European Evidence-based (S3)

Guideline for the Treatment of Acne

(ICD L70.0)

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List of abbreviations

ADR	adverse drug reaction
BPO	benzoyl peroxide
CY	cyst
IL	inflammatory lesions
IPL	intense pulsed light
LE	level of evidence
ne	no evidence
NIL	non-inflammatory lesions
NO	nodule
PDT	photodynamic therapy
sys.	systemic
TL	total lesion
top.	topical
UV	ultraviolet
vs.	versus

1 Introduction

Nast

1.1 Notes on use of guideline

An evidence-based guideline has been defined as ‘a systematically developed statement that assists clinicians and patients in making decisions about appropriate treatment for a specific condition’ [1]. A guideline will never encompass therapy specifications for all medical decision-making situations. Deviation from the recommendations may, therefore, be justified in specific situations.

This is not a textbook on acne, nor a complete, all-inclusive reference on all aspects important to the treatment of acne. The presentation on safety in particular is limited to the information available in the included clinical trials and does not represent all the available and necessary information for the treatment of patients. Additional consultation of specific sources of information on the particular intervention prescribed (e. g. product information sheet) is necessary. Furthermore, all patients should be informed about the specific risks associated with any given topical and/ or systemic therapy.

Readers must carefully check the information in this guideline and determine whether the recommendations contained therein (e. g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, and up-to-date. The authors and publishers can take no responsibility for dosage or treatment decisions.

1.2 Objectives of the guideline

Improvement in the care of acne patients

The idea behind this guideline is that recommendations based on a systematic review of the literature and a structured consensus process will improve the quality of acne therapy in general. Personal experiences and traditional therapy concepts should be critically evaluated and replaced, if applicable, with the consented therapeutic recommendations. In particular, a correct choice of therapy should be facilitated by presenting the suitable therapy options in a therapy algorithm, taking into account the type of acne and the severity of the disease.

Reduction of serious conditions and scarring

As a result of the detailed description of systemic therapies for patients with severe acne, reservations about these interventions should be overcome to ensure that patients receive the optimal therapy. With the timely introduction of sufficient therapies, the development of serious post-acne conditions, severe scarring and adverse psychosocial impact should be reduced.

Promotion of adherence

Good therapeutic adherence is key to treatment success. Adherence is facilitated by knowledge of the product being used, for example treatment duration, the expected onset of effect, the sequence of the healing process, the maximal achievable average effect, expected adverse events, and the benefit to quality of life.

Reduction of antibiotic resistance

The use of topical and systemic antibiotics should be optimized by using appropriate combinations for a predefined duration, in order to reduce the development of antibiotic resistance.

1.3 Target population

Health care professionals

This guideline has been developed to help health care professionals provide optimal therapy to patients with mild, moderate or severe acne. The primary target groups are dermatologists and other professionals involved in the treatment of acne, such as paediatricians and general practitioners. The target group may vary with respect to national differences in the distribution of services provided by specialists or general practitioners.

Patients

The recommendations of the guideline refer to patients who suffer from acne. These are mainly adolescents treated in outpatient clinics. The appropriate therapy option is presented according to the type of acne that is present. The primary focus is the induction therapy of facial acne, recommendations also encompass patients with more widespread acne affecting the trunk (see Chapter 1.6). Non-primary target groups are patients with special forms of acne, such as, occupational acne, chloracne, acne aestivalis, acne neonatorum and acne inverse (hidradenitis suppurativa).

1.4 Pharmacoeconomic considerations

European guidelines are intended for adaptation to national conditions. It is beyond the scope of this guideline to take into consideration the specific costs and reimbursement situations in every European country. Differences in prices, reimbursement systems, willingness and ability to pay for medication among patients and the availability of generics are too large. Therefore, pharmacoeconomic considerations will have to be taken into account when guidelines are developed at national and local levels.

The personal financial and health insurance situation of a patient may necessitate amendments to the prioritisation of treatment recommendations. However, if financial resources allow, the suggested ranking in the therapeutic algorithm should be pursued.

1.5 Considerations with respect to vehicle for topical treatments

The skin type, the sex and stage of disease has to be taken into consideration when choosing the vehicle for topical treatments. The efficacy and safety/ tolerability of topical treatments are influenced by the choice of vehicle.

1.6 Considerations regarding area of involvement

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The face is the primary region of interest for the treatment of acne. Appearance, scarring, quality of life and social stigmatization are important considerations when dealing with facial dermatological diseases.

The recommendations of this guideline apply primarily to the treatment of facial acne. More widespread involvement will certainly favour earlier use of a systemic treatment due to the efficacy and practicability of such treatments.

1.7 Clinical features and variants

Layton/ Finlay

Acne (synonym “acne vulgaris”) is a polymorphic, inflammatory skin disease nearly always affecting the face (99 % of cases). It also commonly affects the back (60 %) and chest (15 %) [2]. Seborrhoea is a frequent feature [3].

The clinical picture embraces a spectrum of signs, ranging from mild comedonal acne, with or without sparse inflammatory lesions (IL), to acne conglobate or aggressive fulminate disease with deep-seated inflammation, nodules and in some cases associated systemic symptoms.

1.7.1 Comedonal acne

Clinically non-inflamed lesions develop from the subclinical microcomedo which is evident on histological examination early in acne development [2]. Non-inflamed lesions encompass both open (blackheads) and closed comedones (whiteheads). Comedones frequently have a mid-facial distribution in childhood and, when evident early in the course of the disease, this pattern is indicative of poor prognosis [4]. Closed comedones are often inconspicuous with no visible follicular opening.

1.7.2 Papulopustular acne

Most patients have a mixture of non-inflammatory (NIL) and inflammatory lesions [5]. Inflammatory lesions arise from the microcomedo or from non-inflammatory clinically apparent lesions and may be either superficial or deep [6]. Superficial inflammatory lesions include papules and pustules (5 mm or less in diameter). These may evolve into nodules in more severe disease. Inflammatory macules represent regressing lesions that may persist for many weeks and contribute markedly to the general inflammatory appearance [5].

1.7.3 Nodular/ conglobate acne

Nodules are defined as firm, inflamed lesions >10 mm diameter, painful by palpation. [7]. They may extend deeply and over large areas, frequently resulting in painful lesions, exudative sinus tracts and tissue destruction. Conglobate acne is a rare but severe form of acne found most commonly in adult males with few or no systemic symptoms. Lesions usually occur on the trunk and upper limbs and frequently extend to the buttocks. In contrast to ordinary acne, facial lesions are less common. The condition often presents in the second to third decade of life and may persist into the

sixth decade. Conglobate acne is characterized by multiple grouped comedones amidst inflammatory papules, tender, suppurative nodules which commonly coalesce to form sinus tracts. Extensive and disfiguring scarring is frequently a feature.

1.7.4 Other acne variants

There are several severe and unusual variants or complications of acne as well as other similar diseases. These include acne fulminans, gram-negative folliculitis, rosacea fulminans, vasculitis, mechanical acne, oil/ tar acne, chloracne, acne in neonates and infants and late onset, persistent acne, sometimes associated with genetic or iatrogenic endocrinopathies. The current guideline do not lend themselves to comprehensive management of all of these variants.

2 Assessment, comparability of treatment outcomes

Finlay/ Layton

2.1 Acne grading

Acne can be largely assessed from two perspectives: objective disease activity (based on measurement of visible signs) and quality of life impact. There are other aspects of measurement, such as sebum excretion rate, colonisation by *Propionibacterium acnes* (*P. acnes*), scarring development or economic impact.

Accurately assessing outcomes from therapy is notoriously difficult in acne [8]. Many different approaches have been adopted but very few are validated. The inconsistent application of a standard method for assessing acne severity makes it very difficult to challenge interpretation of results from interventional studies. There are detailed reviews and reflections on this subject by Lehmann et al. [9], Barratt et al. [10], Witkowski et al. [11], Thiboutot et al. [12], Gollnick et al. [13] and Tan et al. [14].

Proper lighting, appropriate patient positioning and prior facial skin preparation (gentle shaving for men, removal of make-up for women) are helpful in facilitating accurate assessment. Palpation in addition to visual inspection may also help define lesions more accurately.

Mechanisms to assess acne lesions using digital multimodal imaging are being evaluated but have not yet been accepted or validated for use in clinical practice [15]. Patient reported outcomes are now also being considered as an important part of overall assessment [16]. However, the most frequently used outcome measures to assess acne involve grading or counting. These evaluations can be further divided into: (i) an evaluation according to the predominant lesion type; (ii) evaluations of separate individual lesions; (iii) overall or 'global' assessment. Lesion counts are essential for clinical trials as they offer a reliability not evident in global assessment, however counting remains impractical for use in the day-to-day clinic [17] and does not accurately reflect overall severity [18]. In systematic reviews, global grading has been used as an efficacy measure in up to 62% of acne trials [9, 10] and the USA Food and Drug Administration (FDA) has mandated global grading as one of two efficacy measures in which superiority must be demonstrated for approval of acne therapies [18]. However, no one global system has been established as a standard: some utilize quantitative measures e. g. lesion counts and numeric ranges and others are based on qualitative descriptions.

2.1.1 Acne grading systems

2.1.1.1 Sign-based methods

Despite a range of methods being used to measure acne in the 1960's and 1970's, it was the Leeds technique [5] that dominated acne measurement for the next two decades. The Leeds technique included two methods; the grading technique and the counting technique. The grading technique allocated patients a grade from 0 to 10, with seven subgroups between 0 and 2. Photographic guides illustrating each grade are given, but the importance of also palpating lesions is stressed. The experience on which this system was based stemmed from the pre-isotretinoin era, and acne of

the severity described by grades above 2 is now rarely seen. The counting technique involves the direct counting of non-inflamed and inflamed lesions, including superficial papules and pustules, deep inflamed lesions and macules. The revised Leeds acne grading system [19] includes numerical grading systems for the back and chest as well as for the face.

The Echelle de Cotation des Lesions d'Acne (ECLA) or "Acne Lesion Score Scale" system has demonstrated good reliability [20]. However, ECLA scores do not correlate with quality of life scores and the use of both disease and quality of life scores is suggested [21].

Persisting hyperpigmentation after active acne has settled is of great concern to many patients. An instrument to measure this has been described, the post acne hyperpigmentation index (PAHPI) [22].

2.1.1.2 Global assessment techniques

Global assessment scales incorporate the entirety of the clinical presentation into a single category of severity. Each category is defined by either photographs with a corresponding numeric scale or by descriptive text. Grading is a subjective task, based on observing dominant lesions, evaluating the presence or absence of inflammation, which is particularly difficult to capture, and estimating the extent of involvement. Global methods are much more practically suited to clinical practice. In clinical investigations, they should be combined with lesion counts as a co-primary endpoint of efficacy [23]. A simple photographic standard-based grading method using a 0-8 scale has been successfully employed in several clinical trials [24].

A very simple classification of acne severity was described in the 2003 report from the Global Alliance for better outcome of acne treatment [13]. This basic classification was designed to be used in a routine clinic, and its purpose was to map treatment advice onto common clinical presentations. For each acne descriptor a first-choice therapy is advised, with alternatives for females and maintenance therapy. There are five simple descriptors: mild comedonal, mild papulopustular, moderate papulopustular, moderate nodular, and severe nodular/ conglobate. A series of eight photographs span and overlap these five descriptors. Different facial views and different magnifications are used, reducing the comparability of the images.

In 2005, the FDA proposed an investigator global assessment (IGA) that represented a static quantitative evaluation of overall acne severity. To accomplish this, they devised an ordinal scale with five severity grades, each defined by distinct and clinically relevant morphological descriptions that they hoped would minimise inter-observer variability. Indeed, the more detailed descriptive text has resulted in this system being considered to provide even greater reliability than previous global assessments [18].

The Comprehensive Acne Severity System (CASS), was developed by extending a pre-existing 6-category facial IGA scale, ranging from clear through to very severe grading, to include the chest and back [25]. This has been validated and provides a global system that includes a restricted number of categories to allow for a practical and comprehensive approach when assessing treatment outcomes.

In order to give treatment recommendations based on disease activity, the EU Guideline group has considered how best to classify acne patients. It has used the following simple clinical classification:

1. Comedonal acne

2. Mild - moderate papulopustular acne

3. Severe papulopustular acne, moderate nodular acne

4. Severe nodular acne, conglobate acne

Other already existing systems are very difficult to compare with one another. The group has tried to map the existing systems to the guidelines' clinical classification. However, in many cases the systems do not include corresponding categories and often it has to be considered an approximated attempt rather than a precise mapping (Table 1).

Publication	**Comedonal acne**	**Mild-moderate papulo-pustular acne**	**Severe papulopustular acne, moderate nodular acne**	**Severe nodular acne, conglobate acne**
Pillsbury 1956 [26]	-	1 - 4	2 - 4	2 - 4
Kligman 1976 [27]	1 = < 10 2 = 10-25 3 = > 25-50 4 = > 50 (facial comedones)	-	-	-
Michaelsson 1977 [28]	-	0 - 30	20 - 30	20 - >30
Cook 1979 [24]	0 - 1	2 - 4	6	8
Wilson 1980 [29]	0	2 - 4	6 - 8	8
Allen 1982 [30]	0 - 2	2 - 6	6	8
Burke (Leeds) 1984 [5]	0.5	0.75 - 2	2 - 3	3 - 8
Pochi 1991 [23]	Mild	Mild/moderate	Moderate	Severe
O'Brien (Leeds) 1998 (face) [19]	1 - 3	4 - 7	8 - 10	11 - 12, nodulocystic
Dreno 1999 [20]	F1R1 - 5	F1Is1 - 4	F1Is4 - 5, F1Ip 1 - 4	F1Ip 4 - 5
Lehmann 2002 [9]	Mild	Mild/moderate	Severe	Severe
Gollnick 2003 [13]	Mild *comedonal*	Mild *papular-pustular,* moderate *papular-pustular*	Moderate *nodular*	Severe *nodular/ conglobate*
FDA's IGA for acne vulgaris (2005) [18]	1 Almost clear: *rare NIL with no more than 1*	2 Mild: s*ome NIL but no more than a few papule/*	3 Moderate: *many NIL, some IL no more than 1 nodule*	4 Severe: *up to many non-inflammatory and inflammatory*

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	papule	*pustule*		*lesions, but no more than a few nodular lesions*
Del Rosso 2007 [31]	-	Mild	Moderate	Severe
Tan 2007 [25]	-	Mild: *0-5 papules-pustules*	Moderate: *6-20 papules - pustules*	Severe: *21-50 papules - pustules,* Very severe: *>50 IL* Severe
Hayashi 2008 [32]	-	Mild 0-5 Papules and pustules	Moderate 6-20 Papules and pustules	Severe 21-50 papules and pustules >50 very severe
Layton 2010 [33]	-	Mild	Moderate	Severe
Dreno 2011 [34]	0-5	Mild 1-2	Moderate 2-4	Severe 5

Table 1 Comparison of different acne assessment scales. This is an attempt to approximately map the various published acne classifications to the simple four group classification used in this guideline.

2.1.1.3 Quality of life methods

The use of Quality of Life (QoL) measures captures the impact of acne as well as the impact of treatment on the patient's life and as a result supports identification of those vulnerable to psychological complications. Adopting a QoL measure as an integral part of acne management is recommended. In order for quality of life measures to be used more frequently in routine clinical work, they need to be easy to use, the scores need to be meaningful, and they need to be readily accessible. It is possible to measure the impact of acne on quality of life using several questionnaires. There are acne-specific, dermatology-specific and generic measures, which can be used across all diseases.

Acne specific measures include the "Assessments of the Psychological and Social Effects of Acne" (APSEA) questionnaire [35, 36], the Cardiff Acne Disability Index [37, 38] the Acne Quality of Life Scale (AQOL) [39], the Acne-specific Quality of Life Questionnaire (Acne-QoL) [40] and the short version of this, the Acne-Q4 [41]. A recent novel patient reported outcome measure, the Acne Symptom and Impact Scale (ASIS) seeks to capture both symptoms and impacts of facial acne [42, 43].

Dermatology specific measures used in acne include the Dermatology Life Quality Index (DLQI) [44-46], the Children's Dermatology Life Quality Index (CDLQI) [47] and Skindex-29, -16 [48]. Generic measures used in acne include the SF-36 (Mallon) and the General Health Questionnaire [49].

In addition it is possible to measure the secondary impact of acne on the lives of partners and other family members, using a dermatology specific measure, the Family Dermatology Life Quality Index [50] and a generic measure, the Family Reported Outcome Measure (FROM-16) [51].

Acne also affects functional abilities. Patients are prone to embarrassment and social withdrawal, depression, anxiety and anger. The combined use of QoL and psychosocial questionnaires is essential to adequately understand just how severely

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the disease is affecting a patient, and can aid in assessing the efficacy of therapy and justifying clinical decisions. In patients with a severe impact on their quality of life, a more aggressive therapy may be justified.

2.2 Prognostic factors that should influence treatment choice

2.2.1 Prognostic factors of disease severity

A number of prognostic factors relating to more severe disease should be considered when assessing and managing acne. These are outlined and evidenced in review papers published by Holland and Jeremy 2005 [52] and Dreno et al. 2006 [53] and include family history, course of inflammation, persistent or late-onset disease, hyperseborrhoea, androgenic triggers, truncal acne and/ or psychological sequelae. Previous infantile acne may also correlate with resurgence of acne at puberty and early age of onset with mid-facial comedones, early and more severe seborrhoea and earlier presentation relative to the menarche are all factors that should alert the clinician to increased likelihood of more severe acne.

2.2.2 The influence of the assessment of scarring/ potential for scarring on disease management

Scarring usually follows deep-seated inflammatory lesions, but may also occur as a result of more superficial inflamed lesions in scar-prone patients. Acne scarring, albeit mild, has been identified in up to 95 % of patients attending a dermatology clinic [54]. Scars may show increased collagen (hypertrophic and keloid scars) or be associated with collagen loss which is a more frequent consequence of inflammatory acne [55]. The duration of inflammation relates to scar production hence a delay in appropriate management is more likely to result in significant scarring [25, 54].

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Acne scarring should also be included in the assessment of acne severity. Scars can produce significant disfigurement and psychosocial impairment in their own right. The difficulty in evaluation of acne scars is manifold and clinical assessment of scars demonstrates significant variation between assessors [56]. Several different systems have been described to evaluate acne scars (see Table 2). Other techniques have been employed in an attempt to quantify scarring at specified time points in relation to treatment. These include ultrasound [57] surface profilometry using silicone imprints [58], standardized photography [59], and three dimensional in vivo microtopography measurements [60].

However, to date no single validated method to evaluate the extent or volume deficiency of acne scars has been uniformly adopted for use in routine clinical practice.

The presence of scarring should support aggressive management and therapy should be commenced early in the disease process.

Acne Scar System	Severity Scheme	Regional Relevance
Leeds [54]	Numeric (Maximum 30 for each region)	Face, chest and back
Echelle d'Evaluation Clinique des Cicatrices d'Acne [61]	Numeric (maximum 540)	Face

Qualitative Global Acne Scarring Grading System [62]	Four descriptive grades	Face, chest and back
Quantitative Global Acne Scarring Grading System [63]	Numeric (maximum 84)	Face
Patient and Observer Scar Assessment Scale (POSAS) [64]	Numeric (maximum 50 observer/maximum 60 patient)	Face
New evidence-based facial acne scar evaluation tool (FASET) to assess atrophic scars [65]	Global, Dispersion, Numeric	Face

Table 2 Acne scare severity grading systems

3 Epidemiology and pathophysiology

3.1 Epidemiology

Degitz/ Ochsendorf

Acne is regarded as one of the most frequent skin diseases. Epidemiologic studies in Western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%. If mild manifestations were excluded and only moderate or severe manifestations were considered, the frequency was still 20% - 35% [66-69]. Acne is a disease primarily of adolescence. It is triggered in children by the initiation of androgen production by the adrenal glands and gonads. It may begin as early as age 7-9 [70] and usually subsides after the end of growth. However, to some degree, acne may persist beyond teen age in a significant proportion of individuals [71]. Even after the disease has ended, acne scars and hyper- or hypopigmentation are not uncommon permanent negative outcomes [12]. Genetic factors have been recognized [72]. There is a high concordance among identical twins, and there is also a tendency towards severe acne in patients with a positive family history [73]. Multiple genes are probably involved in acne predisposition, among others cytochrome P450-1A1 and several enzymes involved in androgen metabolism [74, 75]. A genome-wide association study revealed a role for the dysregulation of TGFβ-mediated signalling in the susceptibility to acne [76]. Environmental factors also appear to be of relevance for acne prevalence. Of note, diet has recently gained attention. Populations with a natural lifestyle do not develop acne [77], and epidemiologic [78] and investigative studies [79] correlate acne with Western diet.

3.2 Pathophysiology

Dréno/ Gollnick

Acne is an androgen-dependent disorder of pilosebaceous follicles (or pilosebaceous unit). There are four primary pathogenic factors, which interact to produce acne lesions: 1) sebum production by the sebaceous gland, 2) alteration in the follicular keratinization process, 3) *Propionibacterium acnes* follicular colonization, and 4) release of inflammatory mediators.

Patients with seborrhoea and acne have a significantly greater number of lobules per gland compared with unaffected individuals (the so-called genetically prone “Anlage”). Inflammatory responses occur prior to the hyperproliferation of keratinocytes. Interleukin-1α up-regulation contributes to the development of comedones independent of the colonization with *P. acnes*. A relative linoleic acid deficiency has also been described.

Sebaceous lipids are regulated by peroxisome proliferator-activated receptors which act in concert with retinoid X receptors to regulate epidermal growth and differentiation as well as lipid metabolism. Sterol response element binding proteins mediate the increase in sebaceous lipid formation induced by insulin-like growth factor-1. Substance P receptors, neuropeptidases, α-melanocyte stimulating hormone, insulin-like growth factor (IGF)-1R and corticotrophin-releasing hormone (CRH)-R1 are also involved in regulating sebocyte activity as are the ectopeptidases,

such as dipeptidylpeptidase IV and animopeptidase N. The sebaceous gland also acts as an endocrine organ in response to changes in androgens and other hormones. DHEA-S is a stimulator of IL-2 driven T-cells and, therefore, driving the inflammatory process. [80] Oxidized squalene can stimulate hyperproliferative behaviour of keratinocytes, and lipoperoxides produce leukotriene B4, a powerful chemoattractant.

Microcomedones, macules and further developed visible lesions of acne produces chemotactic factors and promote the synthesis of tumour necrosis factor-α and interleukin-1β. Another cytokine, IL-17 has been identified as potentially playing an important role in addition of IL-1β in acne [81]. Cytokine induction by *P. acnes* occurs through Toll-like receptor (TLR) 2 activation via activation of nuclear factor-κB and activator protein 1 (AP-1) transcription factor. *P acnes* activates also Protease activated Receptor (PAR) 2. [82] Both TLR and PAR belongs to the innate immunity and play a crucial role in the modulation and duration of inflammation of acne lesions in association with the antimicrobial peptides. [83] Activation of AP-1 induces matrix metalloproteinase genes, the products of which degrade and alter the dermal matrix and could be a central factor in the development of acne scars. Recent data indicate that the phylotypes of *P acnes* are different comparing healthy controls and acne patients and in addition that different phylotypes of *P acnes* have different pro inflammatory activities, modulating differently the innate immunity. [84-87] *P acnes* as the therapeutic target has become questionable after studies showing that not all follicles are *P acnes* colonized, the number of *P acnes* are not correlating with the intensity of inflammatory reactions and course of the disease, but certain strains are correlating with the severity grade and course of acne. [88] Recently, it could be shown that the inflammasome is activated and IL-1ß is activated [89]. Furthermore, new findings on the role of growth factors such as IGF-1 in the regulation of the sebocytes have demonstrated that transcriptional factors such as FOX-O1 can interact with PPAR gamma and sebocyte differentiation and proliferation and may give some hint to a possible role of diets in the daily practice of acne patients. However, it could be shown for the first time that those growth factors also upregulate TLR 2 and 4. This means that not only *P acnes* is a key for upregulating TLR [90].

The improved understanding of acne development on a molecular level suggests that acne is a disease that involves both innate and adaptive immune systems with a predominant role for innate immunity in the regulation of inflammatory events.

4 Methods - Assessment of evidence

(For further details please see the methods report at www.acne-guideline.com.)

Nast/ Rosumeck

Many different grading systems for assessing the quality of evidence are available in the field of guideline development. For this guideline, the authors used the grading system adopted from the European Psoriasis Guideline (version 2010) [91, 92], already used in the previous acne guideline 2011 [93, 94].

4.1 Grade of evidence (quality of individual trial)

The available literature was evaluated with respect to the methodological quality of each single trial. A grade of evidence was given to every individual trial included:

A Randomized, double-blind clinical trial of high quality (e. g. sample-size calculation, flow chart of patient inclusion, intention-to-treat [ITT] analysis, sufficient sample size)

B Randomized clinical trial of lesser quality (e. g. only single-blind, no ITT)

C Comparative trial with severe methodological limitations (e. g. not blinded, very small sample size)

4.2 Level of evidence (quality of body of evidence to answer a specific question)

When looking at a specific question (e. g. efficacy of BPO relative to adapalene) the available evidence was summarized by aligning a level of evidence (LE), as our criteria were combined with the definition of GRADE [95] as used in the 2011 acne guideline version:

1 ***Further research is very unlikely to change our confidence in the estimate of effect.***

At least two trials are available that were assigned a grade of evidence A and the results are predominantly consistent with the results of additional grade B or C studies.

2 ***Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.***

At least three trials are available that were assigned a grade of evidence B and the results are predominantly consistent with respect to additional grade C trials.

3 ***Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.***

Conflicting evidence or limited amount of trials, mostly with a grade of evidence of B or C.

4 ***Any estimate of effect is very uncertain.***

Little or no systematic empirical evidence; included trials are extremely limited in number and/ or quality.

4.3 Consensus process

All recommendations were agreed on in an online-telephone consensus conference using a formal and structured consensus methodology. The consensus conference was moderated by PD Dr. med. Alexander Nast, who is a certified moderator for the German Association of Scientific Medical Societies (AWMF). All nominated experts were entitled to vote in the consensus conference.

In order to weight the different recommendations, the group assigned a “strength of recommendation” grade (see box below). The strength of recommendation considered all aspects of the treatment decision, such as efficacy, safety, patient preference, and the reliability of the existing body of evidence (level of evidence).

Strength of recommendation

In order to grade the recommendation a “standardized guideline“ language was used:

1) is strongly recommended
2) can be recommended
3) can be considered
4) is not recommended
5) may not be used under any circumstances
6) a recommendation for or against treatment X cannot be made at the present time.

5 Induction therapy

Summary of therapeutic recommendations [1] for induction therapy

Recommendations are based on available evidence and expert consensus. Available evidence and expert voting lead to classification of strength of recommendation.

	Comedonal acne [3]	**Mild to moderate papulopustular acne**	**Severe papulopustular/ moderate nodular acne**	**Severe nodular/ conglobate acne** [12]
High strength of recommendation	-	Adapalene + BPO (f.c.) *or* BPO + Clindamycin (f.c.) [5]	Isotretinoin	Isotretinoin
Medium strength of recommendation	Topical retinoid [4]	Azelaic acid *or* BPO *or* Topical Retinoid [4] *or* Topical Clindamycin + Tretinoin (f.c.) [5] *or* Systemic Antibiotic [5,6,7] + Adapalene [8]	Systemic Antibiotic [5,7] + Adapalene [8] *or* Systemic Antibiotic [5,7] + Azelaic acid [9] or Systemic Antibiotic [5,7] + Adapalene + BPO (f.c.)	Systemic Antibiotic [5,7] + Azelaic Acid or Systemic Antibiotic [5,7] + Adapalene + BPO (f.c.)
Low strength of recommendation	Azelaic acid *or* BPO	Blue Light *or* Oral Zinc *or* Systemic Antibiotic [5,6,7] + Azelaic Acid [9] *or* Systemic Antibiotic [5,6,7] + Adapalene + BPO (f.c.) [10] *or* Systemic Antibiotic [5,6,7] + BPO [11] *or* Topical Erythromycin + Isotretinoin (f.c.) [5] *or* Topical Erythromycin + Tretinoin (f.c.) [5]	Systemic Antibiotic [5,7] + BPO [11]	Systemic Antibiotic [5,7] + Adapalene [8,10] *or* Systemic Antibiotics [5,7] + BPO [10]
Alternatives for females [2]	-	-	Hormonal Antiandrogens + Systemic Antibiotic [5,7] + Topicals (apart from antibiotics) *or* Hormonal Antiandrogens + Topical Treatment	Hormonal Antiandrogens + Systemic Antibiotic [5,7] + Topicals (apart from antibiotics) *or* Hormonal Antiandrogens + Topical Treatment

1 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).

2 low strength of recommendation

3 The recommendation for comedonal treatment passed with vote of 60% agreement only, see chapter 5.1 for more details.

4 adapalene to be preferred over tretinoin/ isotretinoin (see Chapter 5.4.1)
5 Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
6 In case of more widespread disease/ moderate severity, initiation of a systemic treatment can be recommended.
7 doxycycline and lymecycline (see Chapter 5.4.2), limited to a treatment period of three months
8 only studies found on systemic AB + adapalene; topical isotretinoin and tretinoin can be considered for combination treatment based on expert opinion
9 indirect evidence from nodular and conglobate acne and expert opinion
10 indirect evidence from severe papulopustular acne
11 indirect evidence from a study also including chlorhexidin, recommendation additionally based on expert opinion
12 systemic treatment with corticosteroids can be considered
13 the f.c. of clindamycin/tretinoin shows comparable efficacy and safety to the f.c. BPO/clindamycin, downgrading to a medium strength of recommendation was done based on concerns with respect to the development of antibiotic resistance
f.c. fixed combination

5.1 Treatment of comedonal acne

5.1.1 Recommendations for comedonal acne [1]

High strength of recommendation
None

Medium strength of recommendation
Topical retinoids [2] can be recommended for the treatment of comedonal acne.

Low strength of recommendation
Azelaic acid can be considered for the treatment of comedonal acne.
BPO can be considered for the treatment of comedonal acne.

Open recommendation
A recommendation for or against treatment of comedonal acne with visible light as monotherapy, lasers with visible wavelengths and lasers with infrared wavelengths, with intense pulsed light (IPL) and photodynamic therapy (PDT) cannot be made at the present time.

Negative recommendation
Topical antibiotics are not recommended for the treatment of comedonal acne.
Hormonal antiandrogens, systemic antibiotics and/ or systemic isotretinoin are not recommended for the treatment of comedonal acne.
Artificial ultraviolet (UV) radiation is not recommended for the treatment of comedonal acne.

1 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).
2 adapalene to be preferred over tretinoin/ isotretinoin (see Chapter 5.4.1)

5.1.2 Reasoning

General comment: Only one trial looks specifically at patients with comedonal acne. As a source of indirect evidence, trials including patients with papulopustular acne were used and the percentage in the reduction of non-inflammatory lesions was considered as the relevant outcome parameter. Because of the general lack of direct evidence for the treatment of comedonal acne, the strength of recommendation was

downgraded for all considered treatment options, starting with medium strength of recommendation as a maximum.

Due to the usually mild to moderate severity of comedonal acne, generally a topical therapy is recommended.

The best efficacy was shown for topical retinoids, BPO and azelaic acid.

The tolerability of topical retinoids and BPO is comparable; there is a trend towards azelaic acid having a better safety/ tolerability profile than BPO and a comparable profile to adapalene (indirect evidence, see Table 11).

The fixed dose combination of adapalene with BPO shows a trend towards better efficacy against non-inflammatory lesions (NIL) when compared to BPO and a comparable efficacy when compared to adapalene (see Table 4). However, there is also a trend towards inferiority of the fixed combination with respect to the safety/ tolerability profile (indirect evidence, see Table 12).

The fixed dose combinations of clindamycin with BPO showed a trend towards better efficacy against NIL versus clindamycin and comparable efficacy versus BPO (see Table 5). With respect to the safety/ tolerability profile, the combination is comparable to its single components (indirect evidence, see Table 12).

Few and only indirect data on patient preference are available. They indicate patient preference for adapalene over other topical retinoids.

Additional pathophysiological considerations favour the use of topical retinoids (reduction of microcomedones).

5.1.2.1 Efficacy

See Table 3 to Table 5 for summary of efficacy data. Please see methods report for explanation of assessment strategy.

Table 3 Efficacy: Comedonal acne - top. therapy vs. vehicle/ top. therapy

	Vehicle (v)	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	BPO > v LE 1	BPO > aa LE 4	BPO = a LE 1	BPO = i LE 3	t ≥ BPO LE 4*
Azelaic acid (aa)	aa > v LE 1	X	a > aa LE 4	ne	t > aa LE 4
Adapalene (a)	a > v LE 1	X	X	a = i LE 4	a = t LE 1**
Isotretinoin (i)	i > v LE 1	X	X	X	i > t LE 4
Tretinoin (t)	t > v LE 1	X	X	X	X

LE=level of evidence; ne=no evidence; top.=topical
* BPO 5% = tretinoin 0.1% (LE 4); tretinoin 0.025% > BPO 5% (LE 4)
** adapalene 0.1% = tretinoin 0.025% (LE 1); tretinoin 0.05% ≥ adapalene 0.1% (LE 4); TMG 0.1% ≥ adapalene 0.1% (LE 4)

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Table 4 Efficacy: Comedonal acne - top. antibiotics vs. vehicle/ BPO/ azelaic acid/ top. Retinoids

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	Vehicle (v)	BPO	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
Clindamycin (c)	c > v LE 2	BPO ≥ c LE 1	aa ≥ c LE 4*	ne	ne	t = c LE 3
Erythromycin (e)	e ≥ v LE 1	ne	aa = e LE 4	ne	e = i LE 3	ne
Nadifloxacin (n)	n > v LE 4	ne	ne	ne	ne	ne
Tetracycline (t)	ne	BPO > t LE 3	ne	ne	ne	ne

LE=level of evidence; ne=no evidence; top.=topical
* azelaic acid 15% > clindamycin 1% (LE 4); clindamycin 1% = azelaic acid 5% (LE 4)

Table 5 Efficacy: Comedonal acne - top. combination therapy vs. top. therapy/ combinations

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	Vehicle (v)	BPO	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)	Clindamycin (c)	Erythromycin (e)	Adapalene-BPO (a-BPO)	BPO-clindamycin (BPO-c)	Clindamycin-tretinoin (ct)
Adapalene-BPO (a-BPO)	a-BPO > v LE 1	a-BPO > BPO LE 3	a-BPO = a LE 3	ne	ne	ne	ne	X	X	ne
BPO-clindamycin (BPO-c)	BPO-c > v LE 1	BPO-c = BPO LE 1	a = BPO-c LE 3	ne	ne	BPO-c > c LE 1	ne	BPO-c = a-BPO LE 4	X	BPO-c = ct LE 4
Clindamycin-tretinoin (ct)	ct > v LE 1	ne	ne	ne	ct = t LE 1	ct > c LE 4	ne	ne	X	X
Clindamycin-zinc (cz)	ne	ne	ne	ne	ne	cz = c LE 3	ne	ne	ne	ne
Erythromycin-isotretinoin (ei)	ei > v LE 3	ne	ne	ei = i LE 3	ne	ne	ei = e LE 3	ne	ne	ne
Erythromycin-tretinoin (et)	ne	ne	ne	ne	ne	ne	ne	ne	ne	ne
Erythromycin-zinc (ez)	ez > v LE 1	ne	ne	ne	ne	ez > c LE 4	ez ≥ e LE 3	ne	BPO-c > ez LE 4	ne

LE=level of evidence; ne=no evidence; top.=topical

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Light sources

Although in the literature search for the first version of this guideline, there were some studies for the treatment of NIL with laser and light sources, no clear recommendations could be drawn. The published evidence was very scarce.

5.1.2.2 Safety/ tolerability

Only one trial looked specifically at comedonal acne. It showed a superior safety/ tolerability profile for azelaic acid compared with tretinoin (LE 4) [96].

As a source of further indirect evidence, trials in patients with papulopustular acne were considered to evaluate the safety and tolerability profile of the included treatments. For a summary of the data, see Chapter 5.2.3.2.

5.1.2.3 Patient preference

Based on a systematic review by Dressler et al. [97] there is only indirect evidence from trials including patients with mild to moderate papulopustular acne, see chapter 5.2.3.3.

5.1.2.4 Other considerations

Animal experiments, in the rhino mouse model in particular, have shown for decades that retinoids have a strong anti-comedonal efficacy. Clinical trials on the microcomedo, the natural precursor of comedones, have shown that retinoids significantly reduce microcomedo counts. In addition, *in vitro* data provide pathophysiological support for the use of topical retinoids for comedonal acne [98, 99].

5.2 Treatment of papulopustular acne

5.2.1 Recommendations for mild to moderate papulopustular acne [1]

High strength of recommendation
The fixed-dose combination adapalene and BPO is strongly recommended for the treatment of mild to moderate papulopustular acne.
The fixed-dose combination BPO and clindamycin [2] is strongly recommended for the treatment of mild to moderate papulopustular acne.

Medium strength of recommendation
Azelaic acid can be recommended for the treatment of mild to moderate papulopustular acne.
BPO can be recommended for the treatment of mild to moderate papulopustular acne.
A combination of a systemic antibiotic [2,3,4] with adapalene [5] can be recommended for the treatment of moderate papulopustular acne.
The fixed-dose combination clindamycin and tretinoin [2] can be recommended for the treatment of mild to moderate papulopustular acne.[10]
Topical retinoids [6] can be recommended for the treatment of mild to moderate papulopustular acne.

Low strength of recommendation
Blue light monotherapy can be considered for the treatment of mild to moderate papulopustular acne.
Oral zinc can be considered for the treatment of mild to moderate papulopustular acne.

Systemic antibiotic [2,3,4] in combination with azelaic acid [7] can be considered for the treatment of mild to moderate papulopustular acne.
A combination of a systemic antibiotic [2,3,4] with adapalene in fixed-dose combination with BPO [8] can be considered for the treatment of moderate papulopustular acne.
A combination of a systemic antibiotic [2,3,4] with BPO [9] can be considered for the treatment of moderate papulopustular acne.
The fixed-dose combination of erythromycin and isotretinoin [2] can be considered for the treatment of mild to moderate papulopustular acne.
The fixed-dose combination of erythromycin and tretinoin [2] can be considered for the treatment of mild to moderate papulopustular acne.

Open recommendation
Due to a lack of sufficient evidence, a recommendation for or against treatment of mild to moderate papulopustular acne with red light, IPL, Laser or PDT cannot be made at the present time.

Negative recommendation
Topical antibiotics as monotherapy are not recommended for the treatment of mild to moderate papulopustular acne.
Artificial UV radiation is not recommended for the treatment of mild to moderate papulopustular acne.
The fixed-dose combination of erythromycin and zinc is not recommended for the treatment of mild to moderate papulopustular acne.
Systemic therapy with anti-androgens, antibiotics, and/ or isotretinoin is not recommended for the treatment of mild to moderate papulopustular acne.

1 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 limit, legal restrictions, availability, drug licensing).
2 Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
3 doxycycline and lymecycline (see Chapter 5.4.2), limited to a treatment period of three months
4 In case of more widespread disease/ moderate severity, initiation of a systemic treatment can be recommended.
5 only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion
6 adapalene to be preferred over tretinoin/ isotretinoin (see Chapter 5.4.1)
7 indirect evidence from nodular and conglobate acne and expert opinion
8 indirect evidence from severe papularpustular acne
9 indirect evidence from a study also including chlorhexidin, recommendation additionally based on expert opinion
10 the f.c. of clindamycin/tretinoin shows comparable efficacy and safety to the f.c. BPO/clindamycin, downgrading to a medium strength of recommendation was done based on concerns with respect to the development of antibiotic resistance

5.2.2 Recommendations for severe papulopustular/ moderate nodular acne [1]

High strength of recommendation
Oral isotretinoin monotherapy is strongly recommended for the treatment of severe papulopustular/ moderate nodular acne acne.

Medium strength of recommendation
Systemic antibiotics [2,3] in combination with adapalene [4], with the fixed-dose combination of adapalene and BPO, or in combination with azelaic acid [5] can be recommended for the treatment of severe papulopustular/ moderate nodular acne.

Low strength of recommendation
Systemic antibiotics [2,3] in combination with BPO [5] can be considered for the treatment of severe papulopustular/ moderate nodular acne.
For females: Hormonal antiandrogens in combination with systemic antibiotic [2,3] and topicals (apart from antibiotics) can be considered for the treatment of severe papulopustular/ moderate nodular acne.
For females: Hormonal antiandrogens in combination with a topical treatment can be considered for the treatment of severe papulopustular/ moderate nodular acne.

Open recommendation
Due to a lack of sufficient evidence, a recommendation for or against treatment of severe papulopustular/ moderate nodular acne with red light, IPL, Laser or PDT cannot be made at the present time.
Although PDT is effective in the treatment of severe papulopustular/ moderate nodular acne, a recommendation for or against its use cannot be made at the present time due to a lack of standard treatment regimens that ensure a favourable profile of acute adverse reaction.

Negative recommendation
Single or combined topical monotherapy is not recommended for the treatment of severe papulopustular/ moderate nodular acne.
Oral antibiotics as monotherapy are not recommended for the treatment of severe papulopustular/ moderate nodular acne.
Oral anti-androgens as monotherapy are not recommended for the treatment of severe papulopustular/ moderate nodular acne.
Visible light as monotherapy is not recommended for the treatment of severe papulopustular/ moderate nodular acne.
Artificial UV radiation sources are not recommended as a treatment of severe papulopustular/ moderate nodular acne.

1 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 limit, legal restrictions, availability, drug licensing).
2 Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
3 doxycycline and lymecycline (see Chapter 5.4.2), limited to a treatment period of three months
4 only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion
5 indirect evidence from nodular and conglobate acne and expert opinion
6 indirect evidence from a study also including chlorhexidin, recommendation additionally based on expert opinion

5.2.3 Reasoning

Monotherapy with azelaic acid, BPO or topical retinoids showed superior efficacy when compared with vehicle.

Adapalene, azelaic acid and BPO showed comparable efficacy when compared with each other. When comparing the topical retinoids (adapalene, isotretinoin and tretinoin) directly against each other, no relevant difference with respect to efficacy was seen. Some conflicting evidence to the comparability of the efficacy of the treatment options above arises, when looking at the other head to head comparisons indicating superiority of BPO over isotretinoin and tretinoin over azelaic acid.

With respect to the fixed combinations, BPO/ clindamycin shows superiority over both single components.

The three fixed combinations of adapalene/ BPO, clindamycin/ tretinoin as well as erythromycin/ isotretinoin show superiority to one of the components but not to both of the components when compared individually.

Head to head comparisons of the fixed combinations of adapalene/ BPO versus BPO/ clindamycin as well as head to head comparisons of clindamycin/ tretinoin versus BPO/ clindamycin show comparable efficacy.

Due to the risk of developing antibiotic resistance, topical monotherapy with antibiotics is generally not recommended. The potential risk of developing antibiotic resistance was taken into consideration by the expert group. It lead to a medium strength of recommendation for the fixed combination of clindamycin/ tretinoin despite comparable efficacy and safety when compared to the fix combination of BPO/clindamycin. The differentiation between clindamycin/ tretinoin (medium strength of recommendation) and erythromycin/ isotretinoin (low strength of recommendation) was based on evidence showing the lack of development of antibiotic resistance after 16 weeks of treatment with clindamycin/ tretinoin [100] as well as indirect evidence on stronger development of antibiotic resistance to erythromycin [101] and expert opinion on better follicular penetration and galenic of the clindamycin/ tretinoin formulation.

Monotherapy with azelaic acid, BPO, or topical retinoids showed comparable efficacy when compared with each other.

For severe cases, systemic treatment with isotretinoin is recommended based on the very good efficacy seen in clinical practice.

The available evidence on safety and tolerability is extremely scarce and was considered insufficient to be used as a primary basis to formulate treatment recommendations.

The lack of standardized protocols, experience and clinical trial data mean there is insufficient evidence to recommend the treatment of papulopustular acne with laser and light sources other than blue light.

Choice of topical versus systemic treatment

There are limited data comparing topical treatments with a systemic treatment or the additional effect of a combination of a topical plus systemic versus topical treatment only. Most of the available trials compare a topical antibiotic monotherapy with a systemic antibiotic monotherapy.

Issues of practicability between topical and systemic treatments must also be taken into consideration in cases of severe, and often widespread, disease.

The consensus within the expert group was that most cases of severe papulopustular acne or moderate nodular acne, will achieve better efficacy when a systemic antibiotic treatment in combination with a topical treatment or if systemic isotretinoin

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is used. In addition, better adherence and patient satisfaction is anticipated for systemic treatments.

5.2.3.1 Efficacy

See Table 6 to Table 10 for summary of efficacy data. Please see methods report for explanation of assessment strategy.

Table 6 Efficacy: Papulopustular acne - top. therapy vs. vehicle/ top. therapy

	Vehicle (v)	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	BPO > v LE 1	BPO = aa LE 2	BPO = a LE 1	BPO > i LE 3	conflicting LE 4*
Azelaic acid (aa)	aa > v LE 1	X	aa = a LE 4	ne	t > aa LE 4
Adapalene (a)	a > v LE 1**	X	X	i = a LE 4	a = t LE 2-4***
Isotretinoin (i)	i > v LE 1	X	X	X	i = t LE 4
Tretinoin (t)	t > v LE 1	X	X	X	X

LE=level of evidence; ne=no evidence; top.=topical
* tretinoin 0.025% > BPO 5% (LE 4); BPO 5% > tretinoin 0.1% (LE 4); BPO 5-10% = tretinoin 0.05% (LE 4)
** adapalene 0.1% > placebo/vehicle (LE 1); adapalene 0.3% > placebo/vehicle (LE 1)
*** adapalene 0.1% = tretinoin 0.025% (LE 2); tretinoin 0.05% > adapalene 0.1% (LE 4); TMG 0.1% = adapalene 0.1% (LE 3)

Table 7 Efficacy: Papulopustular acne - top. combination therapy vs. top. therapy/ combinations

	Vehicle (v)	BPO	Ada-palene (a)	Iso-treti-noin (i)	Tre-tino-in (t)	Clin-damy-cin (c)	Ery-thro-mycin (e)	Adapa-lene-BPO (a-BPO)	BPO-clinda-mycin (c-BPO)	Clinda-mycin-tretino-in (ct)
Adapalene-BPO (a-BPO)	a-BPO > v LE 1	a-BPO = BPO LE 3	a-BPO > a LE 1	ne	ne	ne	ne	X	X	X
BPO-clindamy-cin (BPO-c)	BPO-c > v LE 1	BPO-c > BPO LE 4	BPO-c > a LE 3	ne	ne	BPO-c > c LE 1	ne	BPO-c = a-BPO LE 4*	X	X
Clinda-mycin-tretinoin (ct)	ct > v LE 1	ne	ne	ne	ct > t LE 1	ct = c LE 2	ne	ne	BPO-c = ct LE 4	X
Clindamy-cin-zinc (cz)	ne	ne	ne	ne	ne	cz = c LE 3	ne	ne	ne	ne
Erythro-mycin - isotretino-	ei > v LE 3	ne	ne	ei > i LE 3	ne	ne	ei = e LE 3	ne	ne	ne

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Erythro-mycin-tretinoin (et)	ne	ne	ne	ne	ne	ne	ne	ne	ne	ne
Erythro-mycin-zinc (ez)	ez > v LE 1	ne	ne	ne	ne	ez > c LE 4	ez ≥ e LE 3	ne	BPO-c = ez LE 4	ne

LE=level of evidence; ne=no evidence; top.=topical
* clindamycin-BPO = adapalene-BPO after 12 weeks of treatment (LE 4); clindamycin-BPO = adapalene-BPO after 2 weeks of treatment (LE 4)

Table 8 Efficacy: Papulopustular acne - top. therapy vs. sys. therapy

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	Isotretinoin	Clindamycin/ erythromycin/ lymecycline	Tetracycline (t)	Doxycycline (d)	Minocycline (m)
Azelaic acid (aa)	ne	ne	ne	ne	ne
BPO	ne	ne	ne	ne	BPO = m LE 3
Clindamycin (c)	ne	ne	c = t LE 1	ne	c > m LE 4
Erythromycin (e)	ne	ne	e > t LE 3	ne	ne
Erythromycin+ zinc (ez)	ne	ne	ez ≥ t LE 3*	ne	ez > m LE 4
Tetracycline (t)	ne	ne	ne	ne	ne

LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical
* erythromycin + zinc liquid > sys. tetracycline (LE 3); erythromycin + zinc gel > sys. tetracycline (LE 3)

Table 9 Efficacy: Papulopustular acne - sys. monotherapy vs. antibiotics/ isotretinoin/ zinc

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	Placebo/ vehicle (v)	Doxycy-cline (d)	Erythro-mycin (e)	Lymecy-cline (l)	Minocy-cline (m)	Tetracy-cline (t)	Isotre-tinoin (i)	Zinc (z)
Clindamycin (c)	c > v LE 3	ne	ne	ne	ne	t > c LE 3	ne	ne
Doxycycline (d)	conflicting LE 3*	X	e = d LE 3	ne	m = d LE 3	ne	ne	ne
Erythro-mycin (e)	ne	X	X	ne	ne	e = t LE 3	ne	ne
Lymecycline (l)	l > v LE 3	X	X	X	m = l LE 4	ne	ne	ne
Minocycline (m)	m > v LE 1	X	X	X	X	m = t LE 2	ne	m > z LE 3
Tetracycline (t)	t > v LE 1	X	X	X	X	X	ne	t > z LE 3
Isotretinoin (i)	i > v LE 4	X	X	X	X	X	X	ne

Zinc (z)	z > v LE 1	X	X	X	X	X	X	X

LE=level of evidence; ne=no evidence; sys.=systemic
* doxycycline 20mg BID or 0.6mg/kg QD = placebo (LE 3); doxycycline 1.2mg/kg or 100mg QD ≥ placebo (LE 3); doxycycline 2.4mg/kg > placebo (LE 3)
* doxycycline 20mg BID or 0.6mg/kg QD = placebo (LE 3); doxycycline 1.2mg/kg or 100mg QD = placebo (LE 1); doxycycline 2.4mg/kg > placebo (LE 3)

Table 10 Efficacy: Papulopustular acne - sys. therapy vs. sys.-top. combination

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	Isotretinoin (i)	Clindamycin (c)	Doxycycline (d)	Lymecycline (l)	Tetracycline (t)
Top. adapalene + sys. doxycycline (a-d)	ne	ne	a-d = d LE 4	ne	ne
Top. adapalene + BPO (f.c.) + sys. doxycycline (a-BPO-d)	a-BPO-d = i LE 4	ne	d-a-BPO > d LE 3	ne	ne
Top. adapalene + sys. tetracycline (ta-t)	i > ta-t LE 4	ne	ne	ne	ne
Top. adapalene + sys. lymecycline (a-l)	ne	ne	ne	a-l > l LE 4	ne
Top. azelaic acid + sys. minocycline (aa-m)	aa-m = i LE 4	ne	ne	ne	ne
Top. tetracycline + sys. tetracycline (t-t)	ne	ne	ne	ne	ne

f.c.=fixed combination, LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

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Combination oral contraceptives (COCs)

For the previous version of the guideline, due to limited evidence, it was difficult to draw conclusions on the differences in efficacy between the anti-androgens. For the update, the data summary from the Cochrane Review by Arowojolu et al. [102] was used. It found that: “COCs reduced acne lesion counts, severity grades and self-assessed acne compared to placebo. Differences in the comparative effectiveness of COCs containing varying progestin types and dosages, though, were less clear. COCs that contained chlormadinone acetate or cyproterone acetate improved acne better than levonorgestrel, although this apparent advantage was based on limited data. A COC with cyproterone acetate might result in better acne outcomes than one with desogestrel; however, the three studies comparing these COCs produced conflicting results. Likewise, levonorgestrel showed a slight improvement over desogestrel in acne outcomes in one trial, but a second trial found the COC groups were similar.” [102]

Light sources

Due to the still very limited evidence, the open recommendation for IPL, laser and PDT were maintained in the update. The low strength of recommendation for a treatment with blue light was kept based on the evidence identified in the 2011 version of the guideline and confirmed by expert voting.

5.2.3.2 Safety/ tolerability

See Table 11 to Table 14 for summary of safety/ tolerability data.

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Table 11, Safety/ tolerability: Papulopustular acne - top. therapy vs. top. therapy

	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	aa > BPO LE 4	BPO = a LE 4	BPO = i LE 4	BPO = t LE 4 / insufficient data*
Azelaic acid (aa)	X	aa > a LE 4	ne	aa > t LE 4
Adapalene (a)	X	X	a > i LE 4	a > t LE 4**
Isotretinoin (i)	X	X	X	insufficient data

LE=level of evidence; ne=no evidence; top.=topical
* tretinoin 0.025% = BPO 5% (LE 4); BPO 5% vs. tretinoin 0.1% (insufficient data); BPO 5-10% vs. tretinoin 0.05% (insufficient data)
** adapalene 0.1% > tretinoin 0.025% (LE 4); adapalene 0.1% > tretinoin 0.05% (LE 4); adapalene 0.1% > TMG 0.1% (LE 4)

Table 12, Safety/ tolerability: Papulopustular acne - top. combinations vs. top. therapy/ combinations

	BPO	Ada-palene (a)	Iso-tre-tinoin (i)	Treti-noin (t)	Clinda-mycin (c)	Ery-thro-mycin (e)	Adapa-le-ne-BPO (a-BPO)	BPO-clinda-mycin (BPO-c)	Clinda-mycin-tretinoin (ct)
Adapalene-BPO (a-BPO)	BPO > a-BPO LE 1	a > a-BPO LE 4	ne	ne	ne	ne	X	X	X
BPO-clindamycin (BPO-c)	BPO-c = BPO LE 1	BPO-c > a LE 4	ne	ne	BPO-c = c LE 1	ne	BPO-c > a-BPO LE 4*	X	X
Clindamycin-tretinoin (ct)	ne	ne	ne	t = ct LE 4	c > ct LE 1	ne	ne	BPO-c = ct LE 4	X
Clindamyin-zinc (cz)	ne	ne	ne	ne	cz = c LE 4	ne	ne	ne	ne
Erythromycin-isotretinoin (ei)	ne	ne	ei = i LE 4	ne	ne	ei = e LE 4	ne	ne	ne
Erythromycin-tretinoin (et)	ne	ne	ne	ne	ne	ne	ne	ne	ne
Erythromycin-zinc (ez)	ne	ne	ne	ne	ez = c LE 4	e > ez LE 4	ne	BPO-c = ez LE 4	ne

LE=level of evidence; ne=no evidence; top.=topical
* clindamycin-BPO > adapalene-BPO after 12 weeks of treatment (LE 4); clindamycin-BPO > adapalene-BPO after 2 weeks of treatment (LE 4)

Topical monotherapy versus systemic monotherapy

Topical treatments usually result in local side effects whereas systemic treatments cause, among others, mostly gastrointestinal effects. It is therefore difficult to accurately compare topical and systemic treatments in terms of safety/ tolerability.

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Systemic antibiotics

From the included trials, no clear conclusion can be drawn as to which antibiotic treatment has the best safety/ tolerability profile.

Table 13 Safety/ tolerability: Papulopustular acne - sys. monotherapy vs. sys. antibiotics/ isotretinoin/ zinc

	Doxycycline (d)	Erythromycin (e)	Lymecycline (l)	Minocycline (m)	Tetracycline (t)	Isotretinoin (i)	Zinc (z)
Clindamycin (c)	ne	ne	ne	ne	t = c LE 4	ne	ne
Doxycycline (d)	X	insufficient data	ne	m = d LE 4	ne	ne	ne
Erythromycin (e)	X	X	ne	ne	t > e LE 4	ne	ne
Lymecycline (l)	X	X	X	l > m LE 4	ne	ne	ne
Minocycline (m)	X	X	X	X	m = t LE 4	ne	m > z LE 4
Tetracycline (t)	X	X	X	X	X	ne	insufficient data
Isotretinoin (i)	X	X	X	X	X	X	ne

LE=level of evidence; ne=no evidence; sys.=systemic

Smith and Leyden [103] performed a systemic review analyzing case reports on adverse events with minocycline and doxycycline between 1966 and 2003. As a result, they suggest that adverse events may be less likely with doxycycline than with minocycline. More severe adverse events seem to appear during treatments with minocycline. Doxycycline however, leads to photosensitivity, which is not seen with minocycline.

See also Chapter 5.4.2 Choice of type of systemic antibiotic.

Combination oral contraceptives

The included Cochrane review by Arowojolu et al. [102] does not provide definite conclusions on tolerability, safety and frequency of adverse events.

For the use of oral contraceptive, relevant safety aspects such as the risk of thrombosis have to be considered.

Systemic treatments with isotretinoin

From the included trials, no clear comparison of the safety/ tolerability profiles of isotretinoin with other systemic treatments can be made. (For a discussion of isotretinoin depression, see Chapter 0)

Table 14 Safety/ tolerability: Papulopustular acne - sys.-top. combination vs. sys. therapy

	Isotretinoin (i)	Clindamycin (c)	Doxycycline (d)	Lymecycline (l)	Tetracycline (t)

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Top. adapalene + sys. doxycycline (a-d)	ne	ne	a-d = d LE 4	ne	ne
Top. adapalene + BPO (f.c.) + sys. doxycycline (a-BPO-d)	a-BPO-d = i LE 4	ne	a-BPO-d = d LE 4	ne	ne
Top. adapalene + sys. tetracycline (ta-t)	not comparable	ne	ne	ne	ne
Top. adapalene + sys. lymecycline (a-l)	ne	ne	ne	l > a-l LE 4	ne
Top. azelaic acid + sys. minocycline (aa-m)	aa-m > i LE 4	ne	ne	ne	ne
Top. tetracycline + sys. tetracycline (t-t)	ne	ne	ne	ne	ne

f.c.=fixed combination, LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

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Light sources

Although in the literature search for the first version of this guideline, there were some studies for the treatment of severe nodular / conglobate acne with laser and light sources, no clear recommendations could be drawn. The published evidence was very scarce.

5.2.3.3 Patient preference

The systematic review by Dressler et al. [97] includes two split-face studies reporting patient preferences for adapalene over tretinoin (low risk of bias).

Two cross-over trials evaluated erythromycin versus clindamycin but only one RCT found a statistically significant difference for patient preferences for erythromycin (unclear risk of bias).

Two split-face studies reported patient preferences for clindamycin 1%/BPO 5%/2.5% over adapalene 0.1%/BPO 2.5% (descriptive data only; unclear risk of bias).

5.2.3.4 Other considerations

For further discussion on the use of isotretinoin as a first-line treatment for severe papulopustular acne, see Chapter 5.4.3.

The expert group feels strongly that the effectiveness seen in clinical practice is highest with systemic isotretinoin, although this can only be partly supported by published evidence. Strong expert voting also took perceived lower relapse rates after treatment with isotretinoin into consideration.

5.3 Treatment of severe nodular/ conglobate acne

5.3.1 Recommendations for severe nodular/ conglobate acne [1]

High strength of recommendation
Oral isotretinoin is strongly recommended as a monotherapy for the treatment of severe nodular/ conglobate acne.

Medium strength of recommendation
Systemic antibiotics [2,3] in combination with the fixed-dose combination of adapalene and BPO or in combination with azelaic acid can be recommended for the treatment of severe nodular/ conglobate acne.

Low strength of recommendation
Systemic antibiotics [2,3] in combination with adapalene [4,5] or BPO [5] can be considered for the treatment of severe nodular/ conglobate acne.
For females: Hormonal antiandrogens in combination with systemic antibiotic [2,3] and topicals (apart from antibiotics) can be considered for the treatment of severe nodular/ conglobate acne.
For females: Hormonal antiandrogens in combination with a topical treatment can be considered for the treatment of severe nodular/ conglobate acne.

Open recommendation
Due to a lack of sufficient evidence, it is currently not possible to make a recommendation for or against treatment with IPL or laser in severe nodular/ conglobate acne.
Although PDT is effective in the treatment of severe nodular/ conglobate acne, it cannot yet be recommended due to a lack of standard treatment regimens that ensure a favourable profile of acute adverse reaction.

Negative recommendation
Topical monotherapy is not recommended for the treatment of conglobate acne.
Oral antibiotics are not recommended as monotherapy for the treatment of severe nodular/ conglobate acne.
Oral anti-androgens are not recommended as monotherapy for the treatment of severe nodular/ conglobate acne.
Artificial UV radiation sources are not recommended for the treatment of severe nodular/ conglobate acne.
Visible light as monotherapy is not recommended for the treatment of severe nodular/ conglobate acne.

1 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 limit, legal restrictions, availability, drug licensing).
2 Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
3 doxycycline and lymecycline (see Chapter 5.4.2), limited to a treatment period of three months
4 only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion
5 indirect evidence from severe papulopustular acne

5.3.2 Reasoning

General comment: Very few of the included trials (described below) looked specifically at patients with nodular or conglobate acne. As a source of indirect evidence, studies of patients with severe papulopustular acne were used and the percentage in the reduction of nodules (NO) and cysts (CY) in these studies was used. In case of use of such indirect evidence, the strength of recommendation was downgraded for the considered treatment options.

Systemic isotretinoin shows superior efficacy in the treatment of severe nodular/ conglobate acne compared with systemic antibiotics, in combination with a topical treatment systemic antibiotic.

The expert group considered that the greatest effectiveness in the treatment of severe nodular/ conglobate acne in clinical practice is seen with systemic isotretinoin. This can only be partly supported by published evidence, due to the scarcity of clinical trials in conglobate acne.

In the experts' opinion, safety concerns with isotretinoin are manageable if treatment is properly initiated and monitored. Patient benefit with respect to treatment effect, improvement in quality of life and avoidance of scarring outweigh the side effects.

5.3.2.1 Efficacy

See Table 15 for summary of efficacy data. Please see methods report for explanation of assessment strategy.

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Systemic monotherapy versus placebo

Systemic isotretinoin has superior efficacy compared with placebo [104] (LE 4*).

* There is only one trial comparing systemic isotretinoin with placebo in nodular/ conglobate acne resulting only in LE 4. However, there are multiple trials comparing different dosage without a placebo group and following expert opinion, there is no doubt about its superior efficacy.

Systemic monotherapy versus systemic monotherapy or combination

See Table 15 for summary of efficacy data.

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Table 15 Efficacy: Nodular/ conglobate acne

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	Sys. isotretinoin (si)	Sys. tetracycline (st)
Adapalene + tetracycline (a-t)	si = a-t LE 4	ne
Azelaic acid + minocycline (aa-m)	si = aa-m LE 4	ne
Sys. tetracycline (st)	si > st LE 3	X
Top. clindamycin (tc)	ne	st > tc LE 3

LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

Light sources

Due to insufficient evidence, it is not currently possible to make a recommendation for or against treatment with IPL, laser or PDT in conglobate acne. See also 5.2.3.1.

5.3.2.2 Safety/ tolerability

See also Chapter 5.2.3.2 on the tolerability/ safety of papulopustular acne treatments.

From the trials specifically investigating severe nodular/ conglobate acne, very little information is available to compare the different treatment options. Almost all patients

suffer from xerosis and cheilitis during treatment with isotretinoin, whereas systemic antibiotics more commonly cause gastrointestinal adverse events.

5.3.2.3 Patient preference

The systematic review by Dressler et al. [97] did not identify any evidence on the treatment preferences of patients suffering from conglobate acne.

5.3.2.4 Other considerations

For comment on EMA directive see also Chapter 5.4.3.

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5.4 General considerations

5.4.1 Choice of type of topical retinoid

Adapalene should be selected in preference to tretinoin and isotretinoin.

5.4.1.1 Reasoning

All topical retinoids show comparable efficacy against IL (see Chapter 5.2.3.1), whereas against NIL the evidence is conflicting (see Chapter 5.1.2.1).

Among the topical retinoids, adapalene shows the best tolerability/ safety profile followed by isotretinoin and tretinoin (see Chapter 5.2.3.2).

Patient preference favours adapalene over tretinoin (see Chapter 5.2.3.3).

5.4.2 Choice of type of systemic antibiotic

Doxycycline and lymecycline should be selected in preference to minocycline and tetracycline.

5.4.2.1 Reasoning

5.4.2.2 Efficacy

Doxycycline, lymecycline, minocycline and tetracycline all seem to have a comparable efficacy against IL (see Chapter 05.2.3.1).

Tetracycline showed better efficacy compared to clindamycin and comparable efficacy with erythromycin.

5.4.2.3 Safety/ tolerability

From the included trials, no clear results can be drawn as to which antibiotic treatment has the best safety/ tolerability profile.

Smith and Leyden [103] performed a systemic review analyzing case reports on adverse events with minocycline and doxycycline between 1966 and 2003. As a result, they suggest that adverse events may be less likely with doxycycline than with minocycline. More severe adverse events seem to appear during treatments with

minocycline. Doxycycline however, leads to photosensitivity, which is not seen with minocycline.

See also Chapter 5.4.2 Choice of type of systemic antibiotic.

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The most frequent ADRs for doxycycline are manageable (sun protection for photosensitivity and water intake for oesophagitis), whereas the most relevant side effects of minocycline (hypersensitivity, hepatic dysfunction, lupus like syndrome) are not easily managed [105].

The phototoxicity of doxycycline is dependent on dosage and the amount of sun light [106, 107].

There is little information on the frequency of ADRs with lymecycline. Its phototoxicity has been reported to be lower than with doxycycline and its safety profile is comparable to that of tetracycline [105, 108].

More severe drug reactions are experienced during treatment with minocycline compared with doxycycline, lymecycline and tetracycline.

5.4.2.4 Patient preference/ practicability

Doxycycline, lymecycline and minocycline have superior practicability compared with tetracycline due to their requirement for less frequent administration.

5.4.2.5 Other considerations

The use of systemic clindamycin for the treatment of acne is generally not recommended as this treatment option should be kept for severe infections.

5.4.3 Considerations on isotretinoin and dosage

The evidence on the best dosage, including cumulative dosage, is rare and partly conflicting. In most trials, higher dosages have led to better response rates whilst having less favorable safety/ tolerability profiles. Attempts to determine the cumulative dose necessary to obtain an optimal treatment response and low relapse rate have not yet yielded sufficient evidence for a strong recommendation. The following recommendation is based more on expert opinion, than on existing published trials.

For severe papulopustular acne/ moderate nodular acne, a dosage of systemic isotretinoin of 0.3 - 0.5 mg/kg can be recommended.

For conglobate acne a dosage of systemic isotretinoin of ≥0.5 mg/kg can be recommended.

The duration of the therapy should be at least 6 months.

In case of insufficient response, the treatment period can be prolonged.

5.4.4 Oral isotretinoin considerations with respect to EMA directive

Bettoli/ Layton/ Ochsendorf/ Bukvić Mokos

The current European Directive for prescribing oral isotretinoin differs from the recommendations given in this guideline.

The EU directive states: “oral isotretinoin should only be used in severe acne, nodular and conglobate acne, that has or is not responding to appropriate antibiotics and topical therapy” [109]. The inference of this being that isotretinoin should now not be used as first-line therapy.

After almost three decades of experience with oral isotretinoin, the published data and opinion of many experts, including the authors of the EU Acne Guideline, support systemic isotretinoin being considered as the first-choice treatment for severe papulopustular, moderate nodular, and severe nodular/ conglobate acne [13, 110-112]. Acne treatment guidelines written some years ago advocated the use of oral isotretinoin “sooner rather than later” [113]. It is recognized that reduction in inflammatory acne may prevent the occurrence of clinical and psychological scarring, improving quality of life and in some cases reducing depression [114, 115]. Delaying the use of oral isotretinoin, which the group considers to be the most effective treatment for severe acne, poses a significant ethical problem. Although comparative trials are missing, clinical experience confirms that the relapse rates after treatment with isotretinoin are the lowest among all the available therapies.

Unfortunately the European Directive, although not supported by convincing evidence-based data, reached a different conclusion. Theoretically, in EU countries clinicians are free to prescribe drugs, such as oral isotretinoin, according to their professional experience and clinical judgment. However, in the event of any medical problems, clinicians could be deemed liable if they have failed to follow recommended prescribing practice [116].

There are a number of good reasons why systemic isotretinoin should be considered as the first-choice treatment for severe acne, including high levels of clinical effectiveness, prevention of scarring and improvement of a patient’s quality of life.

The EMA recommendations include the following points:

1. To start at the dosage of 0.5 mg/kg daily.
2. Not recommended for patients under 12 years of age.
3. To monitor laboratory parameters, primarily liver enzymes and lipids, before treatment, 1 month after starting and every 3 months thereafter.
4. To avoid laser treatment, peeling and wax epilation for at least 6 months after stopping therapy.

The European Guideline group supports these recommendations of the EMA, although expert opinion suggests that being less than 12 years old (point 2) is not necessarily a contraindication for the use of isotretinoin.

Two areas which are potentially open for future review include dosing regimens and abnormal wound healing as a result of oral isotretinoin.

Dosing regimens

It has been demonstrated that starting with a low dose (0.1-0.2 mg/kg/day) of isotretinoin and progressively increasing to the highest tolerated dose may reduce risk and severity of acne flare-ups and facilitate management of and reduce side effects [117]. Over the last few years there have been an increasing number of reports on oral isotretinoin in more mild to moderate disease in which alternative dosing regimens have aimed to achieve efficacy whilst minimizing side effects from treatment [118-120].

In contrast to this other studies have indicated that higher doses, especially in severe nodular/ conglobate acne, are associated with fewer relapse rates [121, 122]. Hence, where possible higher dosages are recommended in severe acne and lower dosages in less severe forms and as potential maintenance treatment. As differences in pharmacokinetics between different brands of isotretinoin cannot be ruled out it is advisable to get acquainted with a certain product and to use this same preparation throughout a treatment period.

Abnormal wound healing

Current recommendations to avoid acne scar repair procedures within 6 months post oral isotretinoin arose from reports in the mid 1980's of delayed wound healing and hypertrophic scarring with conventional and argon laser dermabrasion. More recent small studies suggest that resurfacing procedures do not always impair wound healing despite treatment being performed during oral isotretinoin treatment or early after cessation of isotretinoin [123]. The results from these studies are confounded by small numbers and information bias (lack of blinding and lack of validated assessments in particular) and a lack of control for confounding variables and selection and publication bias.

The group did not identify any evidence to support the avoidance of laser therapy, wax epilation and peeling for at least 6 months after isotretinoin treatment (point 4) [116]. However, the authors acknowledge that oral isotretinoin could interfere with wound healing albeit relatively rare. As further evidence emerges recommendations to avoid acne scar repair procedures within 6 months post isotretinoin should be reconsidered. Earlier treatment of scarring may provide hope that this issue can be effectively addressed on a timely basis.

5.4.5 Consideration on isotretinoin and the risk of depression

Nast

It is recommended to assess prior symptoms of depression as part of the medical history of any patient before the initiation of isotretinoin and during the course of the treatment.

It is recommended to inform patients about a possible risk of depression and suicidal behaviour.

A search for systematic reviews was performed to assess the risk of depression during the treatment with isotretinoin. Published systematic reviews come to different conclusions. All currently existing reviews have methodological limitations with respect to their stringency of inclusion and exclusion criteria and systematic reporting of identified studies.

The systematic review by Marqueling et al. [124] reported that rates of depression among isotretinoin users ranged from 1 % to 11 % across trials, with similar rates in the oral antibiotic control groups. Overall, included trials comparing depression before and after treatment did not show a statistically significant increase in depression diagnoses or depressive symptoms. Some, in fact, demonstrated a trend toward fewer or less severe depressive symptoms after isotretinoin therapy. This decrease was particularly evident in patients with pre-treatment scores in the moderate or clinical depression range. No correlation between isotretinoin use and suicidal behaviour was reported, although only one retrospective trial presented data on this topic.

A systematic review by Bremner et al. [125] took a variety of aspects into consideration: 1) case reports; 2) temporal association between onset of depression and exposure to the drug; 3) challenge-rechallenge cases; 4) class effect (other compounds in the same class, like vitamin A, having similar neuropsychiatric effects); 5) dose response; and 6) biologically plausible mechanisms. It concluded that the literature reviewed is consistent with an association between isotretinoin administration, depression and suicide in some individuals.

In the light of continued uncertainty with respect to the isotretinoin, depression and suicidal behavior, caution and patient information appears reasonable.

5.4.6 Risk of antibiotic resistance

Simonart/ Ochsendorf/ Oprica/ Lomholt

Treatment of acne with longer courses of topical or systemic antibiotics may lead to the induction of antibiotic resistance. This may contribute to the burden of extra deaths and hospital days due to antibiotic resistant pathogenic bacteria that poses a serious problem in the world today, including in Europe. It is well known that one broad spectrum antibiotic can select for multi-resistance against a number of different antibiotics [126]. Furthermore it has been shown, that even low concentrations of antibiotics well below the MIC value may select for even high-level resistance [127, 128]. The use of antibiotics to treat acne may lead to resistance in local *P. acnes* and other local cutaneous bacteria including staphylococci, but importantly, also in members of the patients total microbiome on skin and mucosal surfaces. Resistance may spread from non-pathogenic to pathogenic species.

The first relevant changes in *P. acnes* antibiotic sensitivity were found in the USA shortly after the introduction of the topical formulations of erythromycin and clindamycin. The molecular basis of resistance, via mutations in genes encoding 23S and 16S rRNA, are widely distributed [129]. However, the development of strains with still unidentified mutations suggests that new mechanisms of resistance are evolving in *P. acnes* [129]. Combined resistance to clindamycin and erythromycin is much more common (highest prevalence 91 % in Spain) than resistance to the

tetracyclines (highest prevalence 26 % in the UK) [130]. Use of topical antibiotics can lead to resistance largely confined to the skin of treated sites, whereas oral antibiotics can lead to resistance in commensal flora at all body sites [131]. Resistance is more common in patients with moderate-to-severe acne and in countries with high outpatient antibiotic sales [132]. Resistance is disseminated primarily by person-to-person contact, and so the spread of resistant strains by the treating physicians and by family and friends occurs frequently [12, 129, 130]. Although some data suggest that resistant isolates disappear after antibiotic treatment is stopped [133, 134], other data suggest that resistance persists and can be reactivated rapidly [135].

There has been an increasing number of reports of systemic infections caused by resistant *P. acnes* in non-acne patients, e. g. post-surgery [132]. In addition, a transmission of factors conferring resistance to bacteria other than *P. acnes* is described [136, 137]. Although antibiotic use in acne patients has been shown to be associated with an increased risk of upper respiratory tract infection and with an increased carriage of *S. aureus* [138], the true clinical importance of these findings requires further investigation.

It has been argued that the most likely effect of resistance is to reduce the clinical efficacy of antibiotic-based treatment regimens to a level below that which would occur in patients with fully susceptible flora [130, 139]. Some trials have suggested a clear association between *P. acnes* resistance to the appropriate antibiotic and poor therapeutic response [130, 139]. There is a gradual decrease in the efficacy of topical erythromycin in clinical trials of therapeutic intervention for acne, which is probably related to the development of antibiotic-resistant propionibacteria [101]. In contrast, there is so far no evidence that the efficacy of oral tetracycline or topical clindamycin has decreased in the last decades [101, 140, 141]. However recent studies show a complex population of *P. acnes* with diverse virulence potential and antibiotic resistance patterns. This may explain the difficulties in predicting the clinical effects of antibiotic treatment of acne [142].

Since *P. acnes* is the major skin commensal bacterium found in both acne and healthy skin, the strain-level analysis is important to help understand the role of *P. acnes* in acne pathogenesis and in skin health. It has been demonstrated that the strain population subtypes or clonotypes were significantly different in acne patients and healthy controls [85, 88]. This data could help determine if therapeutic modulations of the local *P. acnes* flora can return the host to a state of health and may open for new treatment options.

Studies on *P. acnes* resistance have highlighted the need for treatment guidelines to restrict the use of antibiotics in order to limit the emergence of resistant *P. acnes* strains. Data indicate that the combination of topical antibiotics with BPO may prevent the development of resistance in local *P. acnes* and staphylococci [143-148]. However, it is not known if resistance may develop in the periphery or outside the treatment zone due to antibiotic gradients or if a low level of systemic absorption can lead to resistance on mucosal surfaces [149, 150]. There is not good evidence that the combination of local antibiotics with retinoids or zinc is efficient to prevent local resistance in *P. acnes* and no data is available on the effect on other cutaneous or mucosal bacteria [148, 151-154].

It is claimed that low dose systemic doxycycline treatment of acne does not induce bacterial resistance [155]. From a microbiological standpoint this is highly surprising and more studies are needed to confirm this. In particular one study showed development of resistance in subgingival plaques during low dose doxycycline treatment of periodontidis [156].

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As a consequence, the use of systemic antibiotics and topical antibiotics should be limited (both indication and duration) and topical antibiotics should preferably be used in combination with BPO and avoided as monotherapy. Other recommendations include stricter cross-infection control measures when assessing acne in the clinic and combining systemic antibiotic therapy with topical broad-spectrum antibacterial agents, such as BPO [12, 53, 130].

6 Maintenance therapy

Summary of therapeutic recommendations for maintenance therapy with respect to acne type before induction therapy

Recommendations are based on available evidence and expert consensus. Available evidence and expert voting lead to classification of strength of recommendation.

A maintenance treatment, especially for the patients with "particular need for a maintenance treatment" as defined below, is recommended.

The low strength of recommendation provided below reflects primarily the lack of good evidence as to which is the best treatment and does not put into question the need for maintenance therapy in general.

	Comedonal acne	**Mild to moderate papulopustular acne**	**Severe papulopustular/ moderate nodular acne**	**Severe nodular/ conglobate acne**
High strength of recommendation	-	-	-	-
Medium strength of recommen-dation	-	-	-	-
Low strength of recommendation	Azelaic Acid *or* Topical Retinoid [2]	Azelaic Acid *or* BPO *or* Topical Retinoid [2]	Adapalene + BPO (f.c.) [3] *or* Azelaic Acid *or* BPO [3] *or* Low Dose Systemic Isotretinoin (max. 0.3mg/kg/d) *or* Topical Retinoid [2]	Adapalene + BPO (f.c.) [3] *or* Azelaic Acid *or* BPO [3] *or* Low Dose Systemic Isotretinoin (max. 0.3mg/kg/d) *or* Topical Retinoid [2]
Alternatives for females [1]	-	-	Continued Hormonal Antiandrogens [4] + Topical Treatment (apart from antibiotics)	Continued Hormonal Antiandrogens [4] + Topical Treatment (apart from antibiotics)

[1] low strength of recommendation
[2] preference for adapalene over isotretinoin / tretinoin
[3] in case of continuing inflammatory lesions
[4] refer to national guidelines and EMA recommendations for precautions with respect to risk and duration of hormonal antiandrogens/combined oral contraceptives

6.1 Recommendations

<u>High strength of recommendation</u>
None

<u>Medium strength of recommendation</u>

None

Low strength of recommendation

Comedonal acne

Azelaic acid can be considered for the maintenance treatment of comedonal acne.
Topical retinoid [1] can be considered for the maintenance treatment of comedonal acne.

Mild to moderate papulopustular acne

Azelaic acid can be considered for the maintenance treatment of mild to moderate papulopustular acne.
Topical retinoid [1] can be considered for the maintenance treatment of mild to moderate papulopustular acne.

Severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne

The fixed-dose combination adapalene and BPO [2] can be considered for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.
Azelaic acid can be considered for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.
BPO [2] can be considered for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.
Low dose systemic isotretinoin (max. 0.3 mg/kg/d) can be considered for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.
Topical retinoid [1] can be considered for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.
For females: Continued hormonal antiandrogens [3] and topical treatment (apart from antibiotics) can be considered for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

Open recommendation

Due to a lack of sufficient evidence, it is currently not possible to make a recommendation for or against maintenance treatment with red light, blue light, IPL, Laser, PDT or oral zinc.

Negative recommendation

Topical and/or systemic antibiotics as monotherapy or combination therapy are not recommended for maintenance treatment of acne.
Artificial UV radiation is not recommended for maintenance treatment of acne.

[1] preference for adapalene over isotretinoin / tretinoin
[2] in case of continuing inflammatory lesions
[3] refer to national guidelines and EMA recommendations for precautions with respect to risk and duration of hormonal antiandrogens/combined oral contraceptives

6.2 Background

Gollnick/ Dréno

Acne is a chronic inflammatory disease that can persist for a number of years, and is known to have a negative impact on the patients' quality of life. Scarring is the most difficult sequela of the disease and has therefore to be avoided by appropriate early intervention using an evidence based treatment strategy. Acne has the general tendency to relapse; however, very little data exists regarding the frequency and/or severity and/or velocity of relapses.

The strategy for treating acne today includes an induction phase followed by a maintenance phase, and is further supported by adjunctive treatments (light, peeling) and/or cosmetic treatments [157].

Education about the physiopathology and the treatment procedures of acne can enhance patient adherence to maintenance therapy. However, the psychosocial benefits of further reconstituting the skin may be the most compelling reason for consistent maintenance therapy. It may also be helpful to explain to patients that acne is often a chronic disease running over years that requires acute and maintenance therapy for sustained remission.

Definition of maintenance treatment / goals of maintenance treatment

No standard definition for maintenance treatment exists/is used.

The European acne guideline version 2011 stated: 'Maintenance therapy can be defined as the regular use of appropriate therapeutic agents to ensure that acne remains in remission'.

Dressler et al. [158] defined 'maintenance is the treatment period that follows a successful induction therapy at the end of which patients had achieved a pre-defined treatment goal'.

The Board of the Global Alliance for better Outcome of Acne (GA) consented the following treatment goals:

- prevention of relapse of more than 10-20% of inflammatory lesions
- preventing reoccurrence of microcomedones
- further improvement of postinflammatory hyperpigmentation and atrophic scarring

Identification of patients with particular need for maintenance treatment

Adapted from a consensus from the Board of the Global Alliance for better Outcome of Acne (GA) the following predictive factors for relapse may serve as criteria to identify patients with particular need for maintenance therapy:

- history of severe of acne
- family history of chronicity of acne/ persisting acne courses
- tendency for scarring
- time until clearance during interventional treatment

- severe seborrhea
- early and fast onset courses in young adolescents
- early and fast onset of conglobate acne in young adolescents
- patients already having the course of acne tarda or persisting adult acne
- female patients with endocrinological disturbances (clinical or/and serological).
- repeated relapse in medical history after previous therapy

Pathophysiological considerations for the maintenance phase

It has been shown that microcomedones significantly decrease during the active treatment phase but rebound almost immediately after discontinuation of a topical retinoid [159].

Therefore, a maintenance therapy to reduce the potential of reoccurring visible lesions should be considered as part of routine care today. In particular, inflammatory lesions are the prominent marker to be suppressed by topical or combined topical and systemic treatment as soon as possible. They almost develop from the recurrence of microcomedones.

Efficacy and safety during maintenance therapies

A systematic review by Dressler et al. [158] identified four randomized controlled trials and three non-randomized intervention studies on acne maintenance treatment.

Three RCTs [160-162] evaluated adapalene 0.1% gel QD maintenance treatment compared to placebo over the course of 12, 16 and 24 weeks each. The pooled effect of two RCTs evaluating adapalene versus vehicle on 'number of patients maintaining at least 50% improvement achieved in the initial study' was statistically significant based on inflammatory and non-inflammatory lesion count [160, 161]. The 24-week open RCT by Zang et al. [162] also reported a higher mean percentage reduction in total lesion count in the adapalene than in the placebo arm. Adapalene showed superior efficacy in maintaining response on NIL and IL compared to placebo/ vehicle.

Poulin et al. [163] assessed the fixed combination adapalene 0.1%/ BPO 2.5% gel QD compared to vehicle QD as maintenance treatment. A statistically significant difference was found at 12 and 24 weeks based on inflammatory and non-inflammatory lesion count: adapalene/ BPO fixed combination showed superior efficacy on NIL and IL compared to placebo.

Reported data on tolerability and safety was limited. Tolerability was reported by all authors with mild but mostly no burning / stinging, erythema or dryness [158].

There is a strong need to develop more standardized study designs to systematically assess maintenance therapy for acne. Due to the set inclusion and exclusion criteria, many trials reporting on long maintenance treatment could not be included, mostly due to the lack of a clearly defined minimum treatment goal which defines responders to enter into a maintenance phase.

Additional clinical trials

Recent clinical trials have in particular looked for the effect of maintenance therapy on microcomedones. In one of those controlled trials it could be shown that adapalene and azelaic acid have been equivalent in preventing relapse and suppressing microcomedone recurrence [159, 164].

Some other trials which further confirms maintenance therapy to prevent relapse but could not be included because of the guideline rules and less defined maintenance treatment inclusion criteria in the past (see above) should be mentioned here. In a vehicle controlled study by Vender et al. [165] prevention with tretinoin 0.04% gel (microsphere) against relapse was shown in patients having been before successfully treated by oral isotretinoin. In another prospective, randomized, double-blind and vehicle-controlled study of 30 patients with acne previously treated with isotretinoin a retinoid combination (retinsphere technology Bi-retix) was applied to one side of the face and vehicle was applied to the other, once daily, for 3months. The relapse rate was significantly lower on the retinoid-treated side compared to the vehicle-treated side.

6.3 Reasoning

Available evidence indicates efficacy of topical retinoids and adapalene/ BPO over vehicle during maintenance treatment.

Pathophysiological data supports use of topical retinoids and adapalene based on their shown efficacy on microcomedones.

Any use of topical or systemic antibiotics is not recommended on a long-term base / during maintenance therapy.

Duration of long term-treatment

The following maintenance treatment periods can be considered:

- 3 to 6 months following clearing after interventional treatment phase can be recommended
- patients with conglobate acne may need long-term maintenance over 6 to 12 months
- acne tarda patients may need individual long-term maintenance over years.

Disclaimer

The development of guidelines is a time and resource intensive process and currently no public funding is available for European guidelines. In order to be able to produce high quality guidelines the EDF uses its membership contributions and asks its cooperative partners for support.

Corporate partners of the EDF have been asked to contribute towards this work. [insert other companies], [insert other companies], and [insert other companies] have contributed funding for the development of the European evidence-based (S3) guideline for the treatment of acne (update 2016) through an educational grant to the EDF. Sponsors had no influence on the content of the guideline. Support was given independent of any influence on methods or results. Sponsors did not receive any information about methods, group members or likely results. The sources of the funding will be disclosed to the members of the group and the users of the guideline after the finalization of the guideline.

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8 Supporting information

Table S1 Comedonal acne

Table S2 Papulopustular acne

Table S3 Conglobate acne

Document S4 Evaluated studies

Document S5 List of abbreviations

Document S6 Methods report