143 Acne and Related Disorders

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Introduction

Acne is a disease which encompasses a variety of clinical features and variants of which the most known is acne vulgaris. However, different courses exist due to several grades of severity, distribution in body areas, age, gender, and internal and external factors manifesting, exacerbating, or prolonging it. Acne is seen today as a chronic disease which continuously needs medical counseling. Physical and psychological scarring often accompanies the disease, and emotional distress is very commonly seen in all ages with manifestation of acne.

Historical Remarks

In the "Papyrus Eber," a disease named "Aku-t" was mentioned which was characterized by lesions well fitting the clinical picture of acne: boiling, blains, sores, pustules, and inflammation. The famous Greek physicians Hippocrates and Aristoteles saw an association with puberty. The Greeks named the disease "ionthos," the Latins "Varus." The pharao King Tut (135–1337 A.D.) undoubtedly had suffered from severe scarring. Most probably Atius, physician at the court of Justinian in East-Rom, used the term "acne" for the first time. Acne most probably arises from the greek "akme" but have been misspelled. It could also derive from aknesis, a rash which does not itch or from the greek word "akun." Lastly the Greeks took most probably over the term "aku-t" and then the word was introduced and finally came into medical latin language "acne."

Genetics and Epidemiology of Acne

Acne has a familial background, but a clear genetic inheritance has not been described yet. Genes encoding for cytochrome P450-1A1 and steroid-21-hydroxylase as well as 11- or 3-HSD may be involved. Environmental factors also appear to be of relevance. Especially, diet has recently gained attention. Populations with a balanced lifestyle seem not to develop significant acne and recent epidemiologic and investigative studies correlate acne with Western diets. The course of the disease in homozygotic twins is very similar, the sebum excretion rate is the same in more than 90%, whereas in heterozygotic ones it drops down to 40% and the severity is different. It has clearly been shown that seborrheic and acne patients have more lobules per single gland in the sebaceous apparatus than people with normal skin, which indicates a genetically prone situation. Nodulocystic courses of acne are more frequently seen in patients with the XYY genotype.

Acne today is regarded as one of the most frequent skin diseases worldwide in all ethnic groups. Epidemiologic studies in Western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%, depending on the method of lesion counting. In the USA, the prevalence in 15–17-year-old children is around 85%. If mild manifestations were excluded and only moderate or severe manifestations were considered, the frequency was still 20–35%. Acne is a disease primarily of adolescence. It is in parallel emerging in children at the start of puberty by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of the growth period. Although comedo formation decreases significantly, the hyperseborrhea still exists up to the fourth or fifth life decade. However, to some degree, acne is going to persist beyond teenage in a significant proportion of individuals (*Fig. 143.1*).

There are not only cases with persisting acne, but also those with reoccurrence or with a first manifestation in the third decade of life. Even after the adolescent type of acne has ceased, scarring and hyper- and hypopigmentation are long-term visible postacne features affecting the patients with negative physical outcome needing further medical and cosmetic care. Recent publications show a higher incidence of facial and persisting acne in certain families with an odds ratio of about >4 in the UK and Han Chinese. The course of disease stops more abruptly in males as compared to

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Prevalence of Acne in Different Epidemiological Studies

Autor	Jahr	Alter (Jahre)	Prävalenz Männer (%)	Prävalenz Frauen (%)	Gruppengröße (n)	Ort
Bloch [20]	1931	15–18	87,8–99,4	87,8–96,6		Schweiz
Hellgren [21]	1963	15–24	29,3–28,8	12,0–24,5	7 495	Schweden
Burton et al. [4]	1971	15–18	100	95–100		UK
Larsson and Liden [22]	1980	15–16	48,3–53,3	37,0–38,8	8 290	Schweden
Rademaker et al. [1]	1989	15–17	85–96	81–85		UK
Bahamadan et al. [23]	1996	14–19	56,4–78,2	n.b.	647	Saudi-Arabien
Freyre et al. [24]	1998	15	50,9–78,4	40,0–59,0	1 087	Peru
Plunkett et al. [25]	1999	20+	9,4–14,2	11,2–16,1	1 457	Australien
Daniel et al. [26]	2000	11–18	69,3–74,7		913	Frankreich
Schäfer et al. [8]	2001	1–87	29,9	23,7	896	Deutschland
Jemec et al. [13]	2002	15–22	40,7	23,8	186	Dänemark

Schäfer et al. JDDG; 2010 • 8:S4–S6

Figure 143.1
Acne epidemiology

females in whom there is today up to 30% persisting acne cases. Interestingly these observations have been already made in a doctoral thesis from Breslau in the early 1900 on female medical students. This means it is not a clear observation in females today, however, it is increasing in number.

Acne is in general considered a disease starting in adolescence; however, acne lesions may already precede the natural signs of puberty and little tiny comedones like milia (acne miliaris) can be seen mostly in children from the seventh to ninth year of life at the sides of the upper nose/glabellar area and lateral cheeks. Rarely, inflammatory lesions are detected. In girls, it may precede the menarche by up to 2.5 years.

A special subtype of acne occurring in early childhood is acne neonatorum during the second and fourth week of life and acne infantum manifesting after the second or third months after birth. Whereas in the first case maternal androgens or intrauterine stress-induced adrenal androgens are responsible, in the second case a temporarily adrenal functional hyperplasia is the cause, which under normal circumstances will fade away after the 9th month of life. Persisting cases, however, are suspicious for adrenal or gonadal androgen–producing tumors or misfunction of 3-, 7-, 11-, or 21-steroidhydroxylases and a pubertas precox.

Prognostic Factors of Disease

A number of prognostic factors have to be considered and are more or less related to the severe courses of the disease. These are outlined and evidenced in a review paper published by Holland and Jeremy (2005) and Dreno et al. and include family history, course of inflammation, persistent or late onset disease, hyperseborrhea, androgenic triggers, scaring, truncal acne, and/or psychological sequelae. Infantile acne may also correlate with resurgence of acne at puberty and one should be aware – even though not clearly proven by statistical evidence that early age of onset with mid-facial comedones, early and more severe seborrhea, and earlier presentation relative to the menarche are connected to the incidence of acne as a baby.

Scarring Assessment/Potential for Scarring Influence on Management

Scarring usually follows deep-seated inflammatory lesions but may also occur as a result of more superficial inflamed lesions in scar-prone patients. Holland and Jeremy published their findings that patients with more severe inflammatory infiltrate in the biopsy have less scarring

than those with a less inflammatory one. If this can be used as a predictor is not clear yet. Ethnic predisposition plays, in addition, an important fact having more scarring in black and Indian skin. More recent results by S. Kang point toward the fact that scars may even arise from skin areas not having involved by a visible lesion at all. This implies that treatment has to be done as early and as sufficient as possible.

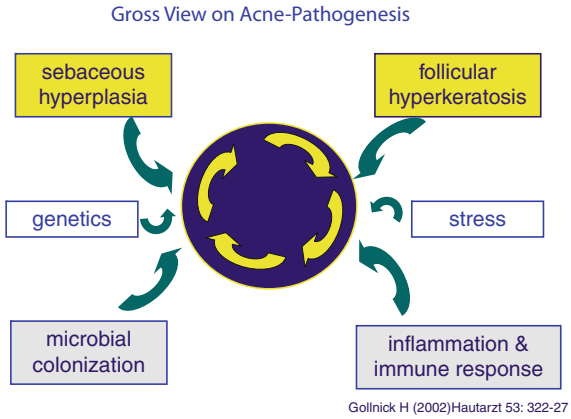
Acne scarring of different types, albeit mild, has been identified in up to 90% of patients attending a dermatology setting. Scars may show increased collagen (hypertrophic and keloid scars) or be associated with collagen loss (ice-pick, boxcar and rolling type of scars). The presence of scarring should support immediate onset of an interventional aggressive management and therapy should be considered as early as possible in the disease process. In the postacne situation, patients suffer long-standing sequelae and ask for additional support by peelings and lasers as well as psychological help.

Pathophysiology

Acne is an androgen-dependent and androgen-driven disorder of the pilosebaceous apparatus. At the beginning of its manifestation, the first nonvisible lesion is the microcomedo in which the colonization with *P. acnes* does not play any role, but sebaceous hyperplasia and increased pathologic cohesion of follicular corneocytes have led to the microscopic changes of the follicular milieu.

Today, four primary pathogenic factors are accepted in different grades of expression and at different time points involved or intermingled in the pathogenesis of acne. These are as follows: (1) increased sebum production by the sebaceous gland, (2) hyperproliferation and disturbed keratinization with increased cohesion of corneocytes in the follicular canal, (3) colonization with Propionibacterium acnes in the lower part of the infundibulum, and (4) release of several inflammatory mediators involved in innate and acquired immunity (◉ *Fig. 143.2*).

Patients with seborrhea and acne have a significantly higher number of lobules per gland as compared to normal healthy persons who never developed acne or seborrhea (so called genetically prone "Anlage"). This means that the androgenic event in puberty acts on a different Anlage. Inflammatory responses occur prior to hyperproliferation of keratinocytes. IL-1α upregulation participates in the development of comedones independent of the colonization with *P. acnes.* A relative linoleic acid



◘ Figure 143.2
Gross view on acne pathogenesis

deficiency has been described by Downing and Strauss, but this can only be a contributing factor because the deficit appearing in the lobules of the gland and consequently in the follicular corneocytes with less barrier function (ceramides) persists despite resolution of comedones in the third life decade when acne resolves but seborrhoea persists (◉ *Fig. 143.3*).

Cycling of the sebaceous follicle is an important part in the cascade of mechanisms interacting in the pathophysiology, leading to certain time points when the microcomedo formation becomes disposed to form a sensitive moment for an injury as a starting point of new lesions.

P. acnes colonizes the skin right after birth and an immune response with IgM and IgG follows. It seems that *P. acnes* at this time point is of a planctonic type, whereas later in puberty it becomes pathologic and starts biofilm production and increases its virulence. Acting on the inflammatory cascade of NF kappa and the proinflammatory cytokines via Toll-like receptor 2 it contributes to a continuous self-perpetuating vicious cycle. Activation of AP-1 induces matrix metalloproteinase genes, whose products degrade and alter the dermal matrix.

However, it should be noticed that inflamed follicles exist showing no *P. acnes* colonization at all. Oxidized squalene (squalene peroxide) can stimulate hyperproliferation in keratinocytes and those lipoperoxides can produce leukotriene B4, a powerful chemoattractant.

The role of free fatty acids formed after the splitting of triglycerides into FFAs and diglycerols has been long overestimated but still contributes to the different factors working in concert in the follicular milieu (◉ *Fig. 143.4*).

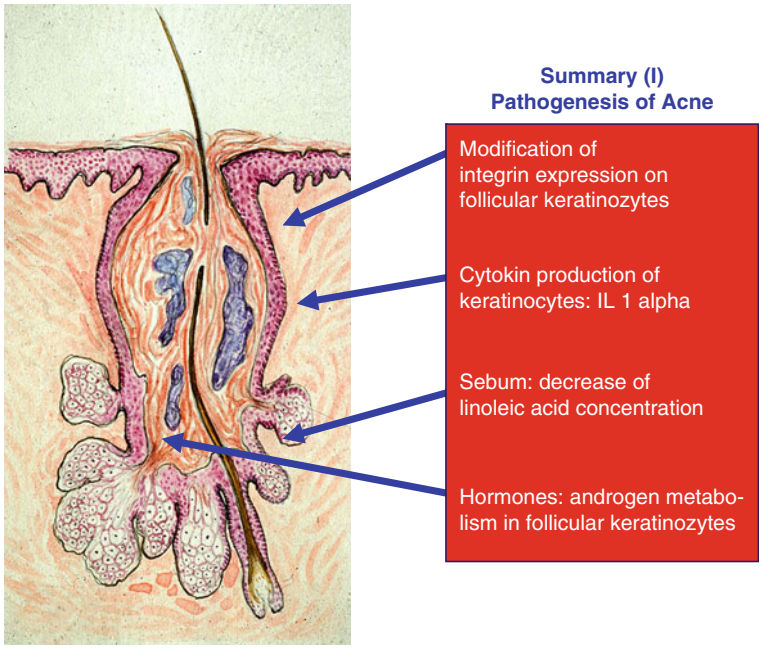


Figure 143.3
Summary of the pathogenesis of disturbed follicular keratinization processes in the follicular infundibulum

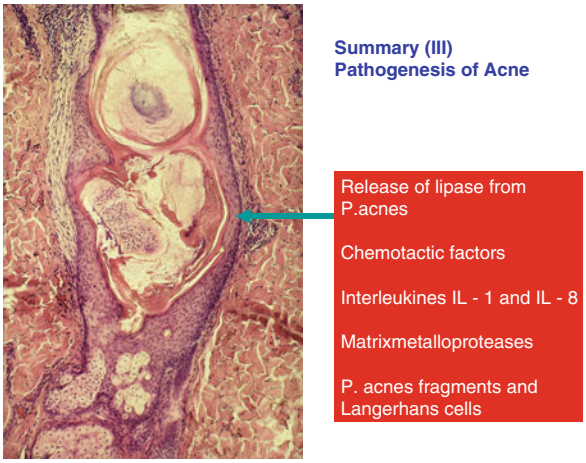


Figure 143.4
Summary of pathogenetic processes in the infundibulum related to P.acnes

Sebaceous lipids are regulated by peroxisome proliferator-activated receptors gamma and alpha (PPAR's) which act in concert with retinoid X receptors to regulate epidermal growth and differentiation as well as lipid metabolism. Sterol response element binding proteins (SREBP) mediate the increase in sebaceous lipid formation induced by insulin-like growth factor-1 via the PIK-3 or/and Akt-pathways. Substance P receptors, neuropeptidases, α-melanocyte stimulating hormone, IGF-1R, and CRH-R1 are also involved in regulating sebocyte activity, and finally the ectopeptidases such as dipeptidylpeptidase IV and animopeptidase N, which are distributed on activated keratinocytes, sebocytes, and T-cells in the inflammatory infiltrate. The sebaceous gland acts on the whole as an endocrine organ in response to changes in androgens and hormones (*Figs. 143.5* and *143.6*).

The role of FoxO1 and the relation of nuclear to cytoplasmic shifting with stimulation of the PPAR gamma and of the androgen receptor are not yet fully discovered; however, a connection to the IGF and insulin-related stimulation of this cascade is a further evidence for research (*Fig. 143.7*).

The improved understanding of acne development on a molecular level suggests that acne is a disease that involves the innate and adaptive immune system and inflammatory events as well as the local and systemic hormonal network. The "Switch-Off Signal" of acne, however, is not understood yet (*Fig. 143.8*).

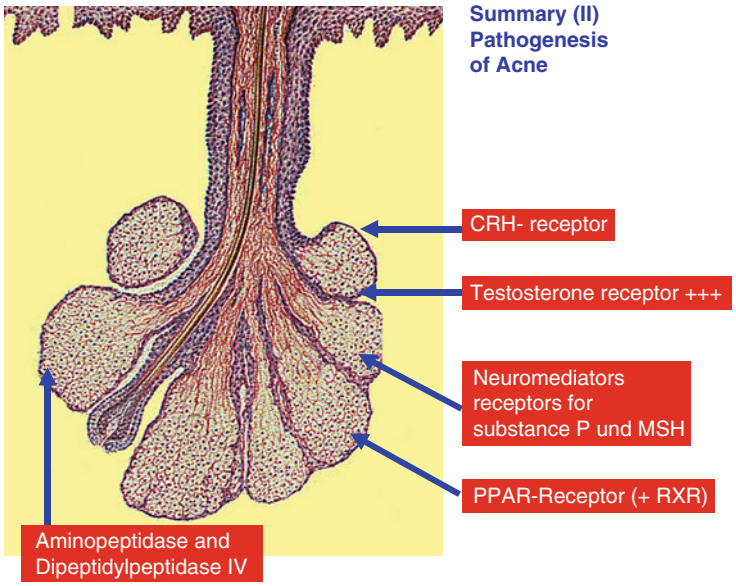


Figure 143.5
Summary of pathogenesis of processes leading to sebaceous hyperplasia

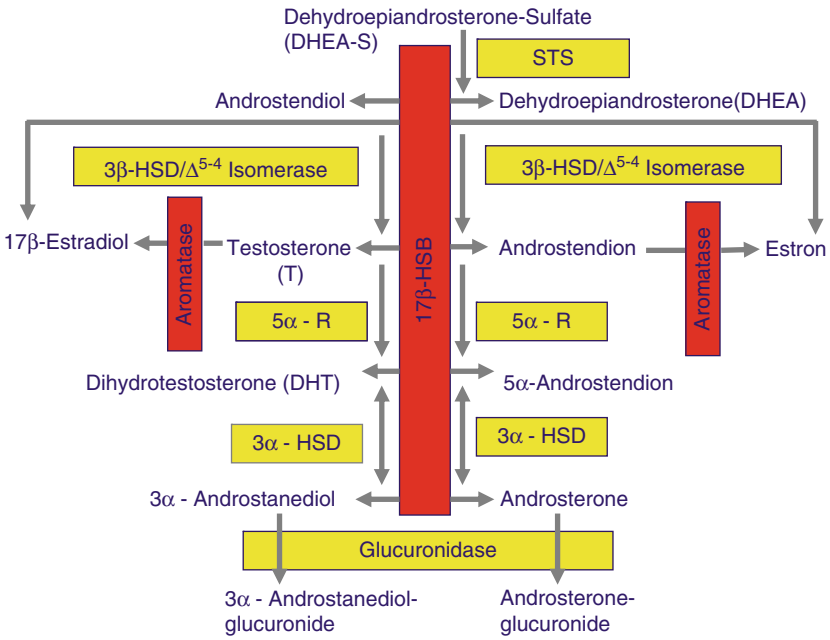


Figure 143.6
Androgen metabolism pathways important in the activation of sebocytes and follicular keratinocytes

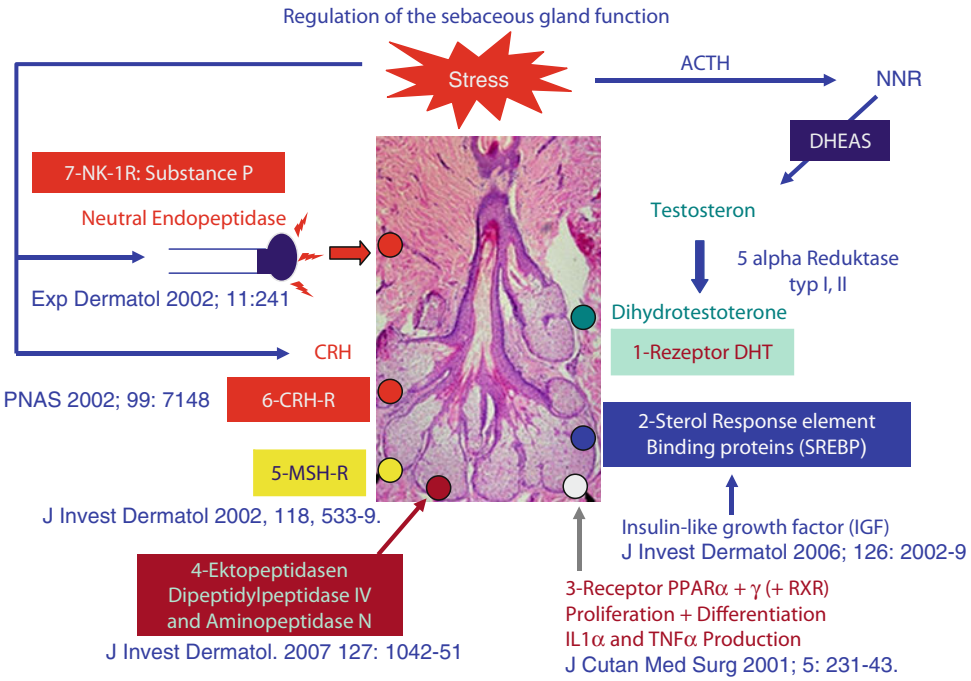


Figure 143.7
Details of the receptors and mediators acting on the sebaceous gland

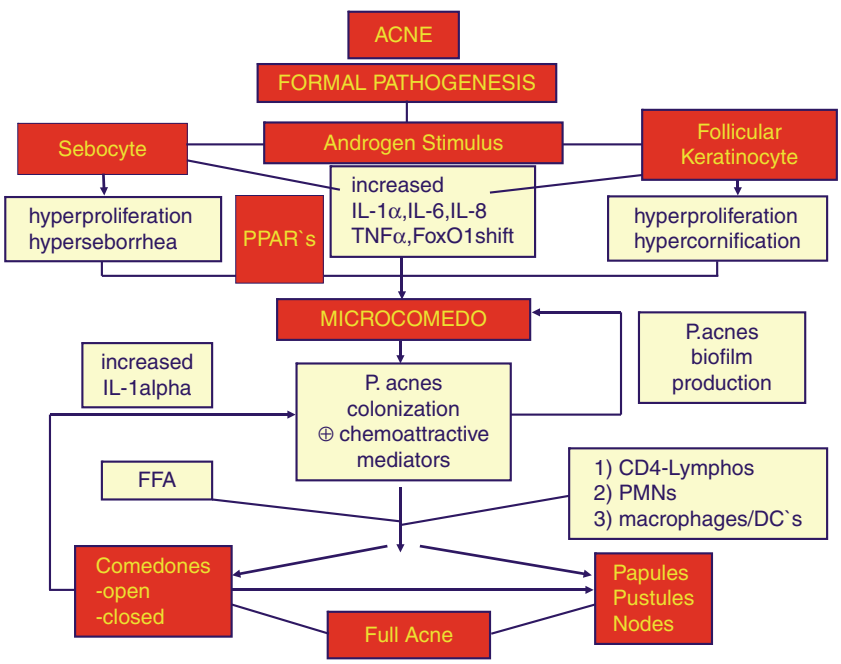


Figure 143.8
Detailed scheme on acne pathogenesis

Clinical Features and Variants

Vulgar acne, synonymous with "acne vulgaris," is a polymorphic, in the very beginning noninflammatory but then characteristically inflammatory skin disease most commonly affecting the face (in 99% of cases) and to a lesser extent the back (60%) and chest (15%). Seborrhea is a hallmark of acne.

The clinical picture embraces a spectrum of signs, ranging from mild comedonal acne, with or without sparse inflammatory lesions, to aggressive fulminate disease with deep-seated inflammation, nodules, and in some cases associated systemic upset. In addition, certain clinical subtypes provoked by internal and/or external factors exist (◉ *Fig. 143.9*).

Comedonal Acne

Clinically, noninflamed lesions develop from the subclinical microcomedo which is evident on histological examination early in acne development. At very early stage of puberty, the comedones are very small and monomorphic, white miliaria like, closely located at the sides of the cheeks at the nose and the outer cheek near the maxilla-orbital area and forehead near the hair margin. Noninflamed lesions encompass both open (blackheads) and closed (whiteheads) comedones which increase in size over the years. These comedones frequently appear in a mid-facial glabellar distribution in childhood and when evident early in the course of the disease; this pattern is probably indicative of poor prognosis. Closed comedones are often inconspicuous with no visible follicular opening and become more visible when stretching the skin or may be prominent producing a sandpaper-like pattern (◉ *Figs. 143.4*, ◉ *143.10*, ◉ *143.11*).

Papulo-Pustular Acne

Most patients with acne vulgaris (A.pap.pustulosa I–III according to Plewig and Kligman) have a mixture of noninflammatory and inflammatory lesions. Inflammatory lesions arise from the invisible microcomedo or noninflammatory lesions and may be superficial or deep in nature. Superficial inflammatory lesions include papules and pustules (5 mm or less in diameter) and these may evolve into deep pustules or nodules in more severe disease. Lesions with a size of 0.5–1 cm are small nodules and characterize the subtype of Acne pap.-pust.nodosa often in the course of the disease developing in addition nodes >1cm. Inflammatory macules represent either initial precursor lesions existing for a short time or regressing lesions that may persist for many weeks and contribute markedly to the general inflammatory erythematous pattern of acne. Scarring may even develop from macules (◉ *Figs. 143.12–143.15*).

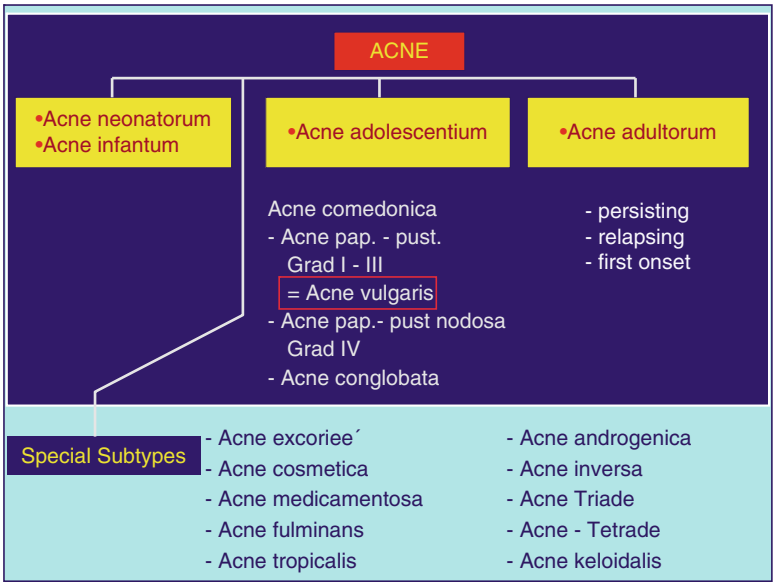


Figure 143.9
Classification of acne and specific subtypes

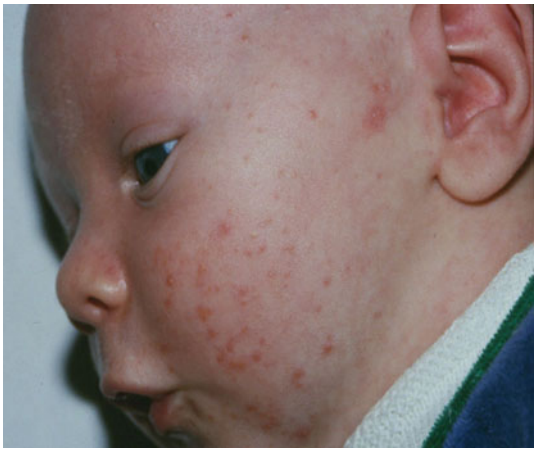


Figure 143.10
Figure Comedones and little papules in acne infantum

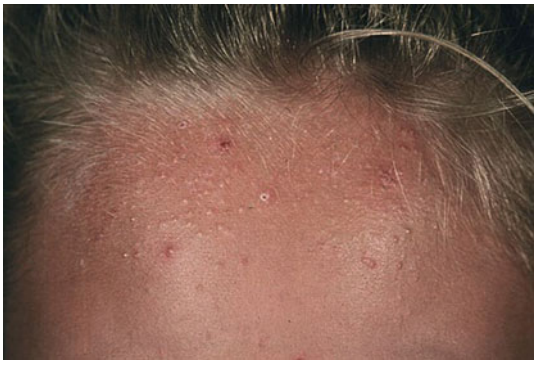


Figure 143.11
Tiny white closed comedones in early development of acne at begin of puberty

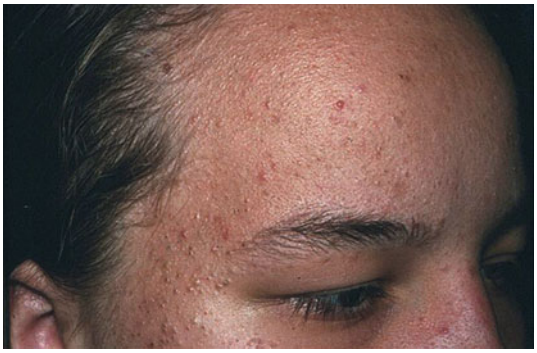


Figure 143.12
Dense distribution of comedones (sandpaper-like type)

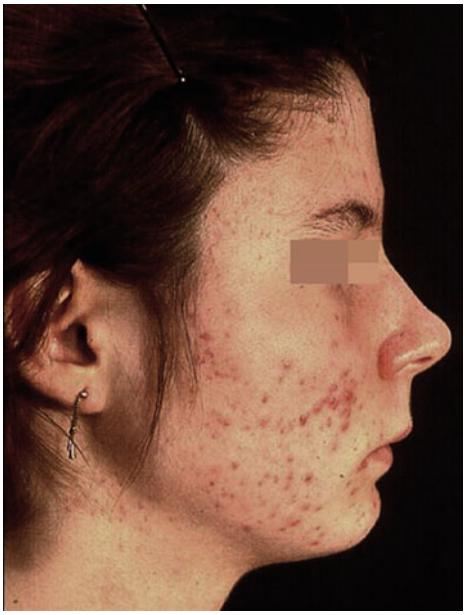


Figure 143.13
Papular-pustular acne grade III with small nodules (accord. Plewig & Kligman)

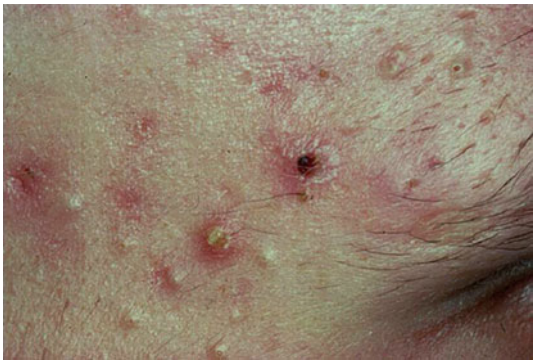


Figure 143.14
Polymorphous inflammatory picture of acne lesions with comedones, papules and pustules

Conglobate Acne

Small nodules are defined as firm, inflamed lesions >5 mm in diameter, painful already by palpation; large nodules are >1 cm in size and may extend to the subcutaneous tissue and confluate over large areas, frequently resulting in painful and exudative sinus tracts and tissue destruction. Conglobate acne (*A. conglobata*) is a rare but severe special form of acne found most commonly in adult males with no or little systemic involvement. Lesions

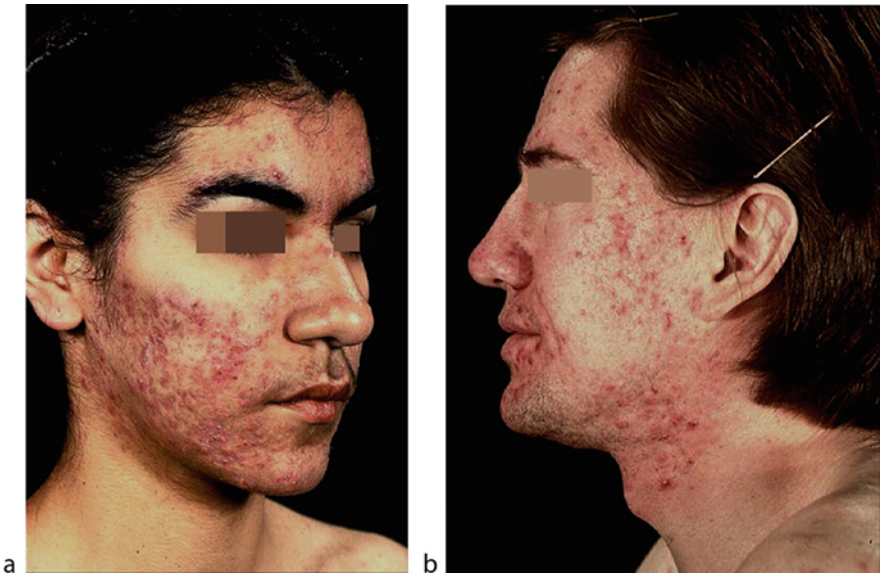


Figure 143.15
Acne papulo-pustulosa nodosa (grade IV accord.Plewig & Kligman)

usually occur on the trunk and upper limbs and frequently extend to the buttocks. In contrast to classic acne, facial lesions are less common or may be missing and only back or chest are involved, however, poor nodular pattern of the face without trunc involvement exists, however, severe only in the face localized cases with sinuses at the cheeks can be observed. The condition often presents in the second to third decade and may persist even into the sixth decade of life. Conglobate acne is characterized by multiple, grouped comedones amid inflammatory papules, tender, suppurative nodules which commonly coalesce to form sinus tracts or a network of rabbit-warren like small undermining fistules.

Extensive and disfiguring scarring of the hypertrophic and keloid type as well as icepick scars, boxcar scars and rolling scars in the face are frequent postacne sequelae (*Fig. 143.16*).

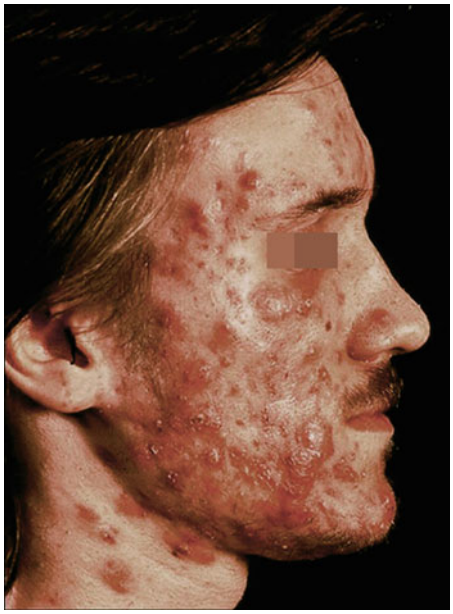


Figure 143.16
Conglobate acne of the face

Other Acne Variants

There are several mild to moderate to severe and clinical different variants or complications of the course of acne. These include acne conglobata as described earlier, but in particular acne fulminans, gram-negative folliculitis, pyoderma fulminans, vasculitic/pyoderma gangrenosum, acne mechanica, oil/tar acne, chloracne, acne in neonates and infants and late onset, adrenogenital syndromes, including HAIR-AN syndrome, Sapho-syndrome, and other rare syndromal manifestations, persistent acne sometimes associated to underlying inborn or iatrogenic-induced endocrinopathies as well as occupational derived provocations.

Therapy

General Remarks

Therapy in acne has changed over the last two decades significantly because new drugs and new formulations have become available. In general, there is a differentiation in acute intervention treatment and maintenance treatment with topical and systemic agents and a combination of both. In addition, adjunctive treatment procedures are available such as lasers and light and chemical peelings as well as cosmeceuticals for postacne or concomitant treatment. More and more guidelines and consensus papers with evidenced-based medicine-related studies support therapeutic decisions today. Acne treatment is long term. Not more than 50% improvement in a moderate acne under oral tetracycline plus topical benzoylperoxide can be achieved in 3 months, for milder cases earlier and for more severe cases even longer. Because of the relapsing character of acne as a chronic disease over 5–10 years, continuous medical counseling and prescriptions and additional adjunctive including psychologic counseling procedures are necessary (*Fig. 143.17*).

Topical Treatment

Topical treatment is based on three out of the four main pathophysiologic factors in acne which are normalization of the disturbed keratinization in the follicular apparatus, the reduction of hypercolonization of *P. acnes*, and anti-inflammatory actions. Until now, no effective drug is available which influences by the topical route the activity of gland hyperplasia with consecutive reduction of hyperseborrhea. Lasers and photodynamic therapy unfortunately reduce seborrhea by complete or partly irreversible damage to the gland followed by subclinical microscarring.

Three main classes of topical substances are on the market worldwide: the different generations of retinoids, benzoyl-peroxide (BPO), azelaic acid (AzA), and antibiotics. Retinoids and BPO function as so-called basic topical agents. Peeling substances are not well evidenced yet based on the interventional phase of treatment.

Retinoids

Within the classes of retinoids, the oldest (first reported in 1962) still in use is tretinoin (all-trans retinoic acid); later isotretinoin (13-cis retinoic acid) came on the market followed by tazarotene and adapalene.

All of them have very good efficacy in normalizing of the disturbed keratinization in the follicular canal by being comedolytic and anticomedogenic. The increased cohesion of corneocytes, filaggrin macroaggregates, tonofilaments, and lipid droplets is reduced. Upregulated and downregulated genes are directly influenced by the retinoids. In addition, there is evidence of an additional anti-inflammatory efficacy of adapalene and tretinoin in

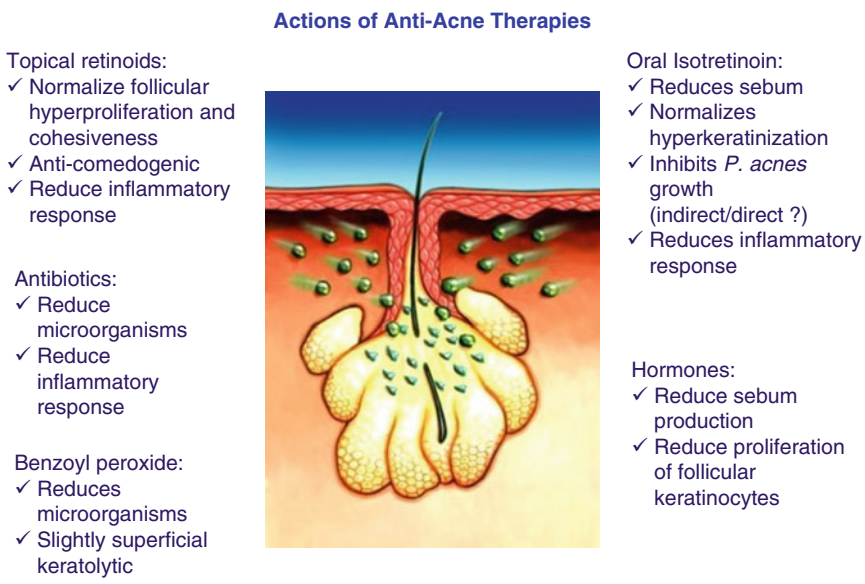


Figure 143.17
Overview of therapeutic armamentarium in acne

downregulating the activity of Toll-like receptor 2 (TLR-2) stimulated by *P. acnes* which finally leads to the activation of proinflammatory cytokines such as IL-6, IL-8, or TNFalpha. Adapalene is, in addition, capable of species-specific inhibition in humans certain lipoxygenases. The additional positive influence on postinflammatory hyperpigmentation and on the collagen matrix in the upper dermis is well known.

All retinoids significantly reduce the number of open and closed comedones and microcomedones as well. After 3 months of treatment, more than 50% of comedones are reduced. There are several types of formulations on the market which vary from country to country but are mostly gels and creams or solutions. All retinoids available are effective as single agents in mild to moderate acne. Tazarotene 0.1% is more effective than tretinoin 0.025% or the more modern galenic formulation 0.1% microsphere gel or adapalene 0.1% gel or cream (EBM level 2c). Adapalene 0.1% is equally effective as the above-mentioned tretinoin gel concentration or tretinoin 0.05% cream or isotretinoin 0.05% (EBM level 2c).

Retinoids are recommended as a monotherapy in comedonal acne and mild acne papulo-pustulosa. Grade II and III of papular-pustular acne according to the Plewig and Kligmans classification should be treated in sequential or fixed combinations with BPO or with topical antibiotics. In those combinations, in addition to the retinoid effects, a reduction of *P. acnes* is markedly achieved. There is one fixed combination of adapalene and BPO 2.5% on the market available now, the first combination of a retinoid with BPO that is pharmacologically compatible. Alternatively, one can use a topical antibiotic or BPO in the morning, followed by the application of the retinoid in the evening.

In severe forms of acne, retinoids are ideal partners in combination with oral antibiotics or in young females already under prescription for an antiandrogenic hormonal pill.

The irritative potential is the mildest with adapalene, followed by isotretinoin and tretinoin and tazarotene, respectively. One can mostly see an initial flare-up of lesions for a couple of days, in particular with tretinoin and tazarotene; erythema, desquamation, and dryness are common to all generations of retinoids. All adverse events fade away over the duration of treatment. In dry atmospheres in the house or in hot temperatures, a moisturizer should be applied in addition. Adapalene has nearly no phototoxicity compared to tretinoin or tazarotene which is important for treating patients in sunny countries. In young females of childbearing age and who wish to become pregnant, a retinoid should not be chosen because of the risk of teratogenicity (*Fig. 143.18*).

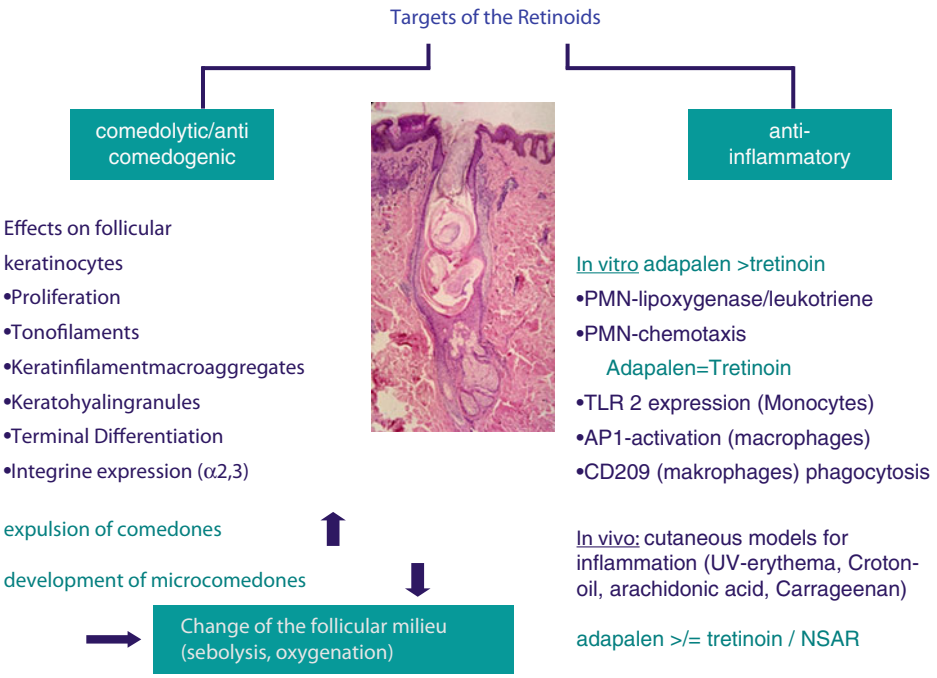


Figure 143.18
Targets for the actions of topical retinoids

Benzoyl-Peroxide

Benzoyl-peroxide is one of the oldest but very effective topical acne drugs introduced already in 1934. It is available in concentrations between 1% and 10% for acne treatment. Controlled studies revealed that a dose of 2.5% is enough for topical treatment in the face. For back and chest, a 5% concentration with more irritation can be applied, which is here better tolerated than in the face. One can use gels, lotions, or washes, the last also as a short contact therapy. As a monotherapy, BPO can be used in mild inflammatory acne, in moderate acne combinations with adapalene in a fixed form, or in sequential applications together with topical antibiotics or retinoids, as has been well documented and evidenced.

The efficacy of BPO is based on its strong antimicrobial potency which is achieved within 2 weeks by reducing *P. acnes* on two log scales from skin samples and in in vitro cultures. It does not allow the development of any resistance of *P. acnes* or staphylococci on the skin. Benzoyl-peroxide is the gold standard of antimicrobial acne treatment. It has only a slight anticomedolytic action by desquamating the upper corneocyte layers at the orifice of the follicular channel, but it is not anticomedogenic.

Depending on the concentration and galenic formulation, one can see a dose-dependent dryness and desquamation of the skin accompanied by burning and redness, which the patient will adapt to over time. Moisturizers will reduce adverse events. Bleaching of hair and clothes can occur and contact sensitization in acne is rare. Benzoyl-peroxide can be used during pregnancy.

In moderate forms in which internal drugs are not applied, as a first step, the combination with adapalene or other retinoids is to be preferred (see above), or the combination in either fixed ones or sequential ones with antibiotics (either erythromycin or clindamycin). Resistances toward topical antibiotics are reduced by these combinations.

For severe forms of acne, BPO can easily be combined with oral antibiotics which lead to an additional antimicrobial effect and a faster onset of therapeutic success. Resistant bacterial strains on the skin under oral antibiotics are reduced. The efficacy of the combination is enhanced and the treatment goal achieved faster.

Antibiotics

Currently, there are two antibiotics which are used most for the topical route: erythromycin and clindamycin. Tetracycline should not be used anymore on the topical way because of high bacterial resistances and phototoxicity. Nadifloxacin is chemically synthesized and belongs to the group of quinolones acting against gram-positive bacteria and gram-negative bacteria. Its use is critically seen because of the possibility of inducing quinolone-resistant staphylococci strains with consequences for negative systemic treatment outcomes.

Both antibiotics erythromycin and clindamycin are macrolides and act via bacteriostatic mechanisms using ribosomal protein synthesis inhibition.

Erythromycin and clindamycin are indicated for the mild papular-pustular acne; however, recent evidence-based guidelines do not recommend these agents as monotherapy but in combination with retinoids, BPO, or AzA. Fixed combinations are available on the market or a sequential use in the morning and the combination partner in the evening. The efficacy is significantly enhanced with reduction of the time course of treatment. A combination with oral antibiotics is obsolete and they should also not be used in comedonal acne. The efficacy of topical erythromycin and clindamycin monotherapy in mild inflammatory acne is evidence based on level 2b.

The local side-effect profile of topical antibiotics is different; on one side, they have a low irritative potential, on the other, they induce resistance in the skin bacterial populations and may even be resorbed and have systemic adverse events. Clindamycin in pregnancy should not be used because of rarely reported colitis events.

Azelaic Acid

Azelaic acid has been available since the beginning of 1980. It is a dicarbonic acid that occurs physiologically in the body. It reduces comedones by repairing the corneocyte dysfunction in the follicle, reducing the increased keratohyalin macroaggregates, and acts by reducing protein synthesis in the pathological proliferating cell. It has an antibacterial effect in reducing the *P. acnes* amount in vitro by one log step. In addition, it is an ROS scavenger and reduces the hyperreactivity of neutrophils. Recent evidence indicates a reduction of certain proinflammatory cytokines. It also restores the postinflammatory hyperpigmentation, similar to retinoids.

AzA is available in creams and gel or lotion in 20% and 15% formulations. It is indicated in comedonal acne and in inflammatory mild acne as a monotherapy. Evidenced studies show a 2b level of similar efficacy when the drug was compared to clindamycin, BPO, or tretinoin. In moderate acne it should be combined with topical antibiotics and retinoids or BPO. It can be well combined with oral

tetracyclines or with oral antiandrogenic drugs. In conglobate acne, a controlled study of minocycline and AzA with oral isotretinoin showed a similar efficacy, however, the long-term outcome was better with isotretinoin. When AzA was used as a maintenance topical treatment, it prevented the relapse to some extent.

The adverse drug profile shows, in particular, a stinging and burning or itching sensation at the beginning of treatment which persists for 10–20 min after application and generally fades within 1–2 weeks. It induces no bacterial resistances and can be used during pregnancy.

Other Topical Treatments

Local abrasives have additional value in comedonal acne, in particular to open the closed comedones to allow topical drugs to better penetrate and to desquamate the comedonal plug.

Topical dapsone is released on the market in the US, however, the efficacy is of minor value compared to other topicals mentioned before.

A large pile of topicals exist from the medico-comeceutical site, but good controlled studies are missing. Except the preparation of retynal ester and glycolic ester or niacinamide and salicylic acid for milder forms of acne and maintenance treatment.

There exist depending on regional availabilities a certain amount of topical formulations which are not proven for any evidence based use.

Systemic Treatment

Oral Antibiotics

Oral antibiotics mostly used in acne are doxycycline, lymecycline, and minocycline. Oral tetracycline hydrochloride is less used today. Other systemic antibiotics such as clindamycin or erythromycin are reserved for special situations. Quinolones, cotrimoxazole, and azithromycin are not well evidence based and should be used only with care and if specific resistances arise or mixed bacterial colonizations are detected on the skin (*Fig. 143.19*).

Tetracyclines, macrolides, and clindamycin inhibit the protein synthesis of bacteria in different ways; cotrimoxazole influences folate metabolism. The number of *P. acnes* is significantly reduced in a short time of 10–14 days.

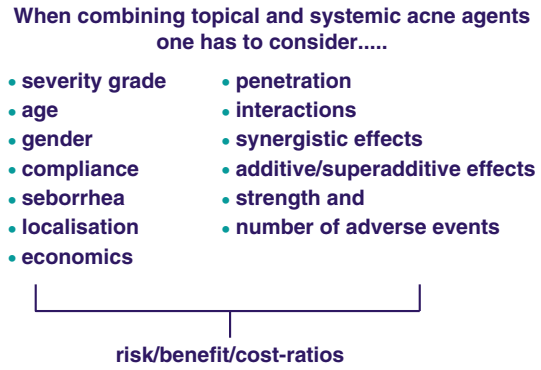


Figure 143.19
Considerations before selecting combination treatments

Today the focus is on the para-antibiotic mechanisms of actions of tetracycline, doxycycline, and minocycline. The inhibition of free fatty acids from the bacterial lipase of *P. acnes* is markedly reduced independent of killing *P. acnes*. In addition, increasing knowledge is being gained over the years in the dose-dependent and direct inhibition of lymphocyte mitosis, inhibition of chemotaxis which reduces pustular formation, and reduced phagocytosis. In particular, the reduced release of proinflammatory cytokines such as IL-1, IL-6, IL8-, and TNF alpha and increase of the anti-inflammatory IL-10 can be measured in vitro and in vivo as well. Furthermore the ROS release is significantly reduced.

Inflammatory moderate acne not responding to topical treatment and severe acne are good examples for evidence-based therapy for oral antibiotics.

A systematic review of all clinical studies between 1962 and 2008 with systemic tetracyclines confirms that no evidence of significant difference exists in terms of efficacy. A clear difference between dose and efficacy could not be figured out. In a double-blind randomized trial with minocycline and combination with and without tazarotene over 3 months and follow-up after another 3 months with oral placebo, minocycline, and tazarotene, a further increase of efficacy could not be found. Therefore, a 3-month oral antibiotic seems to be the appropriate length of application time.

Tetracyclines are usually given in a dosage of 2 × 250 mg/day, doxycycline 100 mg/day, and minocycline 100 mg/day. However, due to the changing view of the use of oral antibiotics as anti-inflammatory drugs, one is trying to apply lower doses. A slow-release minocycline formulation is going to be marketed for acne soon, and a doxycycline retarded formulation is already available on the market for rosacea.

Oral antibiotics can be combined preferentially on the topical route with retinoids and BPO and AzA as well. It significantly increases the efficacy and reduces the time to response >50% of inflammation and reduction of >50% total lesion count.

For the oral route, antibiotics can be combined with oral antiandrogens. In a comparative trial, the relapse rate was higher in the monotherapy arm with antibiotic alone.

The adverse drug profile of oral antibiotics is quite large and of different importance. Resistances of *P. acnes* occur with erythromycin and clindamycin, cross-resistances may come up, and transfer of resistances to other contact persons is possible. Concomitant use of topical BPO is preferable. Increased upper-respiratory infections have been reported.

Main contraindications are liver dysfunctions, hypersensitivity reactions, and renal insufficiency. These reactions are seen in adolescents less often than in patients with late type acne.

Gastrointestinal complaints, diarrhea, and candidiasis are mostly to be seen with tetracyclines. Minocycline can produce hyperpigmentations. Phototoxicity is dose dependent but less often observed with minocycline and doxycycline compared to oxytetracycline. All tetracyclines have the potency of increasing brain pressure.

Hypersensitivity syndrome with LE-like pattern and other autoimmune patterns have been, in particular, reported for minocycline. DRESS syndrome, even in children, exists as single reports with doxycycline and minocycline. Tetracyclines are not indicated in children before the end of dentation because of discoloration of teeth (Fig. 143.20).

Oral Isotretinoin

Oral isotretinoin was first reported as effective in 1971. Because of its teratogenicity it was not followed up longer by Stüttgen, but was then reported to be the most effective drug in conglobate acne by Peck in 1979.

Isotretinoin is the most potent antiacne drug available in particular for the most severe forms.

Isotretinoin is 13-cis retinoic acid, a naturally occurring product in the vitamin A metabolism. It is a monoaromatic retinoid which is chemically modified at the polar end group and the polyene side chain of the original vitamin A. It is related to the all-trans retinoic acid (tretinoin) to which it is under certain conditions converted.

Isotretinoin has multiple mechanisms of action, which are the suppression of the sebaceous gland hyperactivity by increased differentiation and reduced hyperproliferation of sebocytes, normalization of the disturbed keratinization, reduction of the inflammation at the humoral and cellular level, and indirect reduction of the amount of *P. acnes* in the follicle because of a change of the growth condition for the bacterium. In addition, matrix tissue metalloproteinases are normalized. Recent evidence from the lab shows that isotretinoin increases the skin surface levels of neutrophil gelatinase-associated lipocalin important in killing *P. acnes* and defense mechanisms as well as sebocyte apoptosis important in the action of this drug. Recently, a possible antiandrogenic action was discovered. It obviously inhibits the 3-alpha hydroxysteroid oxidation by retinol dehydrogenase which finally leads to reduced amounts of dihydrotestosterone and androstenedione. Both are involved in the activity of the sebocyte function

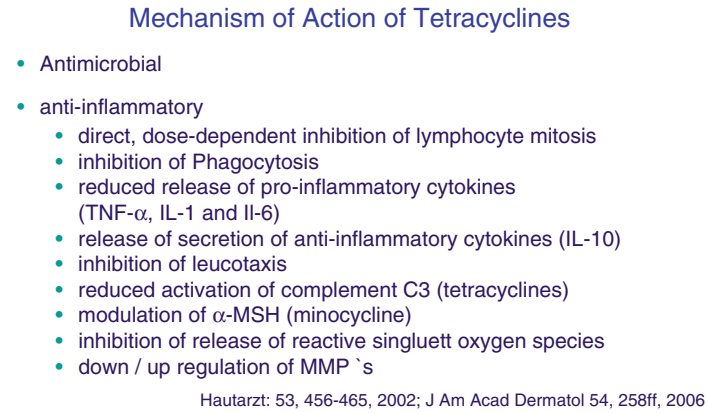


Figure 143.20
Mechanisms of actions of oral tetracyclines – the para-antibiotic anti-inflammatory efficacy

and therefore their reduction leads to a sebosuppressive effect (◉ *Figs. 143.4*, ◉ *143.6*, ◉ *143.7*, ◉ *143.9*, ◉ *143.17*).

Whereas in the past isotretinoin was the drug of first choice in severe recalcitrant nodular and conglobate acne, it was re-ranked by the FDA and the EMEA because of its adverse drug profile, in particular teratogenicity. This means that in those subtypes of acne, first a treatment with oral antibiotics combined with topical basic agents has to be given over 3 months; if this treatment approach is not successful it can be switched to oral isotretinoin. It should also not be given anymore to children under 12 years. The monitoring profile and time schedule of laboratory parameters have been intensified (◉ *Fig. 143.18*).

Isotretinoin is available in 10, 20, and 40-mg capsules. Several generic formulations are available on the market after Roche Comp. has discontinued the production of the original brand Roaccutane/Accutane. However, there is evidence from pharmacological reports that not all of them are of the same efficacy because of minor bioavailability. Eleven out of thirteen generics failed in several tests.

Today the range of doses given is 0.1–1.0 mg/kg bw/day. Usually one starts with 0.5 mg/kg, i.e., 20–40 mg/day, which can be increased to 40–80 mg/day according to the efficacy and side-effect profile, if necessary. There is evidence that a higher dose at the beginning and a cumulative dose of around 120 mg/kg given over a total of 12 months continuously have a lower relapse rate. Relapse rates in general are between 20% and 30% depending on the severity and the age of the patients. Patients respond without tachyphylaxia to a second course of the drug.

Isotretinoin compared to oral antibiotics is more cost effective having less long-term courses of the disease and less relapses.

The adverse drug profile is quite large and consists of mucocutaneous, systemic, and laboratory ones.

Dose-dependent cheilitis, xerosis, and skin fragility and dry nose are the most common skin symptoms. Systemically, myalgias, arthralgias, and headache are frequent and bone toxicity after long-term treatment is a complication; increased triglycerides and cholesterol are less common in adolescents but need to be monitored. The reader is referred to the special references and local regulations in his country.

The most important adverse effect is teratogenicity with craniofacial, cardiovascular, and CNS defects. Strong anticonceptive measurements (double method) and a clear indication in girls >12 years are demanded. Continuous negative pregnancy tests 1 month before treatment, monthly under treatment, and one menstrual cycle after cessation of the drug are necessary. Blood donation is prohibited during treatment and 1 year after.

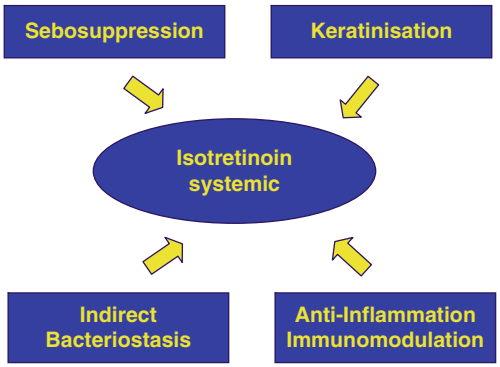


Figure 143.21
Effects of oral isotretinoin in acne

Psychiatric adverse events are critically evaluated over the last 10 years. Any psychiatric disorder, depression, or suicidal ideation is a strong contraindication for isotretinoin prescription. Two large retrospective cohort studies showed that the incidence of an increased risk of depressive mood or suicide attempts is not different in patients under isotretinoin compared to a group with the same severity grade of the disease under oral antibiotics (◉ *Fig. 143.21*).

Hormonal Antiandrogen Therapy

Antiandrogenic hormonal treatment was introduced in the early 1980s when cyproterone acetate and later chlormadinon acetate became available in combination with ethinylestradiol. These hormonal treatments are anticonceptive but in particular dedicated to the treatment of acne and seborrhea.

Acne often starts with adrenarche and the increased amount of circulating adrenal androgens producing hyperseborrhea from the sebaceous gland. Later, the effects from the ovaries and testes follow. Antiandrogenic therapy follows a reduction of circulating free testosterone. A classification of the mechanisms can be made as follows: blockade of the androgen receptor, suppression of ovarian-derived androgens, action on the hypophysis, suppression of the adrenal activity, and finally inhibition of the peripheral androgen metabolism.

The gestagens cyproterone acetate and chlormadinon acetate bind to the progesterone receptor and block the androgen receptor. Gonadotropin secretion is reduced

and consequently the production of androgens from the adrenals and the ovaries. Sexual hormone binding globulin is more available and free circulating testosterone is bound. Another antihormonal pill contains dienogest.

Drospirenone, a derivative of 17-alpha spironolactone, is antiandrogenic, and reduces antimineralocorticoidal efficacy in addition to causing premenstrual perifollicular edema.

Antiandrogenic treatment is foreseen for female patients only. It is indicated in young adolescents with sign of peripheral hyperandrogenism with and without hyperandrogenemia, early signs of the SAHA syndrome (seborrhea, acne, hirsutism, and alopecia), and in females with persisting acne as well as in females with acne and who wish for a hormonal anticonceptive.

Comparing these hormonal treatments the significant efficacy of cyproterone acetate and drospirenone are equivalent. Dienogest and chlormadinon acetate–containing pills are only slightly less effective. Different drugs are available in different countries and therefore all products cannot be mentioned here. Significant treatment effects can be seen on the comedo counts after 6 months, on the seborrhea after 6–9 months, and on hirsutism signs after a year. Monotherapy with antihormonal pills is not recommended. In general, depending on the type of acne, they have to be combined with topical drugs or oral antibiotics or isotretinoin.

Absolute and relative contraindications are, in particular, thrombophilia, chronic venous insufficiency, immobilization, severe obesity, migraine, and liver diseases; however, the individual risk and all other contraindications have to be evaluated with the first prescription by endocrinologic gynecologists.

Other Systemic Treatments

In children with acne and in adults, the use of diaminodisulphone (dapsone) does not have a very good evidence base. It can in certain situations be used as an adjunctive drug.

For oral zinc gluconate, some evidence exists. The use of flutamide is not recommended.

Maintenance Treatment

Acne is a chronic disease and therefore during the course of the disease over more than 5–10 years, long-term treatment is necessary (*Fig. 143.22*). In the center of relapse stands, the microcomedo from which either noninflammatory comedones or inflammatory papules and pustules develop. More than three evidence-based trials (level 2b) have been published in different types of acne in the last 5 years showing that after the interventional treatment phase using an additional course with

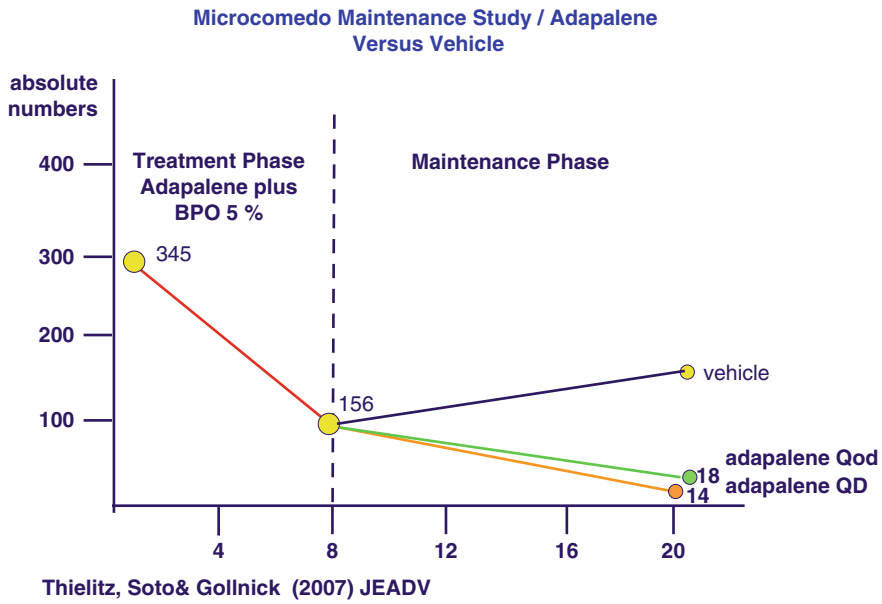


Figure 143.22
Effects of retinoids to prevent development of new microcomedones in maintenance treatment

Facts in Favour for Acne as a Chronic Disease

	Acne	Atopic Dermatitis
basic character	inflammatory	inflammatory
duration	>3 months → > 10–30yrs	>3 months → >5–40yrs
genetic background	yes, long term courses, polygenic	yes, polygenic
age of onset	~10	~1
self limiting	>80% ~3rd life decade	> 80% 2nd or 3rd lifedecade
relapses	frequently	frequently
counselling	intervals / years	intervals / years
medication	continously / intervals	continously / intervals
social impact	yes	yes
psychologic impact	yes	yes
post diseasesequelae		
physical	yes	yes
pychologic	yes	yes

Gollnick,Shear,Finlay(2008)AmJClinDerm 9:279-84

Figure 143.23
Acne as a chronic disease – comparison to atopic dermatitis

monotherapy of a retinoid (adapalene), a relapse could be prevented and even the outcome further improved. This has also been shown in one trial with tazarotene (*Fig. 143.23*).

Adjunctive Treatments

UV light should not be used for the treatment of acne, neither UVA which is comedogenic nor UVB which only produces a camouflage and, on the other hand, contributes to the lifelong cumulative dose of UV.

Visible light, in particular in the blue range (415 nm), can destroy *P. acnes* by activating porphyrins from the bacterium and production of ROS with consecutive destruction of the microbe. A comparative trial with BPO showed similar efficacy (EBM level 2b). Usually three to four applications per week are necessary and after 10 applications the treatment is successful.

Photodynamic therapy with visible light in the range of 550–770 nm plus topical 5-aminolevulinic ester showed, in a placebo-controlled study in mild to moderate acne, a significant improvement (EBM level 2b) and concomitant reduction of seborrhea and of *P. acnes*. Local pain during and shortly after irradiation followed by crusting and some pigmentation are the typical adverse events. It should be mentioned that significant destruction to the gland may harm the patient because the sebaceous gland today is seen as a small endocrinological adjacent organ of the skin which plays a role in the skin homeostasis.

Lasers are increasingly used in active acne with more or less good results depending on the type of laser. Mostly the trials are not well controlled and concomitant treatment is allowed or a conservative treatment arm is missing.

In mild comedonal acne, abrasives with aluminum particles can be used or manual comedo peeling by an experienced cosmetician can be done.

Chemical peeling as an intervention treatment is not established yet; however, it can be used in addition to topical treatments, oral antibiotics, or hormonal antiandrogens, but is contraindicated in parallel to oral isotretinoin. Peelings encompass salicylic acid, glycolic acid, and lactic acid.

Additional substances that can be considered in mild types of acne are retinaldehyde, genistein, and niacinamide.

Scarring

Acne scarring is the most prominent and unwanted outcome of acne. It starts in late puberty and progresses to late-type acne when acne does not cease naturally. It is quite common and because of its different types of scars and distribution it is difficult to treat. Acne scar types are

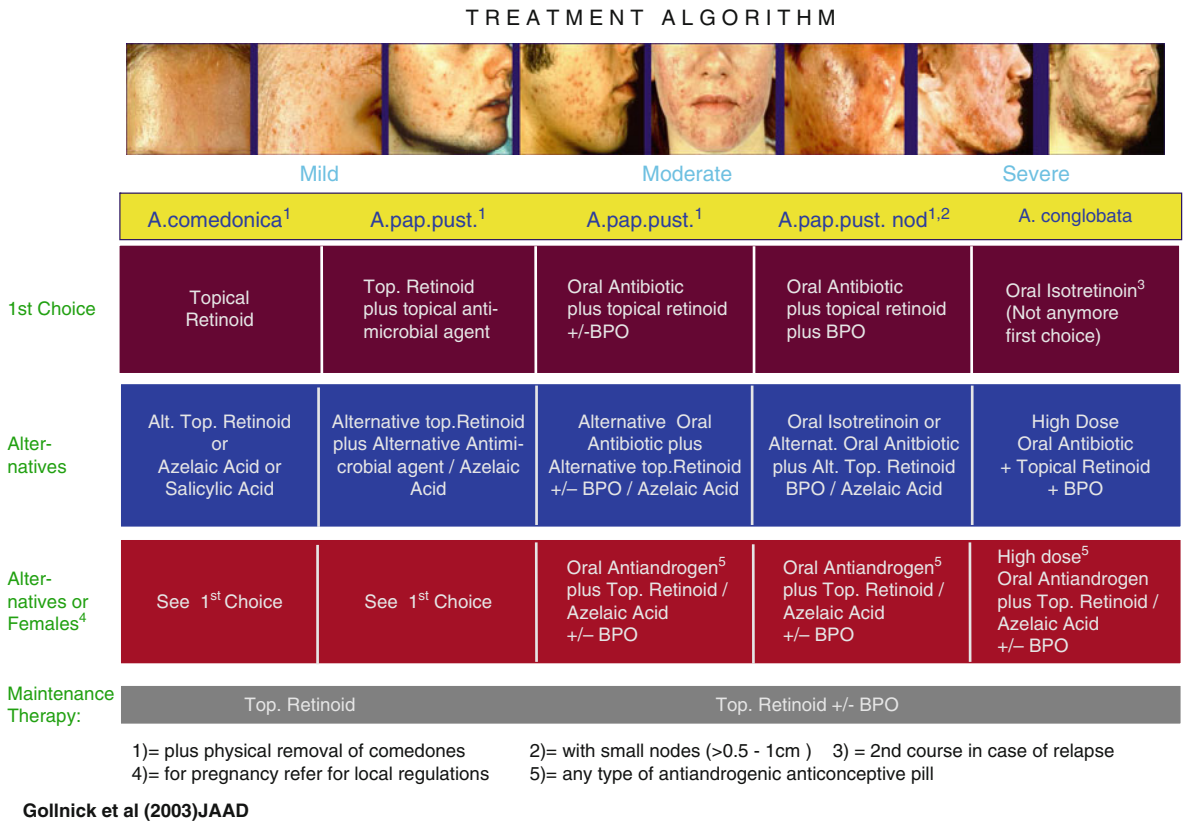


Figure 143.24
Acne treatment algorithm of the Global Alliance for Improvement of outcome in acne treatment

the following: hypertrophic and atrophic scars of which the latter consists of three types: icepick, boxcar, and rolling. All scar types can be mixed. Acne scars can be scored according to the ECCA (echelle d'evaluation clinique des cicatrices d'acne). In general, electrodesiccation, dermabrasion, punch elevation, small excisions or minitransplants, ablative and nonablative lasers, chemical peeling (CROSS technique), and dermafillers are used successfully in the hands of experienced dermatologists. Fractional lasers and microneedling are used in addition (*Fig. 143.24*).

Related Disorders

Hidradenitis Suppurativa

Hidradenitis suppurativa, formerly known as acne inversa, is an acne type of the elderly and therefore will not be discussed here. It is a disease of the terminal hair follicle. The apocrine gland is not the primary focus of the disease. A genetic background is increasingly being discussed. Radical dermatosurgical excisions of the involved areas at the axillas and groins or buttocks are essential. Reduction of smoking and obesity is essential. The use of biologics from the TNF alpha type may initially reduce the inflammatory process in preparation of the following surgery. Isotretinoin is less effective, only very early cases may respond. Acitretin affects positively the keratotic fistulas in the chronic stages.

Rosacea

Rosacea is rare in the second decade of life and a disease of the third and higher decades. However, some cases, in particular with strong family background, can be seen. Those are mostly of the telangiectatic type and have to be evaluated as differential diagnosis to cutaneous and systemic lupus erythematodes and dermatomyositis. Perniones or family related telangiectasia have to be considered.

Gram-negative Folliculitis

Gram-negative folliculitis of the minor or major type is a complication of long-standing oral and/or topical therapy. It is mostly located around the oral and perinasal area. Swabs from the pustules and inner nostrils reveal the pattern of a gram-negative microbial flora. The treatment is difficult and often frustrating. In general, a treatment with topical BPO and AzA alone or combined with oral co-trimoxazole should be used. Oral isotretinoin can be successful. Relapses with all treatments are quite common.

Perioral Dermatitis

Perioral dermatitis was in former times a disease of females in the third decade of life as a result of using excessive moisturizers and thereafter developing pustules around the mouth, which are consecutively treated by topical corticosteroids. Whenever the steroids were stopped a flare-up was observed and again corticosteroids were applied. This mostly led to a vicious cycle. Due to overprotection in skin care of the face with detergents and moisturizers and topical steroids, the disease was also seen around the periorbital area, not only in females but also in males and finally in younger adolescents and even in children in the first decade of life (❯ *Figs. 143.11*, ❯ *143.12*, ❯ *143.22–143.24*).

Most important is to cessation the usage of corticosteroids despite flare-ups. Short oral doxycycline can be used (caveat: not in children before end of dentation) with a local ketoconazole cream in combination with metronidazole (❯ *Figs. 143.10*, ❯ *143.13–143.15*). One crash type therapy is drying by lotio alba and oral doxcycline. Outcome is in general favorable.

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