligna) is a rare form of acne characterized by the sudden onset of painful, haemorrhagic pustules, friable plaques and large, necrotic, ulcerating nodules mainly on the back but may involve the chest, face, neck and shoulders in association with systemic manifestations such as malaise, fever, chill, weight loss, diffuse myalgia, polyarthralgia, erythema nodosum, hepatosplenomegaly, bone lesions, increased inflammatory markers (e.g. leukocytosis, neutrophilia, elevated erythrocyte sedimentation rate or C-reactive protein) and elevated liver enzymes.[12,38,49–51] Characteristically, comedones are uncommon and polyporous comedones are absent.[48] The condition typically occurs in individuals aged 13–16 years with a male to female ratio of 3:1.[49,50] Acne fulminans may be an isolated disorder and may be triggered by isotretinoin therapy[6] or may present as part of syndromes such as pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO), pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa (PAPASH) or pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH).[52,53]

Acne excoriée, or 'picker's acne', results from excessive picking and scratching of the acne lesions.[6,54] Typically, acne excoriée presents with comedones and inflammatory papules.[6] Picking or scratching of the acne lesions exacerbates the acne lesions and may result in excoriations, erosions, ulcerations, scabs and scars.[54] Affected individuals may have obsessive-compulsive personality and body dysmorphic disorders.[6,54] The condition is more common in young women.[6]

Neonatal acne is either present at birth or shortly thereafter, usually within 6 weeks of life.[55,56] The condition is more common in boys.[57] Presumably, neonatal acne results from stimulation of sebaceous glands by maternal and neonatal androgens and colonization of sebaceous glands by *Malassezia* species.[55] Neonatal acne is characterized by papules and pustules usually on the face (forehead, cheeks and nose) (Figure 7) and tends to resolve spontaneously over weeks to months.[55,56]

Infantile acne typically presents between 6 weeks and 12 months of age with a male predominance.[58] Lesions consist of closed and open comedones, inflammatory papules, pustules, nodules, and cysts (Figure 8).[57,58] The site of predilection is the face, especially the cheeks.[58] Infantile acne may result from increased sensitivity of sebaceous glands to circulating androgens or, less commonly, from increased production of androgens.[56,58] Lesions usually resolve within 12 months of initial onset.[58]

Mid-childhood acne is rare and typically presents between 1 and 7 years of age.[55,56] Clinically, mid-childhood acne is characterized by comedones, inflammatory papules and pustules on the face.[56] Mid-childhood acne should always raise the concern for underlying causes of hyperandrogenism such as late-onset congenital hyperplasia, Cushing syndrome or a virilizing tumour.[55,56]

Preadolescent acne, defined by the appearance of acne between 7 and 11 years of age, typically presents with comedones on the central forehead.[55,56] Lesions gradually

Figure 7. A 5-week-old boy with neonatal acne on the face. Note the presence of papules and pustules.

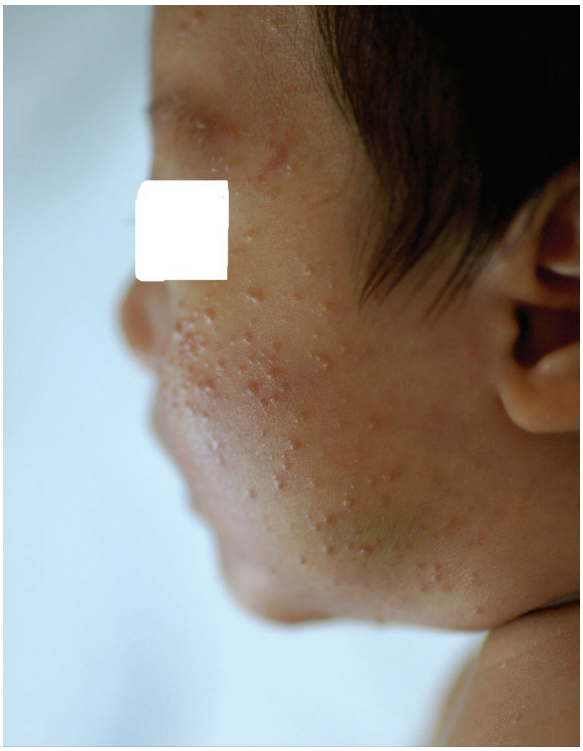


Figure 8. Multiple comedones and inflammatory papules over the cheeks of a 9-month-old boy.

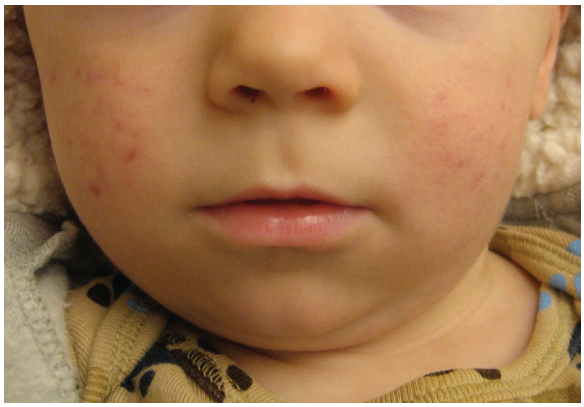
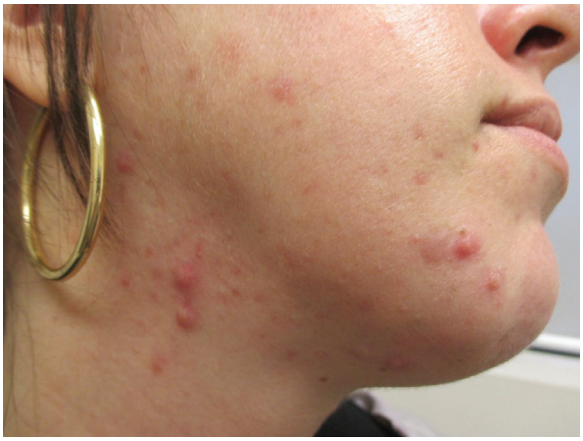


Figure 9. Acne on the chin and neck of a 35-year-old woman presenting predominately with inflamed papules and pustules.



evolve to inflammatory papules and pustules with time and involve the centre of the face.[56] Acne in this age group is usually normal and presumably caused by isolated premature adrenarche.[30,59] At times, it may be the first sign of true precocious puberty, late-onset congenital hyperplasia, polycystic ovarian syndrome or a virilizing tumour.[55,56]

Acne tarda refers to the late onset of acne or persistence/relapse of acne in the third and fourth decade of life.[36,60,61] In adult women, late-onset acne tends to involve the chin, jaw line and neck with a predominance of inflamed papules and pustules with relatively few comedones (Figure 9).[6,60–62] Acne tarda in women is most associated with premenstrual flares.[6,60,61]

Diagnosis and diagnostic evaluation

The diagnosis is mainly clinical based on the characteristic lesions (closed comedones, open comedones, inflammatory papules, pustules, inflamed nodules and inflamed nodulocystic lesions) in a characteristic distribution (face, neck, back, chest, shoulders or upper arms). Laboratory investigations are usually not necessary unless clinically indicated. Serum concentrations of testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate and, in women of childbearing age, luteinizing hormone and follicle-stimulating hormone may be measured and pelvic ultrasound should be performed to look for polycystic ovarian syndrome if there is a suspicion of hyperandrogenism (e.g. hirsutism, clitoromegaly, very early development of pubic or axillary hair).[15,58]

Differential diagnosis

Acne should be differentiated from bacterial folliculitis, pityrosporum folliculitis, acne keloidalis nuchae, milia, miliaria rubra, syringomas, perioral dermatitis, sebaceous hyperplasia, nevus comedonicus, papulopustular rosacea, keratosis pilaris, molluscum contagiosum, facial angiofibromas in tuberous sclerosis, eruptive vellus hair cysts, steatocystoma multiplex and verruca vulgaris (Table 1).[63–69] The distinctive features of each condition allow a relatively straightforward differentiation from acne.

Drug-induced acne or acneiform eruption can be caused by corticosteroids, anabolic steroids, testosterone, isoniazid, lithium, halogens, lithium, isoniazid, epidermal growth factor receptor inhibitors, vascular endothelial growth factor inhibitors, TNF antagonists and capecitabine.[70,71] Compared to classic acne lesions, drug-induced acne is characterized by a history of drug intake, sudden onset of monomorphous, inflammatory papules or papulopustules with few, if any, comedones, unusual age of onset, lesions on the face and neck as well as unusual locations beyond the seborrheic areas, and disappearance of lesions when the offending medication is discontinued (Table 1).[71]

Acne should be differentiated from skin lesions of Birt–Hogg–Dube syndrome (triad of acrochordons, fibrofolliculomas and trichodiscomas), Cowden syndrome (facial trichilemmomas and acral keratosis) and Muir–Torre syndrome (facial keratoacanthomas and sebaceous neoplasms) (Table 1).[34,72]

Complications

Post-inflammatory hyperpigmentation and, less commonly, hypopigmentation may result; the risk is higher in dark-skinned individuals (skin phototypes IV–VI).[6,7] Scarring may result in susceptible individuals, especially with severe variants such as acne conglobata and acne fulminans. In general, the deeper the inflammatory process, the more likely acne lesions will result in permanent scarring.[5,40,73] However, even comedonal acne can result in acne scarring.[40] It has been shown that early and effective treatment of acne vulgaris may reduce the risk of scarring.[6] Acne scars are typically atrophic in nature and, based on their distinctive physical characteristics, can be divided into three basic types, namely boxcar scars (punched-out, U-shaped angular scars with sharply demarcated vertical edge) (Figures 10 and 11), ice pick scars (small, deep punched-out pits, sharply demarcated and V-shaped) (Figure 12) and rolling scars (wider and shallower than ice pick scars; rounded, sloping edges, having a wavelike or undulating appearance; combination of several of these scars in a region of the skin gives a rolling appearance) (Figure 13).[39,74,75] Conversely, acne scars can also be thick such as hypertrophic scars (scars remain within the confines of the original wound borders) (Figure 14) and keloid scars (lesions outgrow the boundaries of the wound scars, invading surrounding normal tissue, and may be pruritic or tender) (Figure 15).[40,74,75]

Morbihan disease, characterized by persistent erythema and solid oedema of the upper two-thirds of the face, is a rare complication of acne.[6,76] Rarely, dystrophic calcinosis cutis may result from inflammatory acne.[77]

Table 1. Differential diagnosis of acne vulgaris.

Condition	Characteristics
Bacterial folliculitis	Absence of comedones; abrupt onset of monomorphic folliculocentric papules and pustules
Pityrosporum folliculitis	Absence of comedones; abrupt onset of pruritic monomorphic folliculocentric papules and pustules along the hairline and on the upper back
Acne keloidalis nuchae	Smooth, firm, discrete, dome-shaped, follicular papules coalescing to form hairless, keloid-like plaques/nodules on the nape of the neck and occipital scalp; comedones characteristically absent
Milia	Asymptomatic, small, firm, white to yellow, smooth, dome-shaped papules; most commonly observed on the eyelids
Miliaria rubra	Pruritic, erythematous papules or papulovesicles; may impact a prickling sensation; occurs in response to heat or exertion
Syringomas	Asymptomatic, soft, skin-coloured to slightly yellowish papules; symmetrically distributed; typically observed in the periorbital region
Perioral dermatitis	Discrete, symmetrical, grouped, flesh-coloured to erythematous papules, papulovesicles and/or papulopustules on an erythematous and scaly base confined to the perioral area; the area immediately adjacent to the vermilion border of the lips is characteristically spared
Sebaceous hyperplasia	Asymptomatic, discrete, yellow or flesh-coloured, dome-shaped papules, most common on the forehead and cheeks; central umbilication in some of the lesions
Nevus comedonicus	Onset before 10 years of age; grouped or linear arrangement of comedones
Papulopustular rosacea	Persistent central facial erythema; telangiectasias; inflammatory dome-shaped erythematous papules and tiny surmounting pustules on the central face; comedones are characteristically absent
Keratosis pilaris	Minute, discrete, keratotic, follicular papules with variable perifollicular erythema; affected skin looks like gooseflesh and feels like sandpaper
Molluscum contagiosum	Discrete, smooth, firm, dome-shaped, waxy papules with characteristic central umbilication
Facial angiofibromas in tuberous sclerosis	Pink to red dome-shaped papules in a butterfly distribution in the malar area; onset of lesions in the preschool years
Eruptive vellus hair cysts	Asymptomatic, monomorphic flesh-coloured papules most commonly on the chest
Steatocystoma multiplex	Multiple, asymptomatic, smooth, round, soft, movable, yellow to skin-coloured papules and nodules; superficial lesions are usually yellowish whilst deeper lesions are skin coloured
Verruca vulgaris	Asymptomatic, well-circumscribed, papule/nodule with a hyperkeratotic and verrucous surface
Drug-induced acne or acneiform eruption	History of drug intake; sudden onset of monomorphic, inflammatory papules or papulopustules with few, if any, comedones; unusual age of onset; lesions on the face and neck as well as unusual locations beyond the seborrheic areas; disappearance of lesions when the offending medication is discontinued
Skin lesions of Birt–Hogg–Dubé syndrome	Triad of acrochordons, fibrofolliculomas and trichodiscomas
Skin lesions of Cowden syndrome	Facial trichilemmomas; acral keratosis
Skin lesions of Muir–Torre syndrome	Facial keratoacanthomas; sebaceous neoplasms

Both active acne and post-inflammatory hyperpigmentation/hypopigmentation and scars from previous acne, especially those on the face and in women, are apt to be embarrassing and psychologically traumatic and may result in anxiety, emotional stress, low self-esteem, feelings of unattractiveness and worthlessness, depression, suicidal ideation, and even suicide.[60,61,78–81] Self-consciousness related to acne can have an adverse effect on interpersonal and sexual relationships, daily and social activities, and quality of life.[82–89]

Prognosis

Acne vulgaris is characterized by a chronic inflammatory and relapsing course for years. With proper treatment, the overall

Figure 10. Boxcar scars on the right cheek.

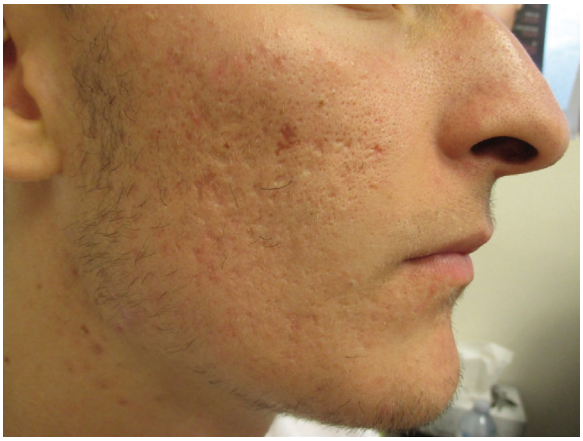


Figure 11. Boxcar scars (close-up view).

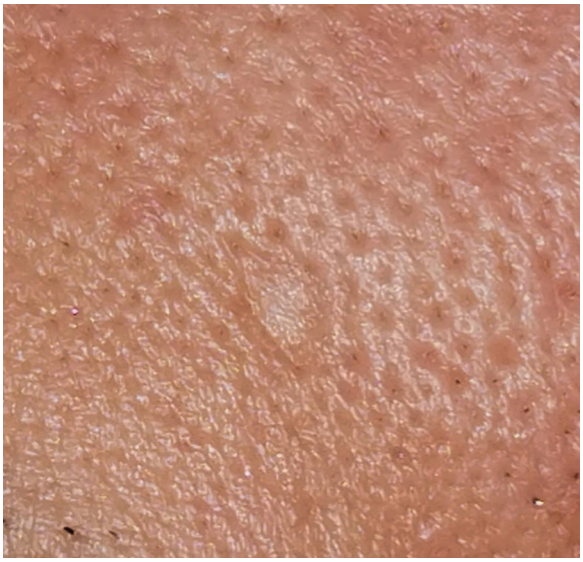


Figure 12. Ice pick scars on the chin.

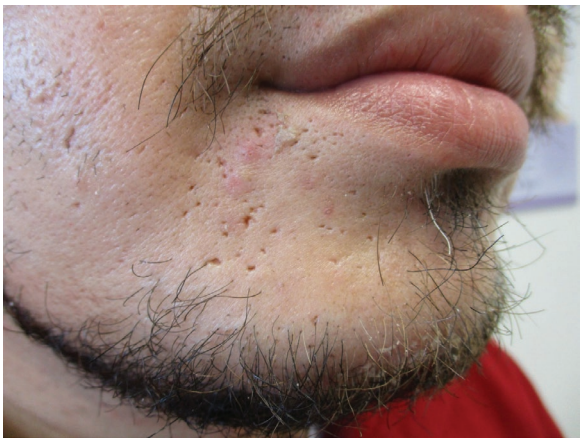


Figure 13. Rolling scar on the left cheek.

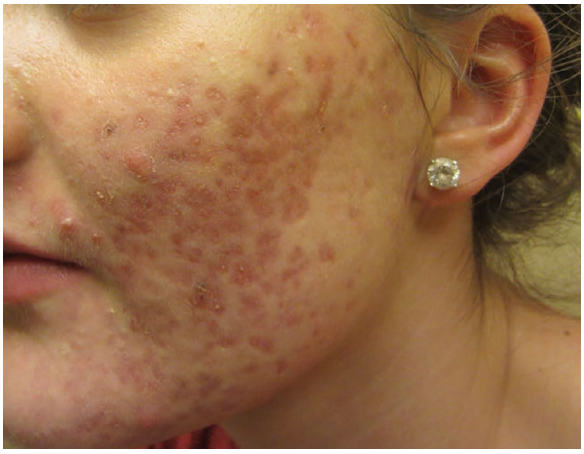


Figure 14. Hypertrophic scars over the chest of a 16-year-old boy.

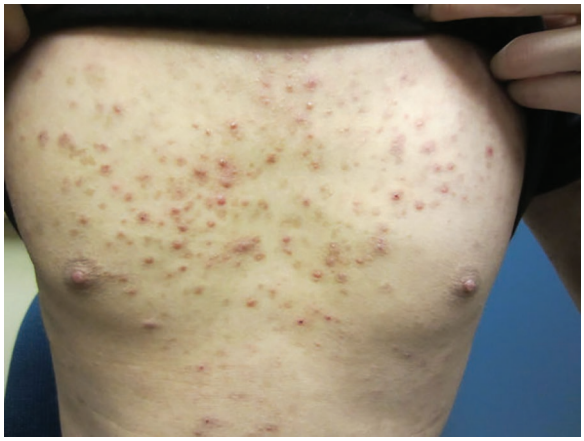
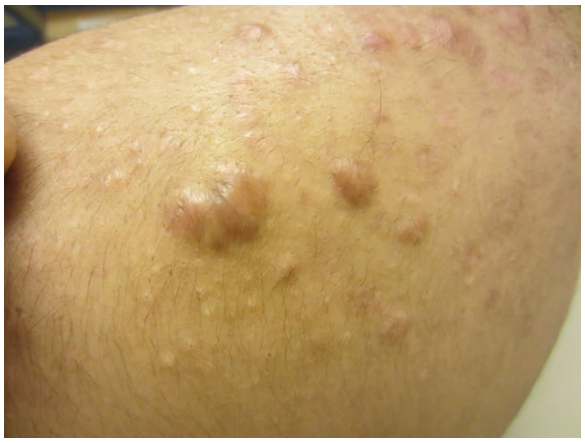


Figure 15. Keloid scars over the left shoulder of a 14-year-old girl.



prognosis is good. The prevalence of acne tends to decrease with increasing age in adulthood and beyond.[69] However, some patients are left with residual scars, the treatment of which is often difficult and not optimal.[7]

Management

The goals of treatment are to provide the patient with the best appearance possible and to minimize scarring and psychological sequelae. The aims of therapy are to prevent follicular hyperkeratosis, reduce *C. acnes*, inhibit fatty acid production and sebum secretion and eliminate comedones.[6,40] In general, topical agents used for the treatment of acne vulgaris have a favourable safety profile.[90] Therefore, topical agents are the first line of treatment for mild-to-moderate acne and can be used as combination therapy for more severe acne.[17,90,91] Systemic therapies are usually prescribed for the initial treatment of moderate-to-severe acne as well as acne that is refractory to topical therapies.[92]

Skin hygiene

Patients should be advised to use gentle skin cleansers rather than scrubs and soaps (especially harsh or drying soaps) as well as non-comedogenic skin care and cosmetic products.[92] Patients can also be advised to pat dry their face after washing rather than rubbing and exfoliating. They should avoid aggressive scrubbing of the skin and picking or squeezing of acne lesions as this can increase the risk of scar formation.[69,92] Use of soap-free face wash and oil-free moisturizers and sunscreens is advisable.[60,61,93]

Topical therapy

Many topical agents are available for the treatment of acne vulgaris. The choice should be based on, amongst others, patient age, sites and severity of the acne, efficacy, safety, and cost of the medication, and patient preference. Most patients would benefit from a combination of medications.[94] Generally, patients with dry skin prefer lotions or creams whereas patients with oily skin may prefer gels.[91]

Topical retinoids (e.g. tretinoin, tazarotene, adapalene, trifarotene), a diverse group of vitamin A derivatives that modulate gene expression, are the drugs of choice for the treatment and maintenance therapy of patients with mild-to-moderate acne vulgaris.[24,31,92,95–100] These agents inhibit keratinocyte proliferation, thereby reducing obstruction of the follicle and preventing the formation of microcomedones.[17,101,102] In addition, these agents have an anti-inflammatory effect.[17] They are effective for the treatment of comedones, inflammatory papules and pustules.[24,92] The major side effects are local skin dryness, flaking, erythema, thinning of the stratum corneum, burning sensation and irritation.[5,40] Some patients may have an exacerbation of acne, so called 'retinoid flare' during the first month of treatment.[90,92] Topical retinoids are usually applied once daily, preferably at night, due to the photolability and photosensitivity associated with their use.[92] With the use of topical retinoids, regular use of broad-spectrum sunscreens and of protective wide-brimmed hats when outdoors should be advised.[92] Typically, patients are started on low concentrations of topical retinoids; the dosing should be slowly titrated up to minimize irritation, which may impact compliance. Topical tazarotene, a retinoid prodrug, is classified as a pregnancy category X drug (whilst the other retinoids are classified as category C; trifarotene is not assigned a category) and should be avoided during pregnancy or lactation.[92] Depending on the severity of acne, topical retinoids may be used alone or in combination with another agent such as benzoyl peroxide and topical or oral antibiotics.[99,100,102] A 2019 systematic review of 54 clinical trials evaluating the safety, efficacy and tolerability of topical retinoids for the treatment of acne showed that topical retinoids are safe and efficacious for the treatment of acne.[103] They are slower to work, so patience is key. Topical retinoids also improve skin tone and hyperpigmentation and reduce atrophic scarring. Optimal results can be obtained when they are used in combination with an antimicrobial agent.[103,104] The difference in efficacy of topical retinoids appears minor.[103] Amongst topical retinoids, adapalene has the best tolerability profile and the least irritating effect.[24,103]

Benzoyl peroxide is a potent topical antimicrobial with rapid bactericidal action.[5,40] The bactericidal effect on *C. acnes* is due to the oxidation of bacterial proteins. Benzoyl peroxide inhibits the lipolysis of sebum triglycerides and decreases the inflammation of acne lesions.[5,40] In addition, benzoyl peroxide has a modest keratolytic and comedolytic effect.[34,99,100] The medication is usually applied once a day.[92] Use of benzoyl peroxide does not induce bacterial resistance and the medication is safe to use during pregnancy or lactation.[98,105,106] Benzoyl peroxide can be used as monotherapy or, more commonly, in conjunction with topical retinoids or antibiotic therapy to increase the efficacy of treatment.[105,107–110] A 2021 systematic review shows that benzoyl peroxide in combination with adapalene is more effective than either treatment used alone, but may cause more side effects.[111] Side effects associated with the use of benzoyl peroxide include skin dryness, peeling of the skin, erythema, stinging, burning, contact dermatitis, and bleaching of clothing, linen and hair.[106] Skin irritation often decreases with time.[31] Just like with retinoids, it is useful to start slowly with benzoyl peroxide-based products to minimize irritation and to improve overall compliance. The Global Alliance to Improve Outcomes in Acne suggests benzoyl peroxide plus a topical retinoid as the first-line therapy for most patients with inflammatory acne.[109] The European Evidence-Based (S3) Guideline for the Treatment of Acne recommends benzoyl peroxide plus topical adapalene or benzoyl peroxide plus topical clindamycin for the treatment of mild-to-moderate acne.[112]

Topical antibiotics have anti-inflammatory properties and, depending on the formulation, are either bactericidal or bacteriostatic.[106] Compared with oral antibiotics, topical antibiotics have the benefit of less systemic toxicity and

systemic side effects.[113] Topical antibiotics should not be used as monotherapy because of the risk of developing bacterial resistance.[24,92,101,114–116] Combining topical antibiotics with topical retinoids or benzoyl peroxide will improve the therapeutic outcome and will reduce the emergence of antibiotic-resistant strains of *C. acnes*.[24,92,101,102,114,115] Generally, topical antibiotics should not be given to patients who are concurrently receiving oral antibiotics.[108] Topical antibiotics, such as clindamycin, erythromycin, dapsone and minocycline, have been successfully used in the treatment of acne.[34] In general, topical antibiotics alone are very well tolerated. Most topical antibiotic regimens use either clindamycin or erythromycin, which are available in a variety of vehicles such as a gel or solution.[113,116,117] The cutaneous side effects associated with the use of clindamycin or erythromycin include local dry skin, erythema, peeling, pruritus, occasional burning and *Clostridium difficile* colitis.[90,106] Dapsone is a sulfone antibiotic with anti-inflammatory and antibacterial properties.[106] The medication exerts its antibiotic effect by inhibiting bacterial DNA synthesis.[55,118] Dapsone is available in 5% and 7.5% gel formulations and is effective as an adjunct treatment for acne vulgaris.[55,92,94,106] The medication is often used in individuals with sensitive skin and in women with acne.[99,100] It is also a viable addition to the armamentarium for the treatment of truncal acne.[72] Side effects of topical dapsone include dryness, peeling, erythema and pruritus at the application sites.[55,92,106] Temporary orange-brown staining of the skin due to dapsone oxidation may occur when dapsone and benzoyl peroxide are used concomitantly.[92,106,118] Topical minocycline is an alternative topical antibiotic that can be used as an adjunct treatment for acne vulgaris.[92,97]

Azelaic acid is a naturally occurring, saturated, straight-chained acid that has antibacterial, anti-inflammatory, antikeratinizing, comedolytic, tyrosinase-inhibiting and antioxidant properties.[90,118] Topical azelaic acid (e.g. 15% or 20% gel) has been used with success for the treatment of acne vulgaris and post-inflammatory hyperpigmentation.[7,52,90,118,119] The medication has a favourable safety profile and is safe during pregnancy or lactation. Side effects are mild and consist mainly of local erythema, dryness, burning, stinging, pruritus, dysesthesia and hypopigmentation in dark-skinned individuals.[116,118] No bacterial resistance to azelaic acid has been reported.[90,118]

Superficial chemical peels, such as lactic acid, retinoic acid, alpha hydroxyl acid, pyruvic acid, salicylic acid, mandelic acid, glycolic acid, Jessner solution and 10–25% trichloroacetic acid, have keratolytic action and can be used for comedonal and mild inflammatory acne lesions.[15,120–123] The appropriate peel should be chosen based on acne activity and the skin type of the patient.[122]

Clascoterone (cortexolone 17 α-propionate) is a topical androgen receptor inhibitor that competes with androgens, specifically dihydrotestosterone, for binding to the androgen receptors within the sebaceous glands and hair follicles.[92,124] The medication was approved by the FDA in 2020 for use in individuals aged 12 years or older.[92] Clascoterone 1% cream has good efficacy for both non-inflammatory and inflammatory acne lesions, especially when combined with a topical retinoid.[124] Irritation of the skin is a potential side effect.[92] As clascoterone is rapidly hydrolysed to cortexolone, hypothalamic–pituitary–adrenal axis suppression is possibly associated with its use.[124]

A short course of topical steroids may be helpful in severe acute inflammatory lesions.[4,40] Fluorinated steroids should not be used as they may cause steroid acne or periorificial dermatitis in susceptible individuals.

New and emerging topical agents that have shown promise for the treatment of acne vulgaris include insulin-like growth factor 1 inhibitors, phosphodiesterase inhibitors, acetylcholine inhibitors, acetyl coenzyme A carboxylase inhibitors, 5-lipoxygenase inhibitors, ectopeptidase inhibitors, IL-1, IL-1α, IL-1β and IL-17A blockers, melanocortin receptor antagonists, peroxisome proliferator-activated receptor modulators, omiganan pentahydrochloride, antimicrobial peptides, lupeol, gold and silver nanoparticles, sodium hypochlorite and epigallocatechin-3-gallate.[3,44,97,109,125–131] Well-designed, large-scale, randomized, double-blind and placebo-controlled studies are necessary to confirm the efficacy and safety of these novel topical agents in order to make formal recommendations regarding their use in the management of acne vulgaris.

Topical therapy can be used, if necessary, for the treatment of post-inflammatory hyperpigmentation. In this regard, post-inflammatory hyperpigmentation can be treated by the use of sun protection (sunscreen, hat, sunglasses), topical hydroquinone, topical azelaic acid, topical retinoids, topical modified Kligman's formula or superficial chemical peels (e.g. lactic acid, alpha hydroxyl acid, linoleic acid, salicylic acid, polyethylene glycol, Jessner solution and 10–25% trichloroacetic acid).[7,102,109]

Systemic therapy

Oral antibiotics are an important therapy for acne unresponsive to topical therapy and the more inflammatory types of acne lesions, including pustules, nodular lesions and abscesses.[31,40,98] They are particularly useful for acne involving the back because of difficulties of applying topical treatments to large areas that are difficult to reach.[31,41,131] These agents administered systemically produce a significant reduction in *C. acnes*.[98] In addition, oral antibiotics have intrinsic anti-inflammatory properties, exerting their action through the inhibition of neutrophil chemotaxis and the alteration of macrophage and cytokine production.[99,100,132] Tetracyclines (doxycycline, minocycline, sarecycline) are preferred because of greater efficacy and better tolerability.[108,116,131] In general, tetracyclines should be taken on an empty stomach as the absorption of tetracyclines is inhibited by food.[55] The recommended dose of doxycycline and minocycline is 50 or 100 mg daily or twice daily.[108] Sarecycline given once

daily can be used in individuals aged 9 years and older.[108] Due to its narrow spectrum of activity, efficacy and safety in individuals 9 years and older, some authors now consider sarecycline to be the antibiotic of choice in the treatment of acne.[133] The recommended dose of sarecycline is based on body weight (60 mg, 100 mg and 150 mg for individuals weighing 33–54 kg, 55–84 kg and 85–136 kg, respectively).[108] Side effects of tetracyclines include nausea, vomiting, diarrhoea, oesophagitis, photosensitivity, pigment deposits in the skin, mucous membrane and teeth (young children), vaginal candidiasis, dizziness, tinnitus, hepatotoxicity, *C. difficile* colitis, allergic reactions, drug hypersensitivity syndrome, lupus-like syndrome, pseudotumor cerebri and impairment of growth.[55,73,98,106,132] The use of tetracyclines is contraindicated for pregnant individuals, individuals with childbearing potential and individuals aged 8 years or younger.[108] Azithromycin (500 mg one to three times per week) and erythromycin (500 mg twice a day) are the macrolides most often used when tetracyclines are contraindicated (e.g. children ≤8 years of age, pregnant women or breastfeeding mothers).[101] Treatment with cephalexin (500 mg twice a day for adults) and trimethoprim-sulfamethoxazole (160/800 mg once to twice a day for adults) is discouraged because of limited data to support their efficacy, unless tetracyclines and macrolides are contraindicated.[101,108] To reduce the risk for the development of antibiotic resistance, oral antibiotics should not be used as monotherapy.[109,134,135] Rather, they should be used in combination with a topical retinoid or preferably benzoyl peroxide.[60,61,99,100,135] In general, oral antibiotics should be limited to the shortest possible duration. The maximum duration of continuous treatment with oral antibiotics should be limited to no more than 6 months; long-term use of oral antibiotics is not recommended.[73,98,101,108]

Oral isotretinoin (13-cis-retinoic acid) decreases sebum production, follicular keratinization and intrafollicular concentration of *C. acnes*.[4,40,108] In addition, oral isotretinoin has a direct anti-inflammatory effect.[108] It is the drug of choice for severe, extensive, nodular acne vulgaris but is also often used in moderate cases where scarring is evident, acne-related psychosocial distress is significant or other treatment modalities have failed.[91,108,109,112,136] Oral isotretinoin shows superior efficacy in the management of severe acne.[112,137,138] The considerable benefits must be weighed against their potential risks.[137,138] The medication is typically given as monotherapy and initiated at a low dose (e.g. 0.5 mg/kg/day) for the first month of therapy to minimize the risk of isotretinoin-induced acne flare due to intense sebocyte apoptosis and the subsequent release of antigens and inflammatory response.[108,138,139,140] The dose can then be increased to 1 mg/kg/day if needed, reaching a total cumulative dose typically within 120–150 mg/kg often given over approximately 6 months, though higher doses or longer durations may be needed.[140] Oral isotretinoin is highly lipophilic and should be taken with food (especially high-fat meals), which will increase absorption of the medication.[137,140] Side effects are dose related and include cheilitis, cutaneous erythema, mucocutaneous and ophthalmic dryness, palmoplantar desquamation, cutaneous atrophy, pruritus, epistaxis and acne flare.[140] Other adverse reactions include alopecia, photosensitivity, corneal opacities, decreased night vision, headache, nausea, vomiting, myalgias, arthralgias, delayed wound healing, pseudotumour cerebri, bone marrow suppression, hepatotoxicity, periostitis, hyperostosis and, rarely, Stevens–Johnson syndrome.[41,139,140] Currently, the causal relationship between isotretinoin therapy and depression, suicidal ideation and inflammatory bowel disease has not been established.[137–140] Laboratory abnormalities associated with the use of isotretinoin include hypertriglyceridaemia, hypercholesterolaemia, abnormal liver function tests, elevated erythrocyte sedimentation rate, anaemia, thrombocytosis and leucopenia.[4,40,140] As isotretinoin is teratogenic, women of childbearing age should not be given oral isotretinoin until pregnancy is excluded and an effective form of contraception is being used during treatment and for 1 month after stopping the medication.[4,38,40] Isotretinoin is also contraindicated in individuals with a history of hypersensitivity to isotretinoin or its component.[140] Concomitant treatment with isotretinoin and tetracyclines should be avoided because of the risk of pseudotumour cerebri.[140] Additionally, vitamin A supplementation may increase the side effects of isotretinoin and should therefore be avoided.[140]

For women in post-menarche with acne, hormonal therapy is a therapeutic option.[69] The use of oestrogens in the form of oral contraceptives in the treatment of acne is based on the ability of oestrogen to suppress the stimulatory effect of androgens on pilosebaceous units leading to decreased size and function of sebaceous glands with a resultant reduction in sebum production and keratinous material accumulation.[108] The use of oral contraceptives should be considered in women in post-menarche typically over the age of 15 years with moderate-to-severe, recalcitrant, pustulocystic or nodulocystic acne who do not respond or are intolerant to conventional therapy as well as in those who experience premenstrual flares, especially along the jawline and lower face, and in those with evidence of hyperandrogenism (e.g. hirsutism, oligomenorrhoea) such as those with polycystic ovarian syndrome.[4,15,40,55,106] For post-pubertal women who desire a contraception method and who have no contraindications to oral contraceptives, an oral contraceptive is preferred to spironolactone as hormonal therapy for acne vulgaris, though the two are often combined for enhanced efficacy.[108] Oral contraceptives containing both oestrogen and progestin (e.g. ethinyl oestradiol and norgestimate; ethinyl oestradiol and norethindrone; ethinyl oestradiol and drospirenone; and ethinyl oestradiol, drospirenone and levomefolate) rather than progestin-only contraceptives should be used, as the latter are not effective and may worsen acne vulgaris.[101,106,108,137] Side effects of oral contraceptives include headaches, nausea, bloating, moodiness, breast tenderness, breakthrough bleeding,

amenorrhoea, hypertension, thromboembolism and, rarely, myocardial infarction and stroke.[137]

Spironolactone is an antiandrogen that blocks androgen receptors (thereby inhibiting the biosynthesis of androgen), inhibits 17-β-hydroxysteroid dehydrogenase (thereby halting the conversion of androstenedione to testosterone), inhibits 5-α-reductase (thereby halting the conversion of testosterone to dihydrotestosterone) and may increase the concentration of sex hormone-binding globulin (thereby decreasing the concentration of free testosterone and dihydrotestosterone).[108] Spironolactone should be considered in women who use oral contraceptives, are refractory to topical acne therapy, have hyperandrogenism or present with late-onset (>25 years old) acne vulgaris.[141] The recommended oral dose is 25–100 mg per day, given once or twice daily.[118] Some authors prefer spironolactone to oral antibiotics due to concerns of bacterial resistance.[142] Side effects of oral spironolactone include menstrual irregularities, breast enlargement, breast tenderness, polyuria, headache, fatigue, dizziness, nausea, anorexia, vomiting, diarrhoea, orthostatic hypotension and hyperkalaemia.[108,137,138,142] To minimize the adverse events of menstrual irregularities and breast tenderness, spironolactone is often prescribed with an oral contraceptive.[97,100] Pregnancy should be avoided and adequate contraceptive measures should be instituted during spironolactone therapy due to concerns of feminization of the male fetus.[7,126,142]

Oral corticosteroids may be considered as an adjunct treatment of acne fulminans, aggressive conglobate acne, severe inflammatory acne and severe acne flare-ups associated with initiation of isotretinoin treatment.[73,106] In addition, oral corticosteroids can be used in patients with congenital adrenal hyperplasia to suppress adrenal production.[108]

The rationale for the use of probiotics in the treatment of acne vulgaris is based on their potential to correct dysbiosis and to mend the epidermal barrier.[138,143] Preliminary studies showed that oral administration of probiotics as an adjunct therapy played an effective role in the treatment of mild-to-moderate acne.[144] Because of the heterogeneity of the available trials, the highly dynamic microbiome that might change over time and the lack of long-term safety data, well-controlled randomized clinical trials are needed to determine the true efficacy of probiotics before they can be recommended for the treatment of acne vulgaris.[143]

Procedural therapies

Manual extraction of comedones, electrocauterization of macrocomedones, intralesional infiltration with triamcinolone, and the draining of cysts and abscesses have been used in selected patients for the treatment of acne lesions.[53,139,145] Laser and light therapy, as well as photodynamic therapy, have been used in the treatment of acne with varying success.[105,121,146] A 2018 Cochrane systemic review of 71 randomized controlled trials (*n*=4211) on the use of different modalities of light therapies for acne yielded mixed results.[147] Well-designed randomized controlled trials on the efficacy of the different modalities of laser and light therapy are needed.

Several physical modalities are helpful in the management of atrophic scars resulting from acne.[4,148] Dermabrasion can help in treating superficial scars if conducted carefully. Deeper scars can be smoothed by dermal fillers such as hyaluronic acid, L-poly-lactic acid, polymethylmethacrylate, platelet-poor plasma gel, platelet-rich plasma and autologous fibroblasts.[55,139,148–156] Other treatment options include chemical peels, skin microneedling, traditional non-fractional ablative laser resurfacing, ablative fractional laser resurfacing, non-ablative fractional laser resurfacing, dermaroller, radiofrequency, punch excision, punch lift/elevation and subcision.[55,148–162] A 2016 Cochrane systematic review of 24 randomized controlled trials (789 individuals aged 18 years or older) examining the efficacy of a wide range of interventions for the treatment of acne scars found insufficient evidence to recommend any particular intervention as the intervention of choice.[163] The authors attributed this to underpowered studies, poor methodology, different baseline variables and a lack of standardized outcome measures.[163] A 2017 systematic review of 36 articles on the efficacy and side effects of dermabrasion, microneedling, dermal fillers and chemical peeling for the treatment of acne scars found that those interventions have varying degrees of efficacy, each with both advantages and disadvantages.[164] Nevertheless, all of the previously discussed interventions are safe with few side effects.[164] More high-quality placebo-controlled trials with a large number of patients are needed to clarify the efficacy and safety of various interventions for the treatment of acne scars.

For hypertrophic acne scars and keloids, treatment may be required for cosmetic purposes. Intralesional corticosteroid injections are the most effective and the first-line treatment for hypertrophic scars and keloids.[159,165,166] If treatment with intralesional corticosteroid monotherapy is unsuccessful, one may consider multimodality therapy such as liquid nitrogen followed by intralesional steroids, followed by silicone gel sheeting and/or pulsed-dye laser therapy.[165,166] If these measures result in an insufficient response, surgical excision with preoperative, intraoperative and postoperative corticosteroid injections as well as pressure dressing, if applicable, can be considered.[165,166]

Complementary therapies

In some cultures, complementary therapies are popular for the treatment of acne. Low-quality evidence suggests topical application of tea tree oil or bee venom may reduce the total number of acne skin lesions.[167] Several studies have shown that topical application of tea tree oil products is as effective as topical benzoyl peroxide or salicylic acid for the treatment of mild-to-moderate acne.[167] Many other plant-derived therapies, such as basil oil and seaweed derivatives, have demonstrated

some positive effects against acne lesions.[168] There is generally a lack of high-quality evidence for the use of herbal medicine, acupuncture or cupping therapy for acne.[169]

Conclusion

Acne vulgaris is a common, chronic, inflammatory disorder of the pilosebaceous unit that affects most adolescents with inflammatory lesions on the face and trunk and may progress to scars. The condition can lead to emotional stress and the impact on quality of life can be significant. The management of acne vulgaris can be a challenge in daily clinical practice. As timely and proper treatment of acne may reduce the risk of scarring, early and effective treatment is of utmost importance. This article provides an updated review on acne with a focus on the management of this condition.

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