

## Key Points

- Acne vulgaris (acne) is a chronic inflammatory dermatosis that requires long-term treatment.
- Topical treatments (retinoids, benzoyl peroxide [BPO], azelaic acid, or antibiotics) are recommended for mild comedonal or inflammatory acne and in combination with systemic treatment for moderate and severe acne.
- The use of systemic treatments is indicated for moderate to severe inflammatory acne vulgaris, for acne that is resistant to topical treatments, and for acne of the trunk.
- Combination treatments are recommended to enhance effectiveness and tolerability and to improve the patient's compliance to the proposed treatment regimen.
- Treatment should aim to reduce the risk of bacterial resistance. Antibiotics (oral or topical) should not be used for more than

3 months and always be combined with topical agents such as retinoids or BPO.

- The treatment choice should be individualized and should take into account the age and the medical history of the patient, the type and severity of acne, the impact of acne on the patient's quality of life, the risk of scarring, and the presence of prognostic factors such as a family history of acne, adult acne, hyperseborrhea, hyperandrogenemia, truncal acne, or a history of infantile acne.
- Topical treatment is recommended as maintenance therapy, usually with a topical retinoid, BPO, or azelaic acid.
- Conglobate acne is a rare but severe form of nodular acne mostly affecting adult males. It presents with numerous comedones, papules, pustules, nodules, abscesses, and draining sinus tracts on the chest, back, and buttocks. Oral isotretinoin is strongly recommended as a monotherapy for conglobate acne.
- Acne fulminans is a rare acne variant affecting adolescent boys. It is characterized by the sudden onset of painful, ulcerative crusting acne in association with systemic signs and symptoms including fever, weight loss, arthralgias, and myalgias.

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C. Dessinioti (✉)  
Department of Dermatology,  
Andreas Syggros Hospital,  
University of Athens, Athens, Greece  
e-mail: [cliodes@hotmail.com](mailto:cliodes@hotmail.com)

B. Dreno  
Department of Dermatology,  
Nantes University Hospital, Nantes, France  
e-mail: [brigitte.dreno@wanadoo.fr](mailto:brigitte.dreno@wanadoo.fr)

## Definition and Epidemiology

Acne vulgaris (acne) is the most common skin disorder, affecting more than 80 % of adolescents, although it may present at any age. It has been defined as a chronic inflammatory dermatosis characterized by comedones and inflammatory lesions, including papules, pustules, and nodules, on sebum-rich body areas such as the face and trunk. It may be associated with a severe psychological and social impairment, as it may result in dysmorphia and permanent scarring, with a risk of low self-esteem and depression.

Conglobate acne is a rare but severe form of nodular acne mostly affecting adult males. It presents with numerous comedones, papules, pustules, nodules, abscesses, and draining sinus tracts involving mainly the chest, back, and buttocks. It frequently results in extensive and disfiguring scarring.

Acne fulminans (also known as acute febrile ulcerative acne or acne maligna) is a rare acne variant affecting adolescent boys. It is characterized by the sudden onset of painful, ulcerative crusting acne in association with systemic signs and symptoms including fever, weight loss, arthralgias, and myalgias. Aseptic, osteolytic bone lesions, visible on radiographs, have also been reported. Acne fulminans can be the dermatologic manifestation of the synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome.

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## Basic Concepts of Pathogenesis

The four major pathophysiologic factors that influence acne pathogenesis include sebaceous gland hyperplasia with hyperseborrhea, follicular hyperkeratinization, hypercolonization of the pilosebaceous unit with *Propionibacterium acnes* (*P. acnes*), inflammation, and immune reaction. Although each of these factors may represent a potential therapeutic target, the sequence of events has not been elucidated yet.

Androgens are central players in acne, as they increase the size of sebaceous glands and the sebum production, and they stimulate keratino-

cyte proliferation in the ductus seboglandularis and the acroinfundibulum, thus contributing to comedone formation. Sebaceous gland lipids exhibit direct pro-inflammatory properties playing a key role in acne pathogenesis. Although the relative amounts of *P. acnes* may not differ between acne patients and normal individuals, it has been proposed that specific *P. acnes* predominate in acne patients and possess specific genes that may increase virulence, promote stronger adherence to the human host, or induce a pathogenic host immune response.

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## Clinical Presentation

The clinical lesions in acne vulgaris are either non-inflamed lesions including open or closed comedones or inflamed lesions including papules, pustules, or nodules.

Acne may be classified based on the age of onset, into childhood, adolescent, or adult acne. This classification is important as there are age-related differences in the clinical presentation and the treatment approach.

Acne may present in childhood, and it is classified depending on the age of presentation, in neonatal, infantile, mid-childhood, and prepubertal acne.

In adolescents, acne presents around 12–14 years of age and usually resolves around 18–20 years of age.

Adult acne affects individuals older than 20–25 years. Adult acne is termed late-onset acne or acne tarda, when it first presents in adulthood, while persistent acne refers to acne continuing from adolescence to the adult years of life. Persistent acne is the most common form of adult acne, accounting for 80 % of cases. There are two clinical forms of adult acne: the inflammatory form consisting of papulopustules and deep inflammatory nodules and the comedonal form characterized by macrocomedones.

Also, acne may be classified according to severity as mild, moderate, or severe and according to the lesions that predominate in a given patient as comedonal, papulopustular, or nodular (Figs. 1.1, 1.2, and 1.3). When there are a similar



**Fig. 1.1** Mild facial acne with few papules and pustules. Several acne scars are present



**Fig. 1.2** Moderate facial acne with some papules and pustules. Acne scars are present

number of comedones and papules, it is referred as comedopapular acne, while in case of a similar number of papules and pustules, it is termed papulopustular acne. Severe cystic acne is characterized by the presence of cysts and numerous comedones, papules, and pustules.



**Fig. 1.3** Severe papulopustular acne

## Differential Diagnosis

The diagnosis of acne is clinical. Acne is not an allergy or an infection, so laboratory evaluations are not necessary to confirm diagnosis, except if other conditions should be ruled out. The comedone is the sine qua non clinical lesion in acne. It is always present in acne and this is the key characteristic that establishes diagnosis.

Childhood acne should be differentiated from:

- Neonatal cephalic pustulosis: *Malassezia furfur* is found in microscopy, presents with pustules and no comedones, and responds to topical ketoconazole.
- Acne venenata infantum: is due to the application of topical oils and ointments.
- Milia: small cysts with keratin plugs. Spontaneous resolution.
- Acneiform eruption: due to maternal use of corticosteroids during pregnancy, no comedones, monomorphous lesions.
- Perioral dermatitis: may be due to the use of topical or inhaled corticosteroids. No comedones.

Adolescent acne should be differentiated from:

- Folliculitis: it presents with follicular pustules. Comedones are absent.

Adult acne should be differentiated from:

- Rosacea: it affects individuals after the age of 30 years. Comedones are absent.
- Perioral dermatitis: it affects individuals mainly after the age of 30 years. It is located around the mouth, nose, and eyes. Comedones are absent.

- Drug-induced acneiform eruptions due to glucocorticosteroids, antiepileptics, antidepressants, growth hormone, cyclosporine, vitamin B12, epidermal growth factor receptor (EGFR) inhibitors, and BRAF inhibitors: recent or current history of drug intake; comedones are absent.

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## General Principles of Treatment

Acne is a chronic disease, and patient education is critical to improve adherence to proposed treatment and optimize clinical results. It should be explained that acne treatment will continue over long periods of time and clinical improvement is not evident early but usually takes some (5–6) weeks to show. Topical treatments are fundamental for the management of acne, so the importance of applying topical agents should be communicated to patients. Topicals should be applied on the entire face and not just on the clinically visible lesions in order to effectively target the microcomedone, the primary acne lesion, that is not visible to the naked eye.

A mild cleanser may be used for washing the face twice daily. The use of noncomedogenic cosmetics and makeup products if camouflage is desired is encouraged. A suitable oil-free sunscreen during the summer and during oral isotretinoin treatment is advisable. Skin care products are often necessary to either complement the use of acne drugs or to counteract the drying effect of some acne medications, such as moisturizing creams during oral isotretinoin treatment and in combination with topical retinoids, in order to avoid topical irritation.

A common question often posed by acne patients is whether a specific food influences their acne. The intake of chocolate has been traditionally held as culprit for acne flare-ups. However, this has remained a myth and not a proven fact, and there are no evidence-based data to either support or refute an association of diet with acne. We suggest our acne patients to follow a balanced diet as part of a healthier mode of life in general.

## Topical Treatments

### Topical Antibiotics

Topical antibiotics include erythromycin, clindamycin, tetracycline, and nadifloxacin. They exert anti-inflammatory properties as well as antibacterial action against *P. acnes*.

Topical antibiotics are indicated for mild to moderate action. They should never be used as monotherapy but should be used in combination with another topical treatment such as retinoids, benzoyl peroxide, or azelaic acid, either in the context of alternate day regimens or as fixed-dose combinations. They are applied once or twice daily for a maximum period of 6 weeks.

### Benzoyl Peroxide (BPO)

BPO has antibacterial, anti-inflammatory, and mild comedolytic actions. Topical BPO is indicated for mild papulopustular acne and for moderate to severe acne in combination with another topical treatment, such as retinoids, antibiotics, or azelaic acid. Also, it may be combined with systemic antibiotic therapy or, in women, with hormonal therapy. BPO is applied once or twice daily for a period that is determined by the treating dermatologist. It may be proposed as maintenance therapy.

### Topical Retinoids

Topical retinoids include adapalene, isotretinoin, tazarotene, and tretinoin. They have comedolytic effects, and, in addition, adapalene exhibits mild anti-inflammatory action. Topical retinoids are indicated for comedonal and mild papulopustular acne. Also, they are indicated for moderate to severe acne in combination with another topical treatment, such as BPO, antibiotics, azelaic acid, and/or a systemic antibiotic or hormonal therapy. They are applied once or twice daily for a period that is determined by the treating dermatologist. They may be proposed as maintenance therapy.

## Azelaic Acid (AZA)

Azelaic acid presents mild comedolytic, antimicrobial, and anti-inflammatory actions. AZA is indicated for comedonal and mild papulopustular acne. Also, it is recommended for moderate and severe acne in combination with another topical treatment such as BPO, retinoids, or antibiotic or in combination with a systemic antibiotic or hormonal therapy. It is applied twice daily, and treatment for at least 12 weeks is usually required for acne improvement.

## Fixed-Dose Combination Topical Formulations

Fixed-dose combination topical agents combine two different agents used for acne treatment, such as combinations of antibiotic/retinoid or antibiotic/benzoyl peroxide or benzoyl peroxide/retinoid. Topical combination treatments target multiple pathogenetic factors at the same time, thus resulting in enhanced effectiveness and improved tolerability. Also, they present the advantage of a simpler application regimen, with a once- or twice-daily application of a single formulation, thus resulting in better adherence by the patient to the proposed treatment.

Topical retinoids in combination with topical antimicrobials have been shown to reduce inflammatory and noninflammatory acne lesions faster and to a greater degree than antimicrobial therapy alone. This may be explained by the fact that combination treatments target several areas of acne pathophysiology simultaneously. In addition, topical retinoids may affect skin permeability and facilitate the penetration of the topical antibiotic.

Clindamycin/zinc gel contains zinc acetate dehydrate applied once or twice daily in a formulation that reduces the extent of absorption of clindamycin through the skin while showing equivalent efficacy and safety to clindamycin lotion. Combinations of zinc with erythromycin may result in reduction of the risk of bacterial resistance.

Once-daily applied topical clindamycin/benzoyl peroxide and twice-daily applied erythromycin/zinc acetate are both effective treatments

for acne, but clindamycin/benzoyl peroxide has an earlier onset of action. Also, a fixed clindamycin phosphate/tretinoin gel formulation applied once daily was more effective and faster acting in reducing acne lesions than clindamycin lotion formulation applied twice daily.

## 5 % Dapsone Gel

Dapsone is a sulfone with both anti-inflammatory and antimicrobial properties. Advances in cutaneous pharmacology have produced a new topical formulation of 5 % dapsone gel, which was shown to be an effective and safe treatment, when applied twice daily for 12 weeks. Glucose-6-phosphate dehydrogenase-deficient patients presented no laboratory abnormalities. It has been proposed that its action may be due to a direct inhibition of leukocyte trafficking and the generation of chemical mediators of inflammation by leukocytes. Alternatively, topical dapsone might act indirectly in acne, by altering the levels and/or activity of propionibacteria.

### Topical Treatments at a Glance

- Topical treatments (retinoids, BPO, AZA, antibiotics) are recommended for mild comedonal or inflammatory acne and in combination with an oral treatment for moderate and severe acne.
- Topical antibiotics should not be used alone but in combination with another agent (e.g., retinoid or BPO) to avoid the risk of bacterial resistance.
- Topical treatments are recommended to be used in combination, either as separate agents or as fixed-dose combination agents.
- Fixed-dose combination agents aim to enhance effectiveness and tolerability and to improve patients' compliance to the propose treatment regimen.
- Topical treatment is recommended as maintenance therapy, usually with a retinoid, BPO, or AZA.



## Systemic Treatments

The use of systemic treatments is indicated for moderate to severe inflammatory acne, for acne that is resistant to topical treatments, and for acne of the trunk. Established systemic acne treatments include oral antibiotics, isotretinoin, and hormonal therapies.

## Antibiotics

Systemic antibiotics for acne treatment include tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, and minocycline) and macrolides (erythromycin, azithromycin).

Antibiotics such as tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, and minocycline), trimethoprim, and macrolide antibiotics (erythromycin) have been a mainstay of treatment for moderate and severe acne and treatment-resistant forms of inflammatory acne, for more than 30 years. The efficacy of tetracycline derivatives in acne vulgaris is believed to be related, besides to their antibiotic effects, also to their anti-inflammatory effects. Anti-inflammatory action may be exerted via reduction in neutrophil chemotaxis, as well as via inhibition of proinflammatory cytokines and matrix metalloproteinase-9 (MMP-9). Nevertheless, data concerning antibiotic use in acne has been based on anecdotal reports, clinical experience, and small clinical trials.

Recommended dosage regimens are 500–1,000 mg/day for tetracycline and erythromycin, 300 mg/day for lymecycline, and 50–200 mg/day for doxycycline and minocycline. Treatment should not exceed 3 months.

Acne treatment with systemic antibiotics may be associated with vaginal candidiasis and gastrointestinal disturbances. Moreover, doxycycline has been associated with photosensitivity, while minocycline has been associated with pigment deposition in the skin, mucous membranes, and teeth, particularly among patients receiving long-term therapy and/or higher doses of minocycline. Rare adverse effects reported with minocycline use include autoimmune hepatitis, a systemic lupus erythematosus-like syndrome, and serum sickness-like reactions (Table 1.1).

Tetracyclines are indicated for individuals older than 8 years, after permanent dentition has been completed, and they are contraindicated during pregnancy and lactation.

Bacterial resistance to antibiotics is an increasing health problem worldwide. Resistance of *P. acnes* is more common with erythromycin; less common with tetracycline, doxycycline, and trimethoprim; and rare with minocycline. Although acne itself is not infectious, antibiotic-resistant propionibacteria should be considered transmissible between susceptible individuals. The use of antibiotics may result not only in an increase of resistance of *P. acnes* but also in an increase in other resistant organisms, such as *Staphylococcus aureus*. In order to avoid this, it is recommended to avoid antibiotic monotherapy, to restrict antibiotic use to a minimum (up to 3 months), and to use combination treatments for acne.

Released in 2006, anti-inflammatory dose doxycycline (40 mg capsule containing 30 mg immediate-release and 10 mg delayed-release beads) administered once daily was approved by the US Food and Drug Administration (FDA) for the treatment of papulopustular rosacea. This formulation presents anti-inflammatory activity devoid of antibiotic effects, so that there is no evidence of antimicrobial selection pressure associated with its use. In patients with moderate acne, doxycycline at a subantimicrobial dose

**Table 1.1** Adverse events associated with oral antibiotic use in acne vulgaris

Antibiotic	Adverse events
Tetracycline	Gastrointestinal upset
	Vaginal candidiasis
	Reduced absorption with food and dairy products
Doxycycline	Gastrointestinal upset
	Photosensitivity
Minocycline	Dizziness
	Rarely, intracranial hypertension
	Hyperpigmentation of skin, oral mucosa, teeth
	Autoimmune hepatitis
	Lupus-like syndrome
	Serum sickness-like reactions
Erythromycin	Gastrointestinal upset
	Vaginal candidiasis
	Resistance of <i>P. acnes</i>

(20 mg twice daily) has been shown to reduce both inflammatory and noninflammatory lesions, while no resistant strains of *P. acnes* were evident.

Moreover, an extended-release (ER) minocycline tablet, administered at a dosage of 1 mg/kg daily for 12 weeks, was FDA approved for moderate to severe inflammatory acne vulgaris in patients over 12 years old. This formulation produces a slower release of active drug, which is believed to reduce the risk of side effects such as acute vestibular adverse reactions, and overall drug exposure with time.

Azithromycin is a methyl derivative of erythromycin that effectively inhibits significant intracellular pathogens, as well as Gram-positive and Gram-negative aerobic and anaerobic bacteria, including *P. acnes*. It has been found to be effective in treating noninflammatory and inflammatory acne lesions. Whether its efficacy is mediated primarily through antimicrobial or anti-inflammatory action remains unclear. There is no data on azithromycin resistance developing in *P. acnes*; however, due to high bacterial resistance to azithromycin in the population (20–27.4 %), its use as a first-line antibiotic therapy for acne is not advised. However, it may be considered as an alternative to conventional anti-acne treatment.

## Isotretinoin

Systemic isotretinoin (13-*cis* retinoic acid), a vitamin A derivative, is the only therapeutic agent that targets all four major factors involved in acne pathogenesis. The European Agency for the Evaluation of Medicinal Products (EMA) recommends that its use should be limited to severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) that has proved resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. However, it has been proposed that oral isotretinoin may be considered as a first-line treatment, in the case of existing prognostic factors that have been proven to influence acne, such as family history, early onset of acne, trunk involvement, persistent and late-onset acne, hyperseborrhea, scarring potential, and severe

psychological impact. Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first-line therapy (e.g., financial resources/reimbursement limitations, legal restrictions, availability, drug licensing).

Isotretinoin is recommended at a dose of 0.3–0.5 mg/kg/day, given in two divided doses, for at least 6 months and until there is sufficient response. A lower clinical response with oral isotretinoin 0.5 mg/kg/day for 6 months, for mild to moderate adult female acne, has been associated with a high-glycemic-load diet, smoking, and early acne onset. Relapse after treatment with oral isotretinoin has been reported in 15–45 % of patients, and it has been associated with early acne, young age at the moment of isotretinoin initiation, family history of acne, prepubertal acne, localization on the trunk, important seborrhea, and a high number of inflammatory lesions at the end of treatment.

Systemic isotretinoin has been associated with a plethora of adverse events, most of which are dose dependent and self-limited. Mucocutaneous xerosis is the most common adverse event, resulting in dermatitis, cheilitis, epistaxis, and conjunctivitis. Laboratory evaluations during therapy should include triglycerides, cholesterol, transaminase levels, creatine phosphokinase, and complete blood counts. Hypertriglyceridemia and hypercholesterolemia have been reported in 25 % of patients but are reversible when isotretinoin is stopped. Elevated liver function tests have also been reported, which return to normal within 2–4 weeks despite continued treatment, and only rarely is treatment discontinuation needed. The most important adverse events are teratogenicity and psychiatric disorders. Isotretinoin is a known teratogen for women, so pregnancy should be avoided during treatment and for 1 month after cessation of treatment. Before treatment initiation, women of childbearing potential should be informed about teratogenicity of isotretinoin and the absolute need of effective contraceptive measures throughout treatment and for 1 month after treatment completion. Some studies and case reports have reported mood disorders, depression, suicidal ideation, and suicides in patients taking isotretinoin, while other studies have failed to

show such an association. There is not enough evidence to establish a causal link between isotretinoin use and suicide or major depression. On the contrary, isotretinoin therapy has been shown to improve anxiety and depressive symptoms in acne patients. Oral isotretinoin should not be combined with oral tetracyclines as there is increased risk of benign intracranial hypertension.

New developments and future trends are low-dose long-term isotretinoin regimens and new isotretinoin formulations (micronized isotretinoin). Intermittent moderate-dose isotretinoin has been proposed for adult patients with mild acne unresponsive or rapidly relapsing after treatment with oral antibiotics. In a study of 80 patients, isotretinoin was used at a dose of 0.5 mg/kg per day for 1 week every 4 weeks for a total period of 6 months. The acne resolved in 88 % of the patients, but 12 months after treatment 39 % of the patients had relapsed. Another intermittent isotretinoin regimen which was found to be a safe and effective option for the treatment of mild to moderate acne consisted of isotretinoin 0.5–0.75 mg/kg/day for 1 week, every 4 weeks, for a total period of 6 months (cumulative dose 35 mg/kg). The importance of continuing effective contraception should be underlined for women taking intermittent isotretinoin regimens.

## Hormonal Therapies

Hormonal agents for acne treatment are indicated for female patients only, and they include antiandrogens and combined oral contraceptives (OC). Hormonal therapies exert their beneficial effects in acne by reducing circulating and local androgens and by opposing the actions of androgens in the pilosebaceous unit.

Appropriate patient selection is important when considering initiating hormonal therapy. Contraindications should be ruled out and treatment should be individualized. Hormonal therapy in acne is indicated for women, when oral contraception is desirable, when repeated

courses of isotretinoin are needed to control acne, and when there are clinical signs of hyperandrogenism, such as androgenic alopecia, and seborrhea/acne/hirsutism/alopecia (SAHA) syndrome. Also, hormonal therapy can be proposed for late-onset acne (acne tarda) and for cases of proven ovarian or adrenal hyperandrogenism. Hormonal therapy can be very effective in females with acne whether their serum androgens are abnormal or not. Most women with acne have normal serum androgen levels, yet will respond if treated with hormonal therapy.

Polycystic ovary syndrome (PCOS) may present with acne as a marker of hyperandrogenism. Oral contraceptive pill therapy is the first-line therapy for women with PCOS, hirsutism, and acne. The choice of OC is important as some progestins are more androgenic (norgestrel, levonorgestrel) and should be avoided, while others are less androgenic. The combination of ethinyl estradiol with drospirenone has the advantage of the antiandrogenic effects of drospirenone. Antiandrogens such as cyproterone acetate in the form of combined oral contraceptive are effective in the treatment of recalcitrant acne in PCOS.

### Systemic Treatments at a Glance

- Among oral antibiotics, doxycycline is recommended as first-choice agent for the treatment of moderate to severe inflammatory acne.
- Oral antibiotic therapy should be discontinued when response is achieved and after a maximum period of 3 months.
- Oral antibiotics should always be combined with a topical agent such as a retinoid, BPO, AZA, or their combinations, to decrease the risk of bacterial resistance.
- Oral antibiotic should not be combined with a topical antibiotic alone.
- Oral isotretinoin is recommended at a dose of 0.3–0.5 mg/kg/day in the recent European Guidelines.
- Hormonal therapy should be individualized for female acne patients.



## Other Treatment Options for Acne

Other therapeutic options that have been used for acne treatment include the extraction of closed and open comedones, laser, and light sources, while chemical peels and lasers may be used for acne scarring.

Laser and light therapies, including blue or red light, intense pulsed light (IPL), and pulsed-dye laser (PDL), have been used for acne. It is known that *P. acnes* produces porphyrins, particularly coproporphyrin III. Visible light is able to activate these porphyrins to produce a photodynamic reaction that has the potential to destroy bacteria. Topical photodynamic therapy (PDT) uses light-activated agents (photosensitizers) that are selectively absorbed into the pilosebaceous unit to amplify the response to light/laser therapy. Topical photosensitizers used for PDT in acne include 5-aminolaevulinic acid (ALA) and methyl aminolevulinate (MAL), although controlled randomized investigator-blinded trials are lacking. The recently published European Guidelines propose an “open recommendation” (neither for nor against) for the use of light, IPL, laser, PDT for the treatment of mild or severe papulopustular/moderate nodular acne, and moderate nodular/conglobate acne, as optimal treatment regimens, frequencies, and device settings remain to be clarified.

There is only a low strength of recommendation for blue light monotherapy for the treatment of mild to moderate papulopustular acne.

## Zinc

Zinc sulfate and zinc gluconate have been used for the treatment of inflammatory acne vulgaris with conflicting results. Oral zinc salts have been used at a dose of 30–150 mg of elemental zinc daily for 3 months. Adverse events during zinc treatment involve the gastrointestinal tract.

The mechanism of action of zinc salts is only partially known. Zinc acts via inhibition of polymorphonuclear cell chemotaxis and inhibition of growth of *P. acnes*. Also, its anti-inflammatory activity could be related to a decrease in TNF- $\alpha$

production and the modulation of the expression of integrins and the inhibition of Toll-like receptor 2 (TLR2) surface expression by keratinocytes.

Zinc gluconate has been proposed as an alternative therapy for inflammatory acne; it may be a useful treatment for pregnant women due to its favorable safety profile, and it may be proposed during summer as it causes no photosensitivity. In addition, zinc gluconate does not induce bacterial resistance, and when combined in a topical formulation with erythromycin, it has been shown to prevent the growth of erythromycin-resistant *P. acnes* strains and to be more effective in inflammatory acne than erythromycin alone.

## European Evidence-Based Guidelines for the Treatment of Acne

Treatment choice should be individualized and should take into account the age and the medical history of the patient, the type and severity of acne, the impact of acne on the patient’s quality of life, the risk of scarring, and the presence of prognostic factors such as a family history of acne, adult acne, hyperseborrhea, hyperandrogenemia, truncal acne, or a history of infantile acne.

The recently published European Evidence-based (S3) Guidelines for the treatment of acne have systemically reviewed well-designed clinical trials of acne treatments and included a structured consensus process. Guidelines were based on the clinical form of acne.

For comedonal acne, topical retinoids are recommended as first-line therapy (Fig. 1.4). Available topical retinoids were found to have similar efficacy, but adapalene is superior due to its better tolerability profile.

For papulopustular acne, fixed-dose combination agents were more efficacious compared to their ingredients used alone. For mild to moderate papulopustular acne, there is high strength of recommendation for the use of fixed-dose combination BPO/adapalene or BPO/clindamycin. AZA, topical retinoids, or BPO is recommended with a medium strength of recommendation. For more widespread mild to moderate papulopustular

**COMEDONAL ACNE**

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Strength of recommendation	Treatment
High	-
Medium	Topical retinoids
Low	BPO AZA
Negative recommendation	Topical antibiotics Hormonal therapy Systemic antibiotics Oral isotretinoin Artificial UVR
Open recommendation (neither for nor against)	Visible light Laser (visible, infrared wavelength) PDT, IPL

**Fig. 1.4** Recommendations for comedonal acne based on the European evidence-based (S3) guidelines

acne, oral antibiotic combined with adapalene is recommended with a medium strength of recommendation. Blue light monotherapy has a low strength of recommendation (Fig. 1.5).

For severe papulopustular/moderate nodular acne, oral isotretinoin has been recommended, while there is medium strength recommendation for systemic antibiotics combined with adapalene, BPO/adapalene, or AZA (Fig. 1.6).

There are very few studies evaluating nodular or conglobate acne. The recommendations for nodular/conglobate acne are presented in Fig. 1.7.

It is recommended that oral antibiotic therapy should always be combined with topical therapy (other than antibiotics). Among oral antibiotics, doxycycline should be preferred as first-line antibiotic, compared to minocycline or tetracycline, as minocycline has been associated with more serious side effects and tetracycline has a more complicated dosage regimen. Topical antibiotic monotherapy is to be avoided due to increased risk of bacterial resistance.

Maintenance therapy (e.g., with a retinoid or BPO or AZA) is of cardinal importance in order to maintain acne remission.

### Treatment Approach for Acne in Different Age Groups

The abovementioned guidelines apply for acne vulgaris during adolescence. Additional special considerations apply for childhood acne, adult acne, and acne during pregnancy and lactation. The proposed treatment approach for acne in different age groups is summarized in Fig. 1.8.

Special considerations of adult female acne include the resistance of acne to standard treatments, the fact that adult skin is more sensitive to possibly irritant topicals and there may be slower response, and the possibility of needing to treating acne during pregnancy or lactation. Patient education is important to increase therapeutic adherence.

<b>MILD-TO-MODERATE PAPULOPUSTULAR ACNE</b>	
<b>Strength of recommendation</b>	<b>Treatment</b>
High	BPO/clindamycin BPO/adapalene
Medium	AZA BPO Topical retinoids Systemic antibiotics + adapalene, for widespread acne
Low	Blue light as monotherapy Erythromycin/tretinoin Erythromycin/isotretinoin Oral zinc Systemic antibiotics + BPO or +BPO/adapalene, for widespread acne
Negative recommendation	Topical antibiotics as monotherapy Systemic treatment with anti-androgens, antibiotics and/or isotretinoin Artificial UVR
Open recommendation	Red light, laser, PDT, IPL

**Fig. 1.5** Recommendations for mild to moderate papulopustular acne based on the European evidence-based (S3) guidelines

Topical monotherapy usually is not sufficient to treat adult acne, as it fails to target the multiple factors implicated in acne pathogenesis. It is proposed to use combination topical treatments or combine oral and topical agents for optimizing results.

For adult women, topical retinoids are indicated for the treatment of mild comedonal and mild to moderate papulopustular acne. Adapalene is better tolerated. Given the oral teratogenicity of retinoids, it is recommended that women avoid pregnancy while using topical retinoids.

Azelaic acid (cream 20 %, gel 15 %) is proposed as first-line monotherapy for inflammatory and noninflammatory adult female acne, as it presents similar efficacy with other topicals, while it is characterized by a favorable tolerability profile. AZA has anti-tyrosinase action and

is suitable to treat postinflammatory hyperpigmentation associated with acne. No harmful effects on fetuses have been reported during two decades of clinical experience with topical AZA.

In accordance with the European Guidelines, topical antibiotics are not proposed as monotherapy for adult female acne. They may be used as part of combination therapy.

BPO may cause photosensitivity and irritation to the adult female skin with erythema and dryness.

Topical combination treatments are indicated for inflammatory adult female acne. The application of a fixed-dose combination agent is easier to use compared to the combined use of different agents, and it may improve the patients' adherence to proposed treatment.

**SEVERE PAPULOPUSTULAR ACNE (SPP) /  
MODERATE NODULAR ACNE (MNA)**

<b>Strength of recommendation</b>	<b>Treatment</b>
High	Oral isotretinoin for SPP
Medium	Systemic antibiotics + adapalene, or + BPO/adapalene, or + AZA, for SPP
Low	Systemic antibiotics + BPO, for SPP, MNA Systemic antibiotics + oral anti-androgens for SPP, MNA (for females) Oral anti-androgens + topical treatment for SPP (for females)
Negative recommendation	Topical monotherapy Oral antibiotics as monotherapy Oral anti-androgens as monotherapy Visible light as monotherapy Artificial UVR
Open recommendation	PDT, IPL, laser

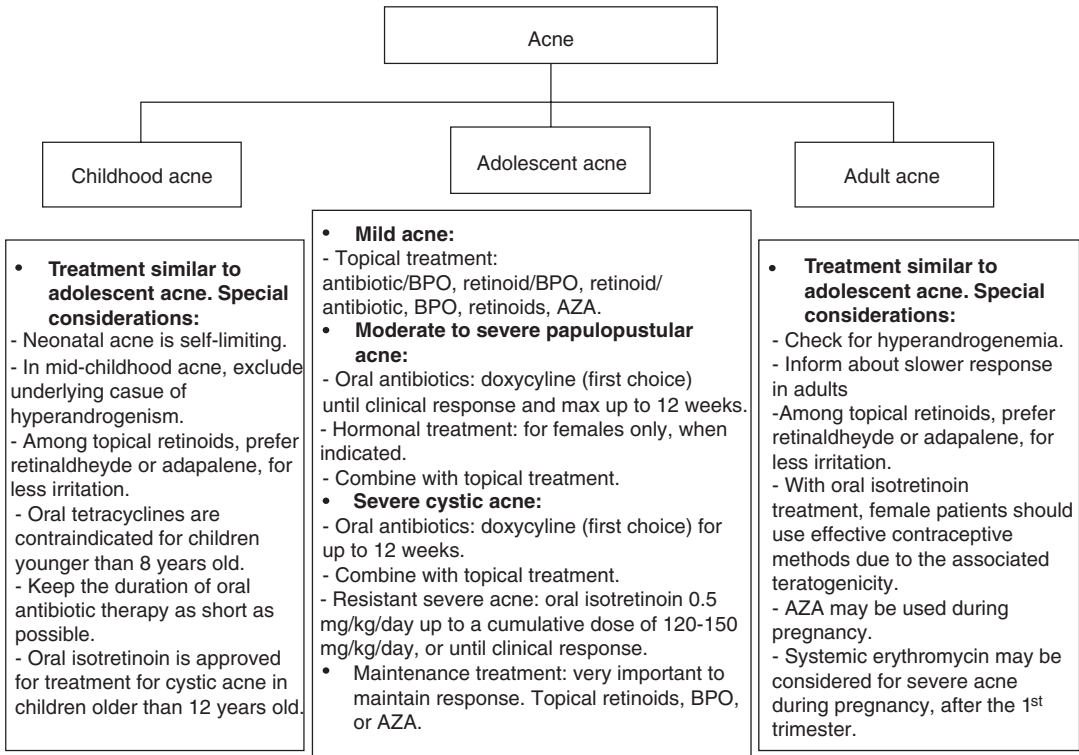
**Fig. 1.6** Recommendations for severe papulopustular/moderate nodular acne based on the European evidence-based (S3) guidelines

**NODULAR/CONGLOBATE ACNE (CA)**



<b>Strength of recommendation</b>	<b>Treatment</b>
High	Oral isotretinoin for CA
Medium	Systemic antibiotics + AZA, for CA
Low	Systemic antibiotics + BPO, or + adapalene, or +BPO/adapalene, for nodular/conglobate acne Systemic antibiotics + oral anti-androgens, for CA (for females)
Negative recommendation	Topical monotherapy for CA Oral antibiotics as monotherapy for CA Oral anti-androgens as monotherapy for CA Visible light as monotherapy for CA Artificial UVR for CA
Open recommendation	IPL, laser for CA Although PDT is effective, it cannot yet be recommended for moderate nodular/conglobate acne due to a lack of stand treatment regimens that ensure a favourable profile of acute adverse reaction

**Fig. 1.7** Recommendations for nodular/conglobate acne based on the European evidence-based (S3) guidelines



**Fig. 1.8** Acne treatment in different age groups

For adult female acne, systemic treatment is indicated for moderate to severe acne, acne with risk of scarring, and acne resistant to therapies.

In accordance with the European S3 Guidelines for the treatment of acne, oral antibiotics are not recommended as monotherapy, but they should be combined with topical therapies, such as BPO, to decrease the risk of bacterial resistance, or azelaic (15 % or 20 %) as an alternative choice for adult women with intolerance to BPO. According to published guidelines, when indicated, oral erythromycin may be taken during pregnancy after the first trimester, whereas oral tetracyclines are contraindicated during pregnancy as they may inhibit the formation of the skeleton of the embryo.

Hormonal therapies (antiandrogens and/or oral contraceptives) are very effective for adult female acne, even when there are no underlying hormonal disorders. Hormonal therapy permits long-term therapy without any risk of emergence of bacterial resistance as is the risk with long-

term antibiotic therapy. Also, hormonal therapy is an alternative choice for females that have relapsed after multiple oral isotretinoin treatments. Hormonal therapy should be combined with topical acne therapies such as antibiotics or BPO. Antiandrogens are contraindicated during pregnancy and lactation.

Topical maintenance treatment is necessary for adult female acne in order to decrease the risk of acne relapse after treatment discontinuation. For adult female acne, adapalene 0.1 % is proposed as first-line maintenance therapy and AZA 15 % or 20 % as an alternative. Topical antibiotics should not be used as maintenance therapy.

## Future Perspectives

Future perspectives in acne treatment include insulin-sensitizing agents; selective inhibitors of key enzymes involved in cutaneous androgen metabolism, such as 5- $\alpha$  reductase type 1, as well



as Toll-like receptor antagonists; and agents targeting proinflammatory molecules that participate in acne pathogenesis.

### Insulin-Sensitizing Agents

Hyperinsulinemia is an important factor in many cases of polycystic ovary syndrome (PCOS). It results from resistance to the effects of insulin on glucose metabolism, which has been found to occur independently of obesity and to be related to hyperandrogenism. Insulin may directly stimulate androgen-responsive pilosebaceous units. Antidiabetic agents that improve insulin sensitivity lower insulin levels and consequently improve ovarian function and plasma androgens. Recent studies, in women with PCOS, provide data for the efficacy and safety of metformin for acne treatment, while it has been suggested that patients who might benefit from metformin treatment are those with PCOS, diabetes, or impaired glucose tolerance.

Metformin, a biguanide, is the most commonly used insulin sensitizer for the treatment of PCOS. It inhibits hepatic glucose production and increases peripheral insulin sensitivity but does not cause hypoglycemia.

Halborne et al. reported in 52 women with PCOS similar self-assessed improvement in mild acne with metformin 1,500 mg daily for 14 months compared to oral contraceptive 35 µg ethinyl estradiol plus 2 mg cyproterone acetate, with no changes in sebum excretion rates. Kolodziejczyk et al. showed that in 39 women with PCOS and fasting hyperinsulinemia, treatment with metformin 1,500 mg daily for 12 weeks resulted in a decline of insulin and free testosterone and an improvement of acne.

Another study by Bergstrom et al. in 188 women with PCOS showed that metformin (500–1,000 mg twice daily) for a 6-month period resulted in improvement in acne severity, testosterone level, insulin resistance, and menstrual irregularities. Ibanez et al. in a randomized open-label trial in 34 adolescent girls with hyperinsulinemic androgen excess evaluated ethinyl estradiol-cyproterone acetate (EE-CA) compared

to a low-dose combination (PioFluMet) of pioglitazone (7.5 mg/day), flutamide (62.5 mg/day), and metformin (850 mg/day) for 6 months. EE-CA and PioFluMet were equally effective in improving acne (reduction of 0.8–1.1 in Leeds acne score after 6 months,  $p \leq 0.001$ ).

### Steroidogenic Enzyme Inhibitors

The skin is a steroidogenic organ that possesses all major enzyme systems for synthesizing androgens de novo from cholesterol and for locally converting circulating weaker androgens to more potent ones. The enzymes involved in cutaneous androgen metabolism, such as 5 $\alpha$ -reductase type 1, steroid sulfatase, and 3- $\beta$  hydroxysteroid dehydrogenase, may represent attractive targets for pharmacologic inhibition in acne treatment.

### Blocking the Activation of Toll-Like Receptors (TLRs)

*P. acnes* has been shown to induce an increased expression of TLR-2, TLR-4, and matrix metalloproteinase-9 (MMP-9) by human keratinocytes and to stimulate keratinocyte proliferation. Blocking the activation of TLRs could therefore represent an attractive therapeutic target.

### Targeting Peroxisome Proliferator-Activated Receptors (PPARs)

PPARs ( $\alpha$ ,  $\delta$ , and  $\gamma$  subsets) are ligand-activated nuclear receptors that form heterodimers with retinoid X receptors and regulate the expression of target genes involved in many cellular functions including cell proliferation, differentiation, and immune/inflammation response. PPARs may be important in the regulation of human sebum production and the development of acne. Activation of PPAR $\alpha$  and PPAR $\gamma$  by their ligands resulted in stimulation of lipid droplet accumulation in cultured immature sebocytes and sebum production was increased in patients. On the other hand, PPAR activators have shown

antiapoptotic, sebostatic, and anti-inflammatory effects in human skin. As increased sebum production is an important element in the pathogenesis of acne vulgaris, targeting PPAR isoforms to interfere selectively with sebum formation may have implications for the treatment of acne.

#### Future Perspectives at a Glance

- Insulin-sensitizing agents
- Selective inhibitors of key enzymes involved in cutaneous androgen metabolism
- Toll-like receptor antagonists
- Targeting PPARs

## Acne Fulminans

Oral corticosteroids are the treatment regimen proposed in reported cases of acne fulminans. Patients may require prednisolone up to 1 mg/kg daily for the effective control of cutaneous, constitutional, and musculoskeletal symptoms. Oral corticosteroids should be gradually tapered after the disease has been controlled. Systemic isotretinoin has been used successfully in acne fulminans but, paradoxically, may precipitate acne fulminans. So, the addition of oral isotretinoin has been proposed after the acute inflammatory phase of the disease has been controlled with oral corticosteroids, with a gradual increase in isotretinoin dose. After 1 year of treatment, the risk of relapse is low and acne fulminans in general does not recur.

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