Not All Acne Is Acne Vulgaris
Harald P. Gollnick, Christos C. Zouboulis

SUMMARY

Background: Acne is the most common skin disease in adolescence, with a prevalence of nearly 100%. About 60% of affected adolescents have mild acne for which they use non-prescription preparations without consulting a physician. The remaining 40% constitute the population of acne patients seen in medical practice. The course of acne can be either acute or chronic; its manifestations can appear in waves, sometimes with dramatically severe inflammation leading rapidly to scarring. Acne often has adverse emotional consequences. Its treatment is markedly better than in the past because of new pharmacological and physicochemical approaches and because evidence-based guidelines are now available.

Methods: This article is based on a selective review of the literature and also incorporates the authors’ own clinical and scientific experience.

Results: Acne vulgaris of grade I or II in an adolescent is generally not hard to treat. In contrast, the more severe grades III and IV and conglobate acne often present a therapeutic challenge, as they are associated with varying constellations of acute lesions, scarring, inflammation, and emotional disturbances. These conditions often require systemic treatment with tetracyclines, which are especially useful because of their para-antibiotic anti-inflammatory effect. Severe cases must be treated with isotretinoin. Women can benefit from anti-androgenic contraceptive drugs. Retinoids or azelaic acid are used in maintenance therapy to suppress the formation of microcomedones, the precursor stage of acne lesions.

Conclusion: A variety of effective treatments for acne are available, depending on the severity of the condition.

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A polymorphic clinical appearance (Figure 1), varying degrees of severity, acute as well as chronic forms, numerous subtypes and wide spectrum of topical and systemic treatment modalities all help define the group of diseases known as acne. The general public and many non-dermatologists consider acne a mild disease which resolves spontaneously in a matter of months to two years. A survey of 504 customers in 48 pharmacies across Germany showed that in choosing products to treat acne, 35% of patients with mild acne treated themselves, following the advice of a pharmacist (22.5%), another individual (3.3%) or relying on their own judgment (9.2%) (e1). This mild form of acne, sometimes called “physiologic acne” with relatively few “pimples” and “blackheads”, accounts for 60% of the cases, responds well to over-the-counter products and will not be further discussed in this article. Instead we will concentrate on the 40% of patients with more severe “clinical acne” who require medical treatment; they primarily are managed by dermatologists (93%) but also by general practitioners (6.3%) and pediatricians (0.6%) (e1). In addition, the complexity of acne is reflected less by acne vulgaris which refers to papulo-pustular acne of grades I–II after Plewig and Kligman, but instead by the more severe courses including nodular acne (conglobate acne), infantile acne, juvenile acne and acne tarda that occurs after the classic age range (>25 years of age) (1, 2). In addition, there are complex cases presenting as part of syndromes, secondary to hormonal disturbances, caused by medications, or as a result of provocation or continuous promotion by exogenous factors (3, e2, e3). In addition, one must separate out a wide range of acniform dermatoses including the recently described PRIDE syndrome secondary to kinase inhibitors as well as classical rosacea, perioral dermatitis and gram-negative folliculitis.

Patients with clinical acne require medical therapy, either because of the severity or duration of their

Acne
A polymorphic clinical appearance, varying degrees of severity, acute as well as chronic forms, numerous subtypes and a wide spectrum of topical and systemic treatment modalities all characterize acne.
Acne is the most common dermatologic diagnosis accounting for 22–32% of cases and is one of the most common reasons for visiting a physician (1.1%).

In addition, acne is a socio-economic problem. In 1995 acne was the most common dermatologic diagnosis in the USA with 10.2 million cases, accounting for 25.4% of the dermatologic diagnoses of all physicians (4). The patients received 6.5 million prescriptions for a systemic acne therapy (either antibiotics or isotretinoin) yearly, costing more than 1 billion US dollars. In 2001, 2.1 billion euros were spent worldwide on acne medications; this is 18.3% of the annual expenditures for treating dermatologic diseases. In 2004, the direct costs in the USA had climbed to over 2.2 billion US dollars (e4).

Scientific advances in the past 20 years have greatly contributed to a better understanding of the pathogenesis of acne and to optimizing the therapeutic approach (4–6). Numerous epidemiologic, socio-economic and psychological aspects of acne have at the same time been extensively evaluated (7–12).

### Learning objectives

- Classification of clinical acne according to degree of severity as prerequisite for choice of therapy
- Using topical and systemic agents and combinations thereof according to guideline recommendations
- Awareness of the psychosomatic and psychiatric complications of acne, the special variants and the problems young acne patients have with compliance.

### Frequency

Acne is the most common dermatologic diagnosis accounting for 22–32% of cases and is one of the most common reasons for visiting a physician (1.1%).

### Cost of therapy

According to a health service study, acne was in 1995 the most common dermatologic diagnosis in the USA with 10.2 million cases, accounting for 25.4% of the dermatologic diagnoses of all physicians.
Methods
This article reflects the experience of the authors, the German S2k and the European S3 guidelines for acne, numerous personal experimental and clinical studies and as well as an extensive selective review of the national and international literature.

Epidemiology
Acne is an almost universal disease (8, 10, 13); nonetheless, its prevalence has been estimated as 0% in rural Brazil (e5) and 100% among children and adolescents in the UK (e6). Acne’s prevalence peaks between age 14 and the start of the 3rd decade (8, 9).

Some 20–40% of the cases persist past the age of 25 years. In a survey of 48 665 employees in Germany, the overall prevalence of acne was 4.2% (9); in the subanalysis the prevalence in the age group 16–20 years was 24.8%. Other studies show a prevalence in adolescents between 9 and 20 years of up to 95%, without separating clinical from “physiologic” acne. As long ago as 1931, a Swiss study reported a prevalence of 88–99% in young men and 88–97% in young women (e7). An English study in 1971 yielded similar results (e6); in Sweden large studies in school children showed a prevalence of clinical acne among 15–16 year olds of 50–54% in boys and 37–39% in girls (e8, e9). The prevalence of moderately severe acne among 15–24 year olds was about 14% (e10).

In a population-based epidemiological study in Hamburg, the prevalence among men was 29.9% and among women 23.7% for a group with a median age of 42 years (e11). Additional studies indicate that up to 40% of women over 25 years of age still have acne, even though the natural course of acne is to exhibit regression by this age (e12). Three well-documented studies show a prevalence of late-type acne especially in patients with a genetic predisposition to be as high as 50–53% (e13–e15). Prospective cohort studies in China (e16), France (e17) and Great Britain (e18) show that familial predisposition is associated with severe forms of acne and persistence into the 3rd decade (odds ratio 3.5). Familial predisposition and especially acne in the mother are significantly associated with a more severe course (10).

Twin studies show identical sebum production in monozygotic twins, of up to 98% (e18). In a study involving 458 monozygotic and 1099 dizygotic twins, 81% (95% confidence interval [CI], 73–87%) of the variability in disease severity was attributed to genetic factors and 19% to environmental or epigenetic factors (e19). Exogenous factors such as androgenic hormones, competitive sports, nicotine and diet with a high hyperglycemic index make the natural course of acne more severe and persistent (4, 5, 8). Well-documented large cohort studies show no association between acne and obesity, instead suggesting that the content of the diet is more important. In the Glasgow alumni cohort study, students with and without a history of acne were compared; a positive acne history correlated with a clearly reduced risk of coronary artery disease but a higher risk for prostate cancer (e20).

Prevalence
In a population-based epidemiological study in Hamburg, the prevalence among men was 29.9% and among women 23.7% for a group with a median age of 42 years.

Clinical course
A wide variety of clinical patterns can be observed. The most common course is a gradual development of clinically apparent disease, which can last months up to a year, then a continuous phase with occasional flares, and finally a slow regression at the end of the 2nd decade or beginning of 3rd decade. This classical pattern has different variants with more rapid onset and...
**TABLE 2**
Summary of treatment recommendations from the European S3 guideline

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Comedonal acne</th>
<th>Mild to moderate papulo-pustular acne</th>
<th>Severe papulo-pustular acne</th>
<th>Severe nodular acne/ conglobate acne*5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation (A)</td>
<td>No evidence</td>
<td>Adapalene plus BPO (f. c.) or BPO plus clindamycin (f. c.) [1a]</td>
<td>Isotretinoin*1 [3b]</td>
<td>Isotretinoin*1 [1b]</td>
</tr>
<tr>
<td>Moderate recommendation (B)</td>
<td>Topical retinoids*3 [2b]</td>
<td>Azelaic acid or BPO or topical retinoids<em>3 or systemic antibiotics</em>2 plus adapalene*5 [2b]</td>
<td>Systemic antibiotics plus adapalene<em>6 or systemic antibiotics plus azelaic acid</em>4 or systemic antibiotics plus adapalene plus BPO (f. c.) [2b]</td>
<td>Systemic antibiotics*10 plus azelaic acid [2b]</td>
</tr>
<tr>
<td>Weak recommendation (C)</td>
<td>Azelaic acid or BPO [3b]</td>
<td>Blue light or oral zinc or topical erythromycin plus topical isotretinoin (f. c.) or topical erythromycin plus tretinoin (f. c.) or systemic antibiotics<em>2, plus BPO</em>4 or systemic antibiotics<em>2, plus tretinoin</em>2, plus adapalene plus BPO (f. c.)*x</td>
<td>Systemic antibiotics<em>6 plus BPO</em>7 [3b]</td>
<td>Systemic antibiotics<em>10 plus BPO</em>10 or systemic antibiotics<em>10 plus adapalene</em>4, 5 or systemic antibiotics*10 plus adapalene plus BPO (f. c.)*9 [3b]</td>
</tr>
</tbody>
</table>

Alternatives for female patients

<table>
<thead>
<tr>
<th>Comedonal acne</th>
<th>Mild to moderate papulo-pustular acne</th>
<th>Severe papulo-pustular acne</th>
<th>Severe nodular acne/ conglobate acne*5</th>
</tr>
</thead>
<tbody>
<tr>
<td>See above</td>
<td>See above</td>
<td>Hormonal anti-androgens plus topical therapy or hormonal anti-androgens plus systemic antibiotics [3b]</td>
<td>Hormonal anti-androgens plus systemic antibiotics*5 [3b]</td>
</tr>
</tbody>
</table>

* Conditions which could make the use of therapy with a low level of evidence as first line treatment necessary (for example, costs/reimbursement/regional legal requirements/availability or approval/drug interactions/associated diseases/allergies/intolerance reactions).

* When there is extensive involvement including extending beyond the face, moderately severe acne may require systemic antibiotics initially.

* Adapalene is preferred over tretinoin/isotretinoin

* Systemic corticosteroids can be considered.

* Doxycycline and lymecycline

* Low level of evidence

* Indirect evidence from a study also including chlorhexidine on the basis of expert recommendation

* Indirect evidence for nodular acne and conglobate acne on the basis of expert recommendation

* Indirect evidence for severe papulo-pustular acne

* Only studies with systemic antibiotics + adapalene, isotretinoin and tretinoin (combination therapy) were considered relevant on the basis of expert recommendation.

f.c.: fixed combination; BPO, benzoyl peroxide. [ ] indicates the evidence level

Adapted from Nast et al. (2)

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**Treatment of mild to moderate papulo-pustular acne**

There is strong evidence for the effectiveness of adapalene + benzoyl peroxide (BPO) (fixed combination) or BPO + clindamycin (fixed combination) in treating mild to moderate papulo-pustular acne.

**Therapeutic options for women**

Hormonal anti-androgens and systemic antibiotics (in principal together with topical combination products) are an alternative for women with severe nodular acne and conglobate acne.
greater severity which reach a plateau, then wax and wane depending on the topical and systemic therapy, and finally undergo natural regression (1, 7). The most disastrous forms are those associated with dramatic progression, maximal inflammation, and a tendency to early scarring; they involve papulo-pustular nodular acne (grade IV) and/or conglobate acne. Each clinical course is unique and influenced by the type of therapeutic intervention. Other patients follow the typical course of papulo-pustular acne grade I–II or chronic inflammatory acne grade III after Plewig and Kligman. The former group often responds well to long-term continuous topical therapy. Finally there are some patients, usually young men, who after a chronic mild course flare dramatically at age 17–18 years.

Even though all forms that start at puberty are associated with elevated androgen [dehydroepiandrosterone sulfate (DHEA-S)] levels, there is no long-term study that correlates androgen levels prior to, at the start of, and throughout puberty with clinical features of acne. Elevation of DHEA-S levels is best documented in women in the 3rd decade. In addition, it is becoming clearer that acne is not a short-term problem but a chronic disease with persistent inflammation over years (7). Many different courses may be observed—clear improvement and then severe relapse, sudden flares, or gradual re-occurrence. Finally the psycho-social aspects of the disease are of great importance for the patients in dealing with their family, partner and friends, as well as coping at school, when starting college or entering the job market (11). For this reason acne has been re-classified in recent years as a chronic inflammatory disease, similar to atopic dermatitis (7) (Table 1). The course of acne confirms to both the older and the most recent definitions of chronicity from the World Health Organization (WHO) (7). In particular, the number of acne patients outside the classic age range, as in acne tarda (14, e11), is increasing. Here one may encounter cases that after naturally regressing flare again in the second half of the 3rd decade, others that never clear, and still others that first become apparent during the 3rd decade. Frequently the patient is a woman who has used hormonal contraception since puberty and then in the 3rd decade stops contraception because of a desire to have children, but develops both increasing amount of sebum and acne of varying degrees of severity (e11).

### Pathogenesis

The classic concept is that acne results from the combination of increased sebaceous gland activity with seborrhea, abnormal follicular differentiation with increased keratinization, microbial hyper-colonization of the follicular canal and increased inflammation primarily through activation of the adaptive immune system. New research results have led to a modification of this classical explanation as more primary pathophysiologic factors have been identified. Along with a genetic predisposition, other major factors include androgens, pro-inflammatory lipids as ligands of sebocyte peroxisome proliferator-activated receptors (PPAR), and other inflammatory pathways. In addition, neuroendocrine regulatory mechanisms, diet and exogenous factors all may contribute to this multifactorial process (3–5) (Figure 2).

#### Cyclic growth of sebaceous follicles and triggers of inflammatory cascade

The hyperproliferation of the follicular epithelium leads to the development of microcomedones. Although clinically not visible, these are the initial lesions

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**Chronic course**

Acne is not a short-term illness, but instead shows a chronic course with persistence over years.

**Pathogenesis**

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in acne and can be found in apparently normal skin of acne patients (e21). It has been proposed that the sebaceous follicles go through a cyclic pattern leading to spontaneous resolution of the microcomedones (e22–e25). Bioactive interleukin (IL)-1 is found in open comedones of untreated patients (e26). There is no correlation between the cytokine level and the number of follicular microbes. Overstimulation of subclinical inflammatory process or lack of negative feedback regulation could be the reasons for the interruption of the normal cyclic process and for the development of clinically relevant follicular inflammation in acne (4, 6).

### Etiologic factors

**Androgens**—especially DHEA-S—play an important role in the early pathogenesis of acne, leading to both increased sebaceous gland volume and increased sebum production.

Lipid synthesis requires androgens and peroxisome proliferator-activated receptors (PPAR) (e35). Neuropeptides (with hormonal and non-hormonal actions) can control the development of clinical inflammation in acne (neurogenic co-control) (15). Substance P can be identified in numerous immune-reactive nerve fibers of acne skin (e36) and sebaceous glands respond to it with the synthesis of the inactivating neutral endopeptidase.

There are elevated levels of corticotrophin releasing hormone (CRH) (16), while adrenal dehydroepiandrosterone can initiate inflammation in sebaceous follicles (e37–e39).

In recent years a dietary hypothesis for the pathogenesis of acne has been brought forward (e40–e44). The relationship between hyperinsulinemia and elevated IGF-1 and reduced IGF-BP has been increasingly supported by controlled cohort studies. The relationship between the number of cigarettes smoked daily and the severity of acne is controversial (e11, e20, e45, e46).

### Etiologic factors

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Synthesis of chemokines and cytokines by keratinocytes can be stimulated by certain Propionibacterium acnes (P. acnes) strains through the activation of toll-like receptor 2 (e47–e49). P. acnes must first develop a biofilm to become a relevant pathogen, then playing an important role in maintaining inflammation (e50, e51).

### Hormone levels

There are elevated levels of corticotrophin releasing hormone, while adrenal dehydroepiandrosterone can initiate inflammation in sebaceous follicles.

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**TABLE 4**

<table>
<thead>
<tr>
<th>Side effects of systemic antibiotics commonly used to treat acne</th>
<th>Tetracycline</th>
<th>Doxycycline</th>
<th>Minocycline</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>(+)</td>
<td>(+)</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Phototoxicity</td>
<td>+</td>
<td>(+)</td>
<td>(−)</td>
<td>−</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Drug-induced lupus erythematosus</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Cholestatic hepatitis, pancreatitis, pseudomembranous colitis</td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
<td>(++)</td>
</tr>
<tr>
<td>Exanthema</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(++)</td>
</tr>
</tbody>
</table>

( ) uncommon, ( ) very uncommon
Therapy
The treatment of acne was slow to profit from the development of new topical and systemic medications. After tretinoin in 1962, two additional topical retinoids became available in the 1980s and 1990s, namely isotretinoin and adapalene. The latter is a retinoid (RAR/RXR/VDR) whose development was made possible by a better understanding of the cytoplasmic and nuclear retinoid receptors and their control of gene expression (18). In the mid-1980s, azelaic acid, a dicarboxylic acid, was introduced into topical therapy. The use of systemic antibiotics in acne therapy was originally based on the knowledge that oral tetracycline could inhibit experimentally induced pustules (19). Initially the goal was to suppress *P. acnes*. Today antibiotic treatment of acne is undergoing a paradigm change, as one shifts to a sub-anti-microbial dose of 40 mg daily in a delayed release formulation, using the para-antibiotic, anti-inflammatory action of these substances (doxycycline, minocycline) (15). Oral erythromycin is almost exclusively reserved for severe acne during pregnancy (1, 2). With the development of the anti-androgenic substances cyproterone acetate and chlormadinone acetate, additional options for women with severe acne became available (14, 20). The development of the spironolactone derivative drospirenone as a component of 4th generation oral contraceptives was the last advance in this area, but enthusiasm has been dampened because of the apparent increased risk of thrombosis.

Because of increasing resistance of *P. acnes*, there are worldwide efforts to replace topical antibiotics with BPO, topical retinoids and azelaic acid, or combinations thereof (17, 19). Since acne is a disease that tends to recur, maintenance therapy to suppress the development of the precursor microcomedones that lead to both inflammatory and non-inflammatory acne lesions is desirable; numerous evidence-based studies in recent years have shown that topical retinoids can accomplish this (1, 2, 18). Physical and chemical treatment methods for acne have not been adequately studied with evidence-based methods (21). Irradiation with blue or blue-red light destroys *P. acnes* via an endogenous porphyrin activation leading to cell death. UVA irradiation is comedogenic, while treatment with UVB irradiation is obsolete. The effects of interventional therapy with lasers, chemical peels, fillers or photodynamic therapy have not been sufficiently studied (21–23) (Table 2). The latter are especially suitable for treating the late manifestations of acne, such as scarring.

**History of acne therapy**
Acne therapy has been slow to profit from the development of new topical and systemic medications.

**Oral erythromycin**
Oral erythromycin is almost exclusively reserved for severe acne during pregnancy.
Indications for isotretinoin
Isotretinoin should be used in severe nodular and papulo-pustular acne at grade IV and when systemic antibiotics fail.

Length of remission following isotretinoin
About 20–30% of patients experience a recurrence after one year. Age and dose are important factors. A low dose is associated with a higher recurrence rate.
Systemic combination therapy

Topical and systemic combination therapy with oral antibiotics is recommended for moderately severe inflammatory acne as standard therapy; it should only be used for milder inflammatory acne that fails to respond to topical therapy.

Use of isotretinoin

Isotretinoin is without question the most effective oral agent for severe acne (papulo-pustular nodular acne, conglobate acne).

Such as hypertrophic and atrophic scars, as well as post-inflammatory hyperpigmentation. The Global Alliance for Better Outcomes in Acne, formed in 2001, organizes regional conferences in Asia, Europe, South America and North America, as well as national acne study groups, in order to develop guidelines and enhance evidence-based studies. The S2k acne guidelines published in Germany in 2010 (1) were the basis for the 2012 European S3 guidelines which are now being advanced to global guidelines (2). They are summarized in Table 3: these are only general recommendations which can be modified and personalized by the treating physicians taking into account the complex nature and variable course of acne.

Based on these guidelines (1, 2) topical monotherapy with antibiotics is not recommended. Instead, topical combination therapy with BPO is recommended for mild papulo-pustular acne. Topical retinoids are recommended as monotherapy for comedonal acne or in combination with BPO or topical antibiotics for milder papulo-pustular acne (Table 2). Topical azelaic acid therapy is the second-line recommendation for comedonal and mild papulo-pustular acne. Topical corticosteroids should not be used in treating acne (Table 3).

Combination therapy with topical drugs and oral antibiotics (doxycycline > minocycline, tetracycline) is recommended for moderate to severe acne, as well as less severe inflammatory acne which fails to respond to topical therapy alone. The systemic antibiotics should not be used alone but instead in combination with topical retinoids, BPO or azelaic acid. For women, oral contraceptives containing anti-androgens are another option. The recommended antibiotic dosages are doxycycline 50 mg daily–b.i.d. to 100 mg b.i.d., minocycline 50 mg b.i.d., tetracycline 500 mg b.i.d., and erythromycin 500 mg b.i.d.; therapy can be continued for three months (Table 4).

Hormonal anti-androgen therapy is not recommended as a first-line monotherapy for uncomplicated acne. Ethinylestradiol in combination with cypionate acetate, chlormadinone acetate, dinogest or drospirenone is recommended only as a combination therapy for women with moderate papulo-pustular acne to conglobate acne (14, 19).

Systemic corticosteroids can play a role in the initial therapy of severe inflammatory acne, in patients with systemic inflammatory manifestations (such as acne fulminans), or to control exacerbations during systemic isotretinoin therapy.

Maintenance therapy with topical retinoids (adapalene > isotretinoin, tretinoin) or azelaic acid is also recommended.

During nursing and pregnancy, possible treatment options include topical therapy with BPO, azelaic acid, erythromycin and chemical peels, as well as lasers and phototherapy. Systemic erythromycin, zinc and corticosteroids can be used in adjusted dosages in severe flares. Topical retinoids and clindamycin are contraindicated during pregnancy.

Therapy with oral isotretinoin: comments

Isotretinoin is without question the most effective oral agent for severe acne (papulo-pustular nodular acne, conglobate acne) (24, e56–e58) (Figure 3). Since its introduction in the 1980s and the detailed knowledge of its side effects, there have been repeated controversies over the indications for its use. Until the beginning of 2002, the above indications were well-accepted and it was understood among physicians experienced in treating acne that isotretinoin—including low-dose therapy—was not indicated in patients with mild acne. The EMA (European Medicines Agency) altered the recommendations at that time, requiring a trial of oral and topical medications in combination; if this failed, then isotretinoin could be employed. The registered indications were correspondingly altered. Physicians worldwide reacted differently then and continue to do so, basing their actions on many years of experience. The authors presented the arguments for isotretinoin as first choice treatment for severe acne to the EMA (25). Dermatologists in private practice and other physicians are in a position of conflict since the publication of the European S3 guidelines, as this document once again recommends isotretinoin as the drug of choice for severe acne (papulo-pustular nodular acne and conglobate acne). The feeling is that the sooner isotretinoin is employed for acne with marked inflammation and a tendency to early scarring, the better it is for the patient. The recommended doses are 0.3–0.5 mg/kg body weight (BW) for severe papulo-pustular nodular acne and ≥0.5 mg/kg BW for conglobate acne; therapy should be continued for 6 months, sometimes even longer (24) (Table 5).

In addition to the risk of teratogenicity with systemic retinoid therapy—just as with high-dose vitamin A administration—one must pay careful attention to the
possible induction of depression and suicidal ideation. This problem has only been reported when isotretinoin was used to treat acne, not when it has been employed to treat ichthyosis or psoriasis (it was used extensively for the latter indication in the USA prior to the introduction of etretinate and acitretin). Prospective cohort studies have shown that acne patients tend to have suicidal ideation as well as depression because of their altered appearance and psychosocial complications (26, e71). During treatment with oral antibiotics, however, suicide and depression were found to be just as common as under treatment with oral antibiotics and in controls (e72). Nonetheless every patient starting on isotretinoin must be assessed for a risk of depression, counselled and then followed closely. Recently, it has been noted that patients treated with high doses of isotretinoin and with repeated cycles have a greater risk of inflammatory colitis but not Crohn disease (27, e73–e75). The risk of rhabdomyolysis has been known for 30 years and is small, but every patient should be warned not to engage in over-strenuous activity at work or sports. Clinical observation and laboratory monitoring are recommended.

Conflict of interest statement
Prof. Göllnick has participated in acne-relevant clinical and experimental studies, symposia and advisory boards of Galderna, Stiefel/GSK, Intendis, Meda, Merz, Hoffmann-LaRoche, Novartis, Schering, Pierre Fabre, IMTM, and Vichy.
Prof. Zouboulis has patents and receives royalties for “Sebocytes, sebocyte cell lines and applications thereof” DE19991003920 as well as “Acne treatment with lipooxygenase inhibitors” DE20011021252. He has served as a paid advisor to Bayer-Schering, Boehringer-Ingelheim, Dermira, Galderna, Intendis, Leo, Merz, and Stiefel/GSK. He has received honoraria for publications from BASF. He has received reimbursement for travel and accommodation costs from Bioderma, General Topics, Glenmark, and Stiefel/GSK. He has received honoraria for organizing scientific continuing medical education symposia from Bayer/Schering, Bioderma, General Topics, Glenmark, and Stiefel/GSK. He has received honoraria for clinical studies from Galderna, Merz, and Stiefel/GSK. He has received honoraria for experimental research projects which he initiated from Galderna, Hoffmann-LaRoche, and MSD.

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This CME unit can be accessed until 20 July 2014.
The CME unit “The Differential Diagnosis and Treatment of Tremor” (Issue 13/2014) can be accessed until 22 June 2014.
The CME unit “Structured Management of Otitis Media” (Issue 9/2014) can be accessed until 25 May 2014.
The CME unit “The Treatment of Type 2 Diabetes” (Issue 5/2014) can be accessed until 27 April 2014.
Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**
What is the prevalence of acne in the general population in Germany?

- a) >1%
- b) <5%
- c) >10%
- d) Around 4%
- e) 25%

**Question 2**
Which factors are statistically significantly associated with a more severe disease course in late-onset acne?

- a) Spicy foods and atopic dermatitis
- b) Obesity and carbohydrate-rich diet
- c) Familial predisposition and acne in the mother
- d) Gender and ethnicity
- e) Biofilm formation and composition of sebum

**Question 3**
Regarding *P. acnes*, which of the following plays an especially important role in determining the severity of acne?

- a) Number of *P. acnes* per cm\(^2\) skin surface
- b) Biofilm formation
- c) O\(_2\) saturation in follicular canal
- d) Composition of sebum
- e) Interfollicular distribution of *P. acnes*

**Question 4**
Repeated cycles of isotretinoin increase the risk of developing which disease?

- a) Hypertension
- b) Inflammatory colitis
- c) Crohn disease
- d) Cardiac arrhythmias
- e) Psoriasis

**Question 5**
Which type of acne or degree of severity requires systemic therapy?

- a) Acne keloidalis
- b) Acne neonatorum
- c) Physiologic acne
- d) Conglobate acne
- e) Acne comedonica

**Question 6**
Which side effects may develop during monotherapy with erythromycin?

- a) Tingling
- b) Burning
- c) Scaling
- d) Xerosis
- e) Bacterial resistance

**Question 7**
What is the recommended second choice therapy for acne comedonica and mild papulo-pustular acne?

- a) Systemic hormone therapy
- b) Systemic glucocorticosteroids
- c) Topical monotherapy with antibiotics
- d) Oral combination therapy with doxycycline and benzoyl peroxide
- e) Topical therapy with azelaic acid

**Question 8**
Which treatment for conglobate acne is best supported by evidence (Level A)?

- a) Azelaic acid
- b) Doxycycline
- c) Topical antibiotics
- d) Isotretinoin
- e) Erythromycin

**Question 9**
Which maintenance therapy for acne is appropriate?

- a) Low-dose doxycycline
- b) Topical erythromycin
- c) Benzoyl peroxide
- d) Topical retinoids
- e) Low-dose oral isotretinoin

**Question 10**
Which medication for acne is contraindicated during pregnancy?

- a) Oral zinc gluconate
- b) Topical erythromycin
- c) Azelaic acid
- d) Benzoyl peroxide
- e) Topical retinoids
Not All Acne Is Acne Vulgaris

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eREFERENCES


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