European Handbook of Dermatological Treatments

Third Edition

Andreas D. Katsambas
Torello M. Lotti
Clio Dessinioti
Angelo Massimiliano D'Erme
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ISBN 978-3-662-45138-0 ISBN 978-3-662-45139-7 (eBook)
DOI 10.1007/978-3-662-45139-7

Library of Congress Control Number: 2015934002

Springer Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer-Verlag GmbH Berlin Heidelberg is part of Springer Science+Business Media (www.springer.com)

Preface

The third edition of the *European Handbook of Dermatological Treatments* follows the successful second edition published in 2003, providing concise yet comprehensive, up-to-date overviews of treatment guidelines and pearls in a plethora of skin diseases.

Over the last years, dermatology has achieved major breakthroughs in molecular and clinical research that have enabled the discovery of new treatments; our therapeutic armamentarium has been enriched with biological agents for psoriasis, also used as off-label promising treatments in other skin diseases, targeted agents for malignant melanoma and basal cell carcinoma, and new treatment modalities for rosacea, acne, atopic dermatitis, and urticaria, to name a few.

The three main sections of the third edition of the handbook are (i) diseases, (ii) drugs, and (iii) methods, encompassing different skin diseases, drugs available for dermatological treatments, and various methods applied in dermatology, including fillers, botulinum toxin, laser, dermoscopy, cryosurgery, and electrosurgery. Each chapter is focused on treatments, also providing a brief synopsis of the etiology and clinical presentation of the skin disease. Each chapter is structured with an abstract and a list of key points, while a comprehensive presentation of dermatological treatments, recent updated guidelines and recommendations, indications, contraindications, modes of action, and dosages are analyzed by our colleagues, experts in the field.

The third edition is enriched with clinical photos aiming to make the reading of the handbook a pleasurable as well as a learning experience. The skin is the most visible organ, and skin diseases can be challenging to effectively treat. The handbook focuses on dermatological treatments; indeed, treating patients is the essence of medicine, following the words of Hippocrates of Kos: "*Primum non nocere*."

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Part I

Diseases

Acne

1

Clio Dessinioti and Brigitte Dreno

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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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_1, © Springer-Verlag Berlin Heidelberg 2015

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.

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 keratinocyte 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.

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

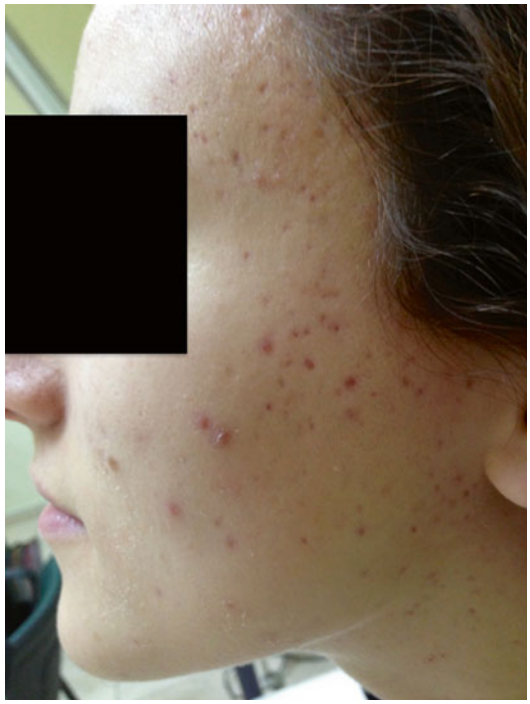


Fig. 1.1 Mild facial acne with few papules and pustules. Several acne scars are present

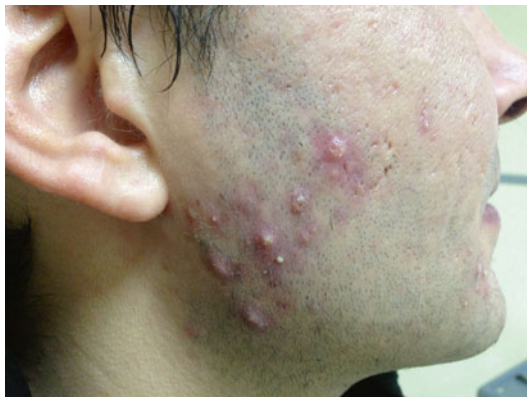


Fig. 1.2 Moderate facial acne with some papules and pustules. Acne scars are present

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.

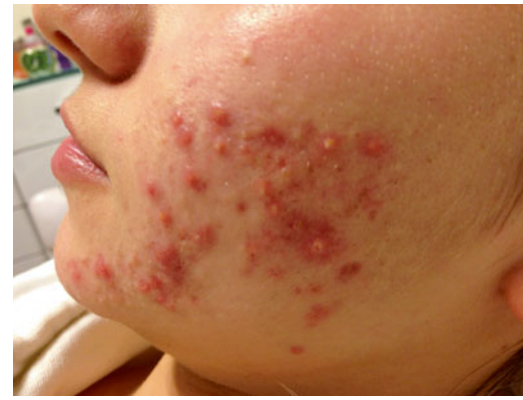


Fig. 1.3 Severe papulopustular acne

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.

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 *P. acnes*

(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 (EMEA) 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-α 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.

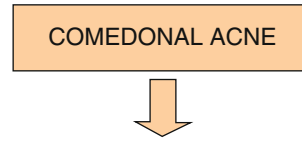
European Evidence-Based Guidelines for the Treatment of Acne

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



Strength of recommendation	Treatment
High	-
Medium	Topical retinodis
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.

MILD-TO-MODERATE PAPULOPUSTULAR ACNE

Strength of recommendation	Treatment
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)

Strength of recommendation	Treatment
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)

Strength of recommendation	Treatment
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 regiments 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

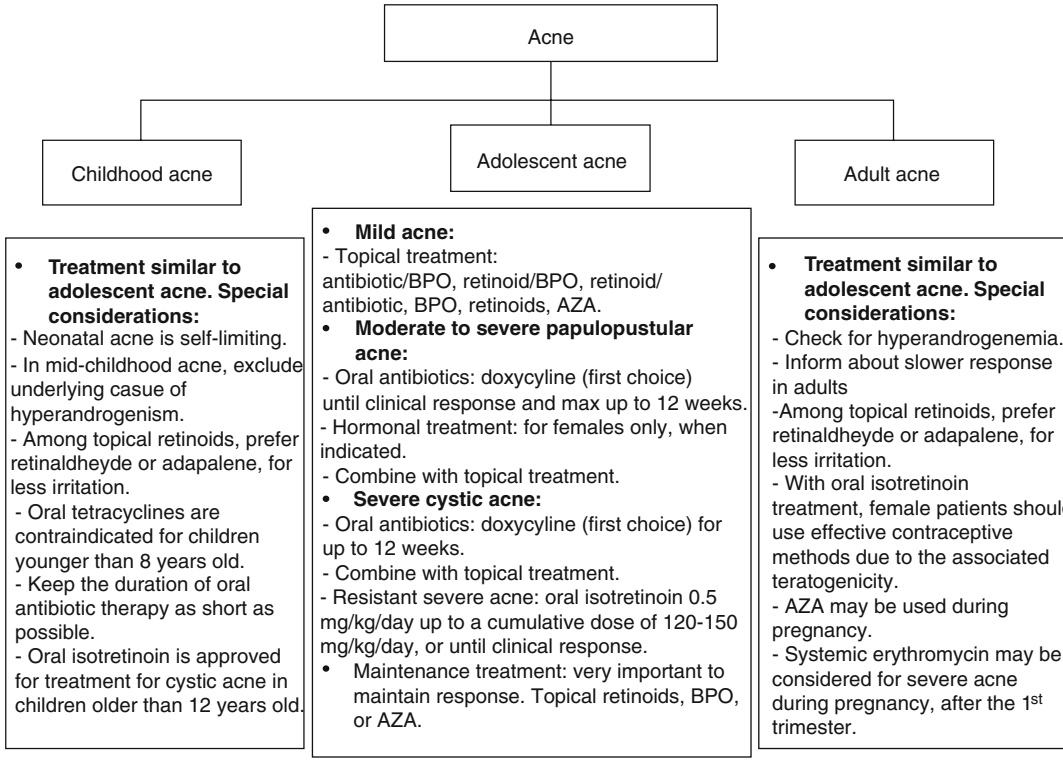


Fig. 1.8 Acne treatment in different age groups

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 intolerability 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-α 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 5α-reductase type 1, steroid sulfatase, and 3-β 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 (α, δ, and γ 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 PPARα and PPARγ 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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Actinic Keratosis

2

Francisco M. Camacho-Martinez

Abbreviations

5-FU	5-fluorouracil
AK	Actinic keratoses
ALA	5-aminolevulinic acid
CIN or SIN	Squamous intraepithelial neoplasia
CO_2	Carbon dioxide
CPG	Computer pattern generator
DFS	Diclofenac sodium
HD-OCT	High-definition optical coherence tomography
IMG	Ingenol mebutate gel
IMIQ	Imiquimod
KIN	Keratinocytic intraepithelial neoplasia
LED	Light-emitting diodes
MAL	Methyl ester 5-aminolevulinic acid
PDT	Photodynamic therapy
PpIX	Photosensitiser protoporphyrin IX
RTCs	Randomised controlled trials
SCC	Squamous-cell carcinoma
UVR	Ultraviolet radiation
SORT	Strength of recommendation taxonomy
SPF	Sun protection factor

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Definition and Epidemiology

Actinic keratoses (AK) are common skin lesions in relation to disordered keratinocyte proliferation that are the result of cumulative ultraviolet radiation (UVR) from sun exposure. This chronic, long-term sun exposure results in mutagenic changes in epidermal keratinocytes and the development of various skin lesions ranging from actinic keratosis to invasive squamous-cell carcinomas. In consequence, currently we consider KA as "in situ" squamous-cell carcinoma (SCC) or a real "malignant neoplasm" from the very beginning. It should be considered a superficial squamous-cell carcinoma in the same form as there are superficial basal-cell carcinomas (Camacho 2014).

AK lesions may appear as rough, scaly spots or papules always on sun-exposed skin. The presence of certain clinical features such as large size, erythema, inflammation, induration, hyperkeratosis, ulceration or bleeding suggests risk of disease progression to invasive SCC. AK can be observed as a unique element or several elements over a field cancerization. In consequence, AK as an isolated element or as various elements, including the field of cancerization, will need different types of therapies.

AK appears on the skin of persons with phototype I to III who have received too much actinic radiations in a short time (acute AK) or during their lifetime (chronic AK) due to professional activity (e.g. sailors, farmers and drivers). Although it is almost certain that, sooner or later,

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_2, © Springer-Verlag Berlin Heidelberg 2015

100 % of these persons will present with AK, of the remaining people who had been exposed to the sun, it is unpredictable what percentage will develop AK.

AK is most frequent in sunny countries, e.g. Australia, part of the USA (such as California), southern Europe (e.g. Italy, France, Spain) and so on. Prevalence studies show clear differences depending on the country, being higher when closer to the equator. The prevalence in Australia is almost 60 % of population over the age of 40, in Italy of 1.4 % in persons with more of 45 years, in United Kingdom of 15.4 % in men of more than 40 years whereas in women of the same age was only of 5.9 % but this proportion increased till 34.1 % and 18.2 % respectively in patients with 70 years old (Guidelines ILDS 2015). In sum, despite its high prevalence large-scale records to estimate the exact incidence and prevalence in our environment have not been carried out.

Basic Concept of Pathogenesis

The natural history of actinic keratosis depends partly on environmental factors such as exposure to ultraviolet radiation, carcinogens and ionising radiation and partly on constitutional factors such as skin phototype, age, immune status or competence for DNA repair.

These neoplasms are extremely common on the sun-exposed skin of middle-aged and elderly fair-skinned individuals who live in sunny climates. It can be a consequence of chronic solar radiation, but occasionally they may also be due to exposure to x-radiation and to ultraviolet light from artificial sources. The last cause is very important because many persons, habitually young women, receive excessive amounts of this kind of radiation, from tanning beds.

But we go back to the concept of field cancerization since it would help us to understand the UVR aetiology of AK. Since the first explanation of Slaughter's concept of field cancerization in 1953, the knowledge of the mechanisms implicated in cancer after UVR exposure has progressively increased. Genetic alterations found in keratinocytes, mainly mutations in the TP53 gene, give rise to clonal units with a loss of cellular control. Additionally, molecular disturbance localised in the dermis may contribute to the development of skin cancer within field cancerization. These discoveries have allowed us to understand better how it is possible for a second skin tumour to appear, close to the primary one previously removed and localised in the same anatomical area.

The p53 chromosomal mutation, found in over 90 % of human cutaneous squamous-cell carcinomas, is also found in 50 % of AK, including renal transplant recipients – this may occur as an early step in transplant-associated skin carcinogenesis. Chronic UVB can produce molecular and genetic changes not only in the altered skin but also in all the photoexposed skin; in consequence, AK is currently considered as a "disease of field", not as an isolated lesion. UVB should modify the genetic material of keratinoblasts and fibroblasts, modifying the dermoepidermal interrelations and producing a clone of abnormal cells that, for some time, stay in the epidermis but, sooner or later and in unpredictable percentages, will go to the dermis as invaders. Excessive UV exposition also induces the expression of other tumor suppressor genes as $p14^{ARF}$, $p15^{ARF}$ and $p16^{ARF}$ in AK, SCC and peripheral tissues.

The UVB radiation is directly related to the presence of AK on skin phototypes I to III. The ozone layer in the stratosphere is a natural filter for UVB radiation, but as its thickness decreases, it allows more UVB to reach the earth's surface. Depletion of the ozone layer is another aetiological factor contributing to the incidence of AK.

There are other cocarcinogen factors that must be taken into account. For example, prior therapy with methotrexate might put patients treated with psoralen and UVA (PUVA) at risk of developing skin cancer.

Contact with environmental carcinogens has also been related to a higher risk to developing nonmelanoma skin cancer. Hydrocarbons act by direct contact, whereas arsenic is acquired by ingestion of contaminated water or alternative therapies. Ingestion of arsenic is associated with a high incidence of premalignant lesions, and its

effect can be potentiated by other factors such as sun exposure, smoking and pesticides.

Clinical Presentation

A dry and hyperpigmented photo-ageing skin that exhibits *dermatoheliosis* – previously named "chronic actinic degeneration" or "solar degeneration" – begins to develop multiple 1–2 mm rough lesions. They are circumscribed lesions that have irregular edges and are slightly elevated but frequently easier to visualise. They may be flesh coloured or rosy, erythematous with telangiectasias or deeply pigmented. Generally, the hyperkeratotic surface is formed by yellow or brown adherent scales, but when they are pulled up, they reveal some slight horny downward proliferation inside the follicular pores. The pull-up manoeuvre of the hyperkeratotic scales produces, in the majority of cases, small painful erosions and minimal haemorrhage.

Several years ago, we considered three types of AK in accordance with its quantity of hyperkeratosis: grade 1, easily seen and slightly palpable; grade 2, well developed and easily palpable; and grade 3, hyperkeratotic lesions. These different AK types were also nominated as KIN (keratinocytic intraepithelial neoplasia) by its similitude with the gynaecological CIN or SIN (squamous intraepithelial neoplasia) by its relation with SCC. This classification of three grades was not successful because the evolution of AK is not similar to CIN, not being obligated to pass.

Common locations for the lesion are the skin surfaces exposed to the sun such as the face, mainly the forehead, cheeks, nose and ears; back of the hands; forearms; and, occasionally, shoulders and scalp in men with premature baldness. The scalp is also the typical location of field cancerization. AKs on the face and the neck are thin, whereas those on the scalp, back of the hands or on the forearms are often thicker.

The normal course of development for AK is for hard horny proliferations known as "verrucous keratosis" to grow. In these circumstances, it is easier to display the progression to deep invasion. Although there are authors who have communicated that AK commonly undergoes spontaneous regression, there is no proof of this. Recently a review of natural history of AK has been published (Werner et al. 2013). According with this review, the actual risk of progression of single AK lesion to invasive SCC remains unclear (ranged from 0.0 % to 0.53 % per AK lesion per year). Although the rate of regression of single AK lesions was generally seen to be 20 % to 30 % with up to 63 % in one study, spontaneous regression of complete fields of AK were only seen in 0.0 % to 7.2 % of patients. One study assessed the rate of recurrences in AK fields after a complete regression and showed recurrences in 57 % of the observed fields (Guidelines ILDS 2015).

Diagnosis

Usually, the diagnosis of AK is possible on the basis of the clinical appearance. Sometimes biopsy may be performed. The cells of the stratum malpighii present a chaotic arrangement. Some of these cells present pleomorphism and anaplasia of their nuclei, and others present individual dyskeratosis with formation of corps ronds and grains. As the cytologic features of the neoplastic cells of AK are indistinguishable from those of thicker squamous-cell carcinomas, this justifies the theory of Ackerman that these two conditions, despite their different names, are really one and the same.

Microscopic study includes a wide spectrum of histological patterns, and even several patterns can coexist in the same lesion. These patterns range from hypertrophic form (warty) to other atrophic forms. The WHO describes six histological types of AK: hypertrophic, atrophic, bowenoid, acantholytic, pigmented and lichenoid. Additionally the pagetoid pattern has been described:

1. Hypertrophic, characterised by pronounced hyperkeratosis intermingled with areas of parakeratosis. The epidermis is thickened in some areas which shows irregular downward proliferation limited to the uppermost dermis. Atypia is minimal and exclusive of basal keratinocytes.

2. Atrophic, with slight hyperkeratosis and the epidermis on the whole is atrophic. The basal-cell layer shows atypical cells with large hyperchromatic nuclei that lie close together, and these cells may proliferate into the dermis as buds and duct-like structures.
3. Bowenoid, indistinguishable from that of Bowen's disease or carcinoma "in situ". Differential diagnosis might be made with "lumican" stain since it is positive in 91.8 % of Bowen's disease and negative in all AK.
4. Acantholytic or "Darier type", with intercellular clefts or lacunae as resulting from anaplastic changes in the lowermost epidermis that produce dyskeratotic cells without intercellular bridges. Within suprabasal clefts or lacunae, a few acantholytic cells may be observed. This form of AK was considered by Ackerman as a miniature type of pseudoglandular squamous-cell carcinoma and provided evidence to support his theory that AK and squamous-cell carcinoma were synonymous (Ackerman 1997). There is an acantholytic variety known as "epidermolytic AK" in which the acantholyses appear between normal and atypical keratinocytes.
5. Pigmented, with accumulation of the melanin within atypical basal keratinocytes and melanophages.
6. Lichenoid, with a dense band-like dermal infiltrate in the dermoepidermal interphase which damages the basal-cell layer producing degenerated basal cells known as "hyaline or colloid bodies".

Recently, new noninvasive evaluation techniques of skin cancer have evolved in the last years. In addition to dermatoscopy, new modalities of imaging include cross-polarised light and UV light photography, confocal reflectance microscopy and optical coherence tomography. With these tools precise diagnosis and monitoring of response to treatments in field cancerization and actinic keratosis are possible with no need of invasive biopsies. With dermatoscopy, a red pseudonetwork ("strawberry") pattern was significantly associated with AK (Zalaudek et al. 2012). Innovative high-definition optical coherence tomography (HD-OCT) demonstrates the following features in AK: disruption of the stratum corneum, architectural disarray, cellular/nuclear polymorphism in the stratum granulosum/stratum spinosum and bright irregular bundles in the superficial dermis. Reflectance confocal microscopy reveals characteristic features with good histological correlation: in the stratum corneum, corneocyte disruption is revealed as the presence of bright, highly refractile cells with polygonal morphology, whereas parakeratosis appears as round dark structures in the middle of the corneocytes; atypical keratinocytes are observed in the stratum granulosum and spinosum with dark nuclei and irregular shapes and sizes; the superficial dermis reveals varying degrees of solar elastosis, identified by its moderate–high brightness and a highly irregular reticulate pattern; and round blood vessels are observed crossing the dermal papillae.

Differential Diagnosis

It is possible that the following dermatoses have difficulties of diagnosis with AK: solar lentigo, basal-cell carcinoma, seborrheic keratosis and Bowen's disease. Really, the most problematic differential diagnosis is with solar lentigo since in many occasions both can coincide (Fig. 2.1a, b).

Solar Lentigo

Darkly and unevenly pigmented, inflamed, uniformly dark brown, macular, irregular outline, sharp margination, scalloped borders, occasionally with hypopigmented areas and light brown areas. Size from 0.5 to 2.0 cm; locations on the head and neck. Dermatoscopy shows linearly striated pigmented network that has been likened to a "fingerprint" pattern. Confocal features: variable presence of refractile particles/globules in the stratum corneum and inside the superficial epidermis; honeycomb and/or cobblestone epidermal pattern that are preserved; large, polymorphic and numerous dermal papillae; hyperrefractile papillary rings formed by round, uniform cells; and occasional large, bright cells

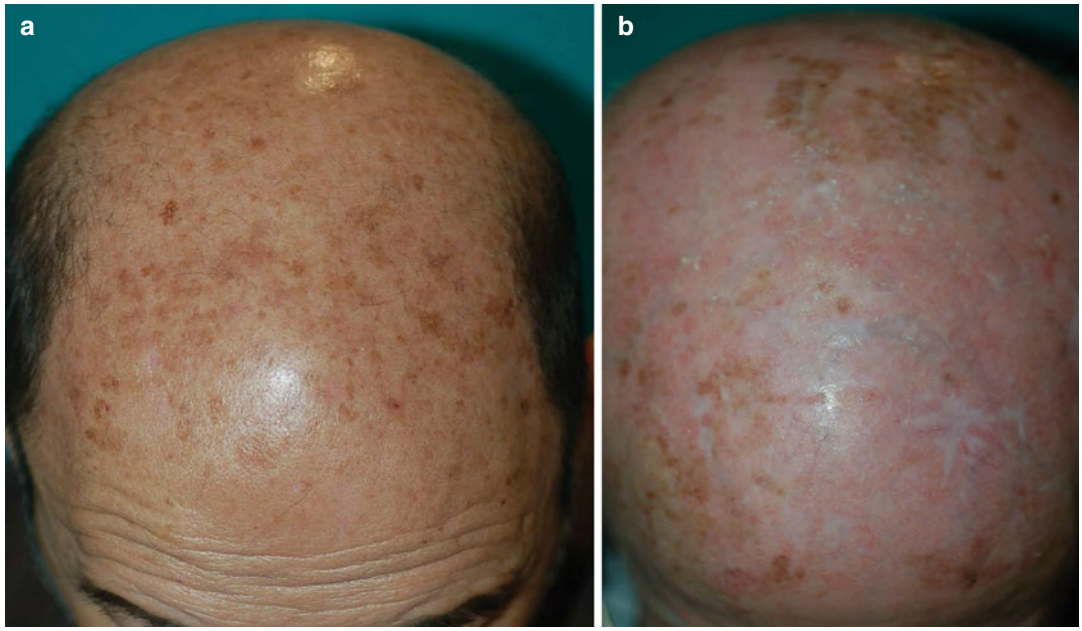

Fig. 2.1 (**a**) Solar lentigo. (**b**) Actinic keratoses. In this patient a scar can be observed. It is a consequence of squamous-cell carcinoma excised previously

in the dermis (melanophages) (Hirokawa and Lee 2011; Alsner et al. 2012).

Basal-Cell Carcinoma

Small telangiectatic vessels on its surface, pearly rolled border. Pigment and ulceration can be present. Dermatoscopy in nonpigmented forms: fine telangiectasias with subtle translucency, white streaks/white areas ("chrysalis" structures), translucency, milky-pink to red background, small ulceration and arborising vessels. In pigmented forms: island of pigment (blue-grey globules, blue-grey ovoid nests) and pigmented distribution pattern in maple-leaflike or spoke-wheel-like. Confocal features: elongated, monomorphic nuclei; nuclear polarisation along a single axis; and refractile stroma with frayed collagen bundles (gossamer), prominent inflammatory infiltrate, increased vascularisation and variable epidermal detachment (nucleated corneocytes, loss of the honeycombed pattern and nuclear pleomorphism of the keratinocytes) (Hirokawa and Lee 2011; Alsner et al. 2012).

Seborrheic Keratosis

Verrucous surface, soft and friable consistency and located on the trunk and occasionally in the face and scalp. Dermatoscopy: milia-like cysts, comedo-like openings and hairpin vessels. Confocal features: cerebriform-looking epidermal architecture, bright cysts often surrounded by a dark halo, bright cobblestone pattern in the stratum spinosum and poorly defined, bright polygonal cells in the upper dermis (melanophages) (Hirokawa and Lee 2011; Alsner et al. 2012).

Bowen's Disease (Intraepidermal Carcinoma)

Sharply demarcated, scaly, often hyperkeratotic, sometimes fissured macule, papule or plaque devoid of hairs; plaque may be composed of confluent reddish lenticular papules and nodules of variable size; tend to extend gradually with age in an annular or polycyclic pattern. Dermatoscopy features: dotted/glomerular vessels, diffuse

yellow opaque scales and microerosions are prevalent among intraepidermal carcinoma. Confocal features: disruption of the stratum corneum with evident parakeratosis; alteration of the epidermal pattern with severe keratinocyte detachment; and round, nucleated dyskeratotic cells present in the epidermis but never infiltrating the dermis (Zalaudek et al. 2012; Alsner et al. 2012).

General Principles of Treatment

AKs have the potential to spontaneously regress, remain stable or progress to nonmelanoma skin cancer. Given the high rates of regression and low rates of malignant transformation, some dermatologists think that not all AKs need to be treated. Others believe that AKs should be treated as a superficial squamous-cell carcinoma and in consequence must be removed using one of the several different methods of therapy selected by the dermatologists (Table 2.1).

Surgical Treatments

Radiosurgery

The original techniques in electrosurgery (electrodessication, electrocoagulation) after curettage have been replaced by machines that use radiofrequency waves. This enables AK to be removed easily under anaesthetics. It is the recommended technique for single or isolated AK (it allows to remove easily the AK after anesthesia, for which we used the Klein method) (Table 2.2).

Table 2.1 Treatment possibilities for actinic keratoses

(a) Surgical treatments
Radiosurgery
Cryosurgery
Dermabrasion
Laser
Surgical extirpation
(b) Medical treatments
5-fluorouracil
Imiquimod
Diclofenac
Ingenol mebutate
Medium-depth chemical peel
Oral retinoids
Photodynamic therapy (topical 5-aminolevulinic acid)
(c) Photoprotection

Cryosurgery

Currently liquid nitrogen freezing is the most commonly used method to destroy AK. Up to 98.8 % cure rate has been reported, but more recent data indicate smaller cure rates (Schmitt and Bordeaux 2013). It is an easy method that permits removal of AK without the need for anaesthesia. It is possible to use cryoprobes of different sizes. When the AK has developed fully, it is preferable to first perform curettage and then to use a cryoprobe. When the patient presents with multiple AKs, it is better to use cryospray in a centrifugal or paintbrush pattern. Consequently, the spray technique is the most adequate (gold standard) for field cancerization. Cryosurgery is undoubtedly the most used method based on ease; excellent cosmetic outcome results; grace, despite being painful; and efficiency, but does not allow histological study (Table 2.2).

Dermabrasion

Dermabrasion is a method that is useful to treating multiple AKs or field cancerization. Diamond fraises or wire brushes with a range between 800 and 33,000 rpm are used. It has the inconvenient in that the patient must stay in hospital at least 1 week. It is well known that only this technique treats AK successfully and provides long-term prophylaxis. As laser has become the most frequently used method of resurfacing, some believe that dermabrasion will soon be absent from the dermatologic tool box. Nevertheless dermabrasion remains an effective, economical and, some might argue, superior, resurfacing modality addressing many indications, one of them the treatment of actinic damage and AK (Hanke et al. 2013) (Table 2.2).

Laser

Carbon dioxide (CO_2) laser skin resurfacing is being used with increasing frequency in

Table 2.2 Treatments of actinic keratoses

Isolated (single). ≥ 1 and ≤ 5 palpable of visible AK lesion per field	Surgical techniques	Medical treatments	Photo-Protection
	Radiosurgery +++	5-fluorouracil +/–	+++
	Cryosurgery (cryoprobe) +	Imiquimod ++	
	Dermabrasion +/–	Diclofenac +/–	
	Laser ++ (CO_2)	Ingenol mebutate +/–	
	Surgical extirpation +++	Medium-depth chemical peel -	
		Oral retinoids -	
		Photodynamic therapy -	
Field cancerization. ≥ 6 distinguishable AK in one body region or field (multiple AK lesion), and contiguous areas of chronic actinic sun damage and hyperkeratosis	Radiosurgery +/–	5-fluorouracil ++	+++
	Cryosurgery (spray) +++	Imiquimod +	
	Dermabrasion +++	Diclofenac ++	
	Laser (laser-abrasion) ++	Ingenol mebutate +++	
	Surgical extirpation -	Medium-depth chemical peel +++	
		Oral retinoids +/–	
		Photodynamic therapy +++	

+++ Recommended
++ Acceptable
+ Occasionally
+/– Exceptionally
(–) Not recommended

dermatologic practice. The ultrapulse CO_2 laser, introduced in 1990, is an excellent method to remove keratoses; it is relatively easy to perform. The results are better, and the operative time for full-face resurfacing is markedly reduced when using computer pattern generator (CPG), a computer scanning device, in conjunction with the ultrapulse laser (Camacho 2005a). Full-face laser resurfacing is one of the treatment modalities that can treat whole surface areas, offering an effective and efficient treatment option that successfully reduces the number of actinic keratoses on diffusely damaged skin and may show a prophylactic benefit for preventing nonmelanoma skin cancers. Investigations with fractional technologies have demonstrated that treatment with ablative lasers is superior when compared with non-ablative fractional photothermolysis. However ablation of the epidermis is complicated by prolonged recovery time and higher risk of secondary effects. Recent studies with fractionated 1927 nm non-ablative thulium laser show a promising new therapeutic option for the treatment of actinic keratosis based on the clinical and histological findings as well as on the reported patient satisfaction and safety (Weiss et al. 2013).

Surgical Extirpation

This procedure should be only considered when the AK is a firm horny papule with the possibility