GUIDELINES

European Evidence-based (S3) Guidelines for the Treatment of Acne

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I Introduction

Nasty/Rzany

I.1 Notes on use of guidelines

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.

I.1. Objectives of the guidelines

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 traded 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 and severe scarring 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, to reduce the development of antibiotic resistance.

I.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 (see Chapter 1.6). Non-primary target groups are patients with special forms of acne, such as, occupational acne, chloracne, acne aestivalis, acne neonatorum, acne inverse (hidradenitis suppurativa).

I.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 prioritization of treatment recommendations. However, if financial resources allow, the suggested ranking in the therapeutic algorithm should be pursued.

I.5 Considerations with respect to vehicle for topical treatments

The skin type 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 largely influenced by the choice of vehicle.

I.6 Considerations with respect to body area

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.

I.7 Clinical features and variants

Layton/Finlay

Acne (synonym 'acne vulgaris') is a polymorphic, inflammatory skin disease most commonly affecting the face (99% of cases). Less frequently it also 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 aggressive fulminate disease with deep-seated inflammation, nodules and in some cases associated systemic symptoms.

I.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.

I.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 deep pustules or 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]

I.7.3 Nodular/conglobate acne

Small nodules are defined as firm, inflamed lesions >5 mm diameter, painful by palpation. Nodules are defined as larger than 5 mm, large nodules are >1 cm in size. 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.

I.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 guidelines do not lend themselves to comprehensive management of all these variants.

II Assessment, comparability of treatment outcomes
Finlay/Layton

II.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, scarring development or economic impact.

There are inherent difficulties in objectively measuring acne. Over 25 different methods have been described[7] but there is no consensus as to which should be used. Most methods are non-validated and consequently the results of separate trials cannot be directly compared. There are detailed reviews on this subject by Barratt et al.,[8] Witkowski et al.,[9] Thiboutot et al.,[10] and Gollnick et al.[11]

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.

II.1.1 Acne grading systems

II.1.1.1 Sign-based methods
Many methods for measuring acne have been described, ranging from global assessments to lesion counting.[7,9] Despite a range of methods being used to measure acne in the 1960's and 1970's, it was the Leeds technique[12] 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 palpating lesions is also 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[13] 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.[14] However, ECLA scores do not correlate with quality of life scores and the use of both disease and quality of life scores is suggested.[15]

II.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 a photographic repertoire with corresponding numeric scale or 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.[16] A simple photographic standard-based grading method using a 0–8 scale has been successfully employed in a number of clinical trials.[17]

In 2005, the US FDA proposed an IGA (investigator global assessment) 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 minimize 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.[16]

A very simple classification of acne severity was described in the 2003 report from the Global Alliance for better outcome of acne treatment.[11] 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 female patients 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.

To give treatment recommendations based on disease activity, the EU Guidelines 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 narrowing rather than a precise mapping (Table 1).

II.1.1.3 Quality of life methods
Simpson and Cunliffe[25] 'consider the use of quality of life and psychosocial questionnaires essential to adequately understanding just how the disease is affecting the patient, and to better understand the progress of the disease'. The impact of acne on quality of life can be measured using general health measures, dermatology-specific measures or acne-specific measures. In order for quality of life measures to be used more frequently in the routine clinical work,

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 these guidelines

Publication	Comedonal acne	Mild–moderate papulopustular acne	Severe papulopustular acne, moderate nodular acne	Severe nodular acne, conglobate acne
Pillsbury 1956[18]	–	1–4	2–4	2–4
Michaelsson 1977[19]	–	0–30	20–30	20 to >30
Cook 1979[17]	0–1	2–4	6	8
Wilson 1980[20]	0	2–4	6–8	8
Allen 1982[21]	0–2	2–6	6	8
Burke (Leeds) 1984[5]	0.5	0.75–2	2–3	3–8
Pochi 1991[16]	Mild	Mild/moderate	Moderate	Severe
O'Brien (Leeds) 1988 (face)[13]	1–3	4–7	8–10	11–12, nodulocystic
Dreno 1999[14]	F1R1–5	F1Is1–4	F1Is4–5, F1Ip 1–4	F1Ip 4–5
Lehmann 2002[7]	Mild	Mild/moderate	Severe	Severe
Gollnick 2003[11]	Mild comedonal	Mild papular–pustular, moderate papular–pustular	Moderate nodular	Severe nodular/conglobate
Layton 2010[22]	–	Mild	Moderate	Severe
Tan 2007[23]	–	Mild: 0–5 papules–pustules	Moderate: 6–20 papules–pustules	Severe: 21–50 papules–pustules, very severe: >50 IL severe
FDA's IGA for acne vulgaris (2005)[24]	1 Almost clear: rare NIL with no more than 1 papule	2 Mild: *some* NIL but no more than a few papule/pustule	3 Moderate: many NIL, some IL no more than 1 nodul 4 Severe: up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions	–

IL: inflammatory lesions; NIL: non-inflammatory lesions.

they need to be easy to use, the scores need to be meaningful and they need to be readily accessible. Clinicians must be convinced that the information gained from using them is of benefit in guiding them to make optimum clinical decisions for their patients, and they need to become aware that the use of these measures may help to justify their clinical decisions. Quality of life measures can influence the choice of therapy. In patients with a severe impact on their quality of life, a more aggressive therapy may be justified.

II.2 Prognostic factors that should influence treatment choice

II.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[26] and Dreno *et al.* 2008[27] 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 menarche are all factors that should alert the clinician to increased likelihood of more severe acne.

II.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 90% of patients attending a dermatology clinic.[28] Scars may show increased collagen (hypertrophic and keloid scars) or be associated with collagen loss. The presence of scarring should support aggressive management and therapy should be commenced early in the disease process.

III Methods
(For further details please see the methods report at http://www.acne-guidelines.com.)

Nast/Rzany

III.1 Nomination of expert group/patient involvement
All experts were officially nominated by the European Dermatology Forum (EDF) or the European Academy of Dermatology and Venereology. They were selected according to their clinical expertise, publication record and/or experience in the field of evidence-based medicine and guideline development. None of the experts received any financial incentive other than reimbursement of travel costs.

Participation of patients was difficult to realize, since no patient organization exists. Attempts to invite patients currently treated by the involved experts did not succeed. Patients were invited to participate in the external review. Patient preference was considered as an important outcome and trials looking at patient preferences were included.

III.2 Selection of included medications/interventions

There is a vast array of treatment options available for acne. The options are further extended by the availability of different vehicles and formulations. When choosing a treatment, different skin types, ethnic groups and subtypes of acne must also be considered.

The authors of this guideline selected the most relevant treatments in Europe to be included in the guideline. The fact that a certain treatment was not selected as a topic for this guideline, does not mean that it may not be a good treatment for acne. Additional treatment options may be considered for a later update.

Fixed-dose combinations were considered as long as they were licensed in a European country (e.g. adapalene + benzoyl peroxide (BPO), clindamycin + BPO, erythromycin + tretinoin, erythromycin + isotretinoin, erythromycin + zinc).

Treatment options consisting of more than two topical components were not included because of the likeliness of reduced patient adherence and/or because of a limitation in the feasibility of discussing all possible combinations and sequences.

III.3 Generation of evidence for efficacy, safety and patient preference

III.3.1 Literature search and evaluation of trials

An extensive search of existing guidelines and systematic reviews was performed at the beginning of the project. The search was performed in Medline, Embase, and Cochrane (for search strategies see the methods report at http://www.acne-guidelines.com). The date of the systematic searches was March 10th 2010 for topical and systemic interventions and April 13th 2010 for laser and light therapies. The results were checked for the inclusion criteria and trial quality using a standardized literature evaluation form. Existing systematic reviews (e.g. Cochrane) and other guidelines served as an additional basis for the body of evidence in this guideline. Pooling of the trials was not attempted due to the lack of common outcome measures and endpoints and the unavailability of some primary data (for details of search strategies, standardized evaluation form and references of included reviews see methods report at http://www.acne-guidelines.com).

III.3.2 Extrapolation of evidence for specific acne types

The aim of this guideline is to give recommendations for specific clinical conditions, e.g. the severity of acne, and not to assess the different medications one by one without respect to clinical stage. However, most trials did not look in detail at subtypes but include patients with 'acne vulgaris' in general. Therefore, for some recommendations, 'indirect evidence' was generated from looking at suitable outcome parameters:

1 The percentage 'reduction of non-inflammatory lesions' was the efficacy parameter considered for comedonal acne.
2 Efficacy in papulopustular acne was assessed by 'reduction in inflammatory lesions', 'reduction in total lesion count' and other acne grading scales.
3 The generation of evidence for nodular/conglobate acne was particularly difficult, since very few trials included nodular/conglobate acne. Consequently, treatment recommendations also took into account indirect data from trials of severe papulopustular acne.

The evidence from clinical trials almost always focuses on facial acne. Trials that examined acne at other locations (e.g. back), were considered as indirect evidence and the level of evidence was downgraded accordingly.

III.3.3 Minimal clinically important difference in assessing the efficacy of two therapeutic options for acne

Very little attention has been given during clinical trials to the question of a minimal clinically important difference from the perspective of the patient. It would be helpful to know the extent of reduction in the number of acne lesions required for patients to consider that there has been a clinically important improvement. One study has been identified that empirically validated a non-inferiority margin of 10–15% for facial acne lesion counts as appropriate.[356]

The consensus view of the authors of this guideline is that a treatment should achieve at least a 10% greater reduction in the number of lesions to demonstrate superior efficacy. Hence, for the evaluation of superior or comparable efficacy throughout the evidence generation process, a 10% difference in efficacy (lesion reduction) was considered relevant.

III.3.4 Qualitative assessment of evidence

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 for the European Psoriasis Guidelines with some adaptations taken from the GRADE system.[29–31]

III.3.4.1 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, limited sample size: at least 15 patients per arm).
(C) Comparative trial with severe methodological limitations (e.g. not blinded, very small sample size, no randomization).

III.3.4.2 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) using the following criteria:

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.

III.3.4.3 Consensus process

All recommendations were agreed in a consensus conference of the authors using formal consensus methodology (nominal group technique). The consensus conference was moderated by Prof. Dr. med. Berthold Rzany MSc, who is a certified moderator for the German Association of Scientific Medical Societies (AWMF). All members of the author committee were entitled to vote in the consensus conference.

In general, a high consensus (>90%) was aimed for. In the absence of a consensus, this was noted in the text and reasons for the difference in views were given. All consensus statements are highlighted in a grey box throughout the text.

To weigh 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

To grade the recommendation a 'standardized guidelines' 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.

III.3.5 Peer review/piloting

An extensive external review was performed. National dermatological societies [European Dermatology Forum (EDF) members], other specialties [paediatrics, gynaecologists, general practitioners as organized in the European Union of Medical Specialists (UEMS)] and patients (patient internet platforms) were invited to participate. Access was open and it was possible for anybody to comment via the internet (using the platform http://www.croco-doc.com). The expert group piloted the guidelines within their own practices and performed a trial implementation within their clinics. (For further details see the methods report at http://www.acne-guidelines.com.).

III.3.6 Implementation, evaluation, updating

Implementation will be pursued at a national level by local medical societies. Materials such as an online version, a short version and a therapeutic algorithm will be supplied.

Strategies for evaluation (e.g. assessment of awareness, treatment adhesion and patient changes) are in preparation and will mostly be pursued at a national level.

Guidelines need to be continually updated to reflect the increasing amount of medical information available. This guideline will not be valid after 31.12.2015. In case of important changes in the meantime (e.g., new licensed drugs, withdrawal of drug licensing, new important information) an update will be issued earlier. The guidelines committee under the coordination of the division of evidence-based medicine (dEBM) will access the necessity for an update by means of a Delphi vote.

IV Epidemiology and pathophysiology

IV.1 Epidemiology
Degitz/Ochsendorf

Acne is one of the most frequent skin diseases. Epidemiological studies in Western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%, depending on the method of lesion counting. If mild manifestations were excluded and only moderate or severe manifestations were considered, the frequency was still 20–35%.[32–35] Acne is a disease primarily of adolescence. It is triggered in children by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of growth. However, to some degree, acne may persist beyond adolescence in a significant proportion of individuals, particularly women.[36] Even after the disease has ended, acne scars and dyspigmentation are not uncommon permanent negative outcomes.[10] Genetic factors have been recognized; there is a high concordance among identical twins,[37] and there is also a tendency towards severe acne in patients with a positive family history for acne.[38] So far little is known about specific hereditary mechanisms. It is probable that several genes are involved in predisposing an individual to acne.

These include the genes for cytochrome P450-1A1 and steroid-21-hydroxylase.[39] Racial and ethnic factors may also contribute to differences in the prevalence, severity, clinical presentation and sequelae of acne.[40,41] Environmental factors also appear to be of relevance to the prevalence of acne; populations with a natural lifestyle seem not to develop acne.[42] In particular, diet has recently gained attention, with epidemiological[43] and investigative studies[44] indicating a correlation between acne and Western diet.

IV.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 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. Oxidized squalene can stimulate hyperproliferative behaviour of keratinocytes, and lipoperoxides produce leukotriene B4, a powerful chemoattractant.

Acne produces chemotactic factors and promotes the synthesis of tumour necrosis factor-α and interleukin-1β. Cytokine induction by *P. acnes* occurs through Toll-like receptor 2 activation via activation of nuclear factor-κB and activator protein 1 (AP-1) transcription factor. Activation of AP-1 induces matrix metalloproteinase genes, the products of which degrade and alter the dermal matrix.

The improved understanding of acne development on a molecular level suggests that acne is a disease that involves both innate and adaptive immune systems and inflammatory events.

V Therapeutic options

5.1 Summary of therapeutic recommendations

Recommendations are based on available evidence and expert consensus. Available evidence and expert voting lead to classification of strength of recommendation (Table 2).

VI Treatment of comedonal acne

VI.1 Recommendations for comedonal acne*

High strength of recommendation
None
Medium strength of recommendation
Topical retinoids† can be recommended for the treatment of comedonal acne
Low strength of recommendation
BPO can be considered for the treatment of comedonal acne
Azelaic acid can be considered for the treatment of comedonal acne
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
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

*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).
†Adapalene (see chapter 9.1).

VI.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.

Choice of topical vs. systemic treatment

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

Table 2 Summary of therapeutic recommendations[*,†]

	Comedonal acne	Mild-to-moderate papulopustular acne	Severe papulopustular/ moderate nodular acne	Severe nodular/conglobate acne§
High strength of recommendation	–	Adapalene + BPO (f.c.) or BPO + clindamycin (f.c.)	Isotretinoin*	Isotretinoin*
Medium strength of recommendation	Topical retinoid‡	Azelaic acid or BPO or topical retinoid‡ or systemic antibiotic† + adapalene¶¶	Systemic antibiotics¶ + adapalene¶¶ or systemic antibiotics¶ + azelaic acid‡‡ or systemic antibiotics + adapalene + BPO (f.c.)	Systemic antibiotics¶ + azelaic acid
Low strength of recommendation	Azelaic acid or BPO	Blue light or oral zinc or topical erythromycin + isotretinoin (f.c.) or topical erythromycin + tretinoin (f.c.) or systemic antibiotic†,¶ + BPO†† *or* systemic antibiotic †,¶ + azelaic acid¶¶ *or* systemic antibiotics †,¶ + adapalene + BPO (f.c.)§§	Systemic antibiotics¶ + BPO††	Systemic antibiotics¶ + BPO†† or systemic antibiotics¶ + adapalene§§,¶¶ or systemic antibiotics¶ + adapalene + BPO (f.c.)§§
Alternatives for female patients	–	–	Hormonal antiandrogens + topical treatment or hormonal antiandrogens + systemic antibiotics**	Hormonal antiandrogens + systemic antibiotics**

*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).

†In case of more widespread disease/moderate severity, initiation of a systemic treatment can be recommended.

‡Adapalene to be preferred over tretinoin/isotretinoin (see Chapter 9.1).

§Systemic treatment with corticosteroids can be considered.

¶Doxycycline and lymecycline (see Chapter 9.2).

**Low strength of recommendation.

††Indirect evidence from a study also including chorhexidin, recommendation additionally based on expert opinion.

‡‡Indirect evidence from nodular and conglobate acne and expert opinion.

§§Indirect evidence from severe papularpustular acne.

¶¶Only studies found on systemic AB + adapalene, isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.

f.c.: fixed combination.

VI.2.1 Efficacy

Superior efficacy was defined as a difference of ≥10% in the reduction of non-inflammatory lesions in head-to-head comparisons (see also Chapter 3.3.3.).

VI.2.1.1 Topical monotherapy vs. placebo

Superior efficacy against NIL compared with placebo is demonstrated by: azelaic acid[45–47] (LE 1), BPO[48–60] (LE 1), and the topical retinoids[49–51,60–75] (LE 1) (Table 3).

Among the topical antibiotics, clindamycin[57,58,72,76–79] (LE 1) and tetracycline[80,81] (LE 1) show superior efficacy against NIL compared with placebo. Topical erythromycin[59,66,82–85] (LE 1) shows only a trend towards superior efficacy against NIL compared with placebo (Table 4).

VI.2.1.2 Topical monotherapy vs. topical monotherapy

The efficacy of adapalene and isotretinoin on NIL is comparable to the efficacy of BPO (adapalene[50,51,60,86–88] LE 1, isotretinoin[49] LE 3; Table 3).

Tretinoin shows a trend for comparable-to-superior efficacy on NIL compared with BPO[89–91] LE 4; Table 3) and superior efficacy compared with azelaic acid (LE 4).

Table 3 Efficacy: comedonal acne – topical therapy vs. topical therapy

Efficacy: comedonal acne – top. therapy vs. top. therapy						
	Placebo/vehicle (v)	BPO	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	BPO > v LE 1	X	BPO > aa LE 3	BPO = a LE 1	BPO = i LE 3	t ≥ BPO LE 4
Azelaic acid (aa)	aa > v LE 1	BPO >aa LE 3	X	aa = a LE 4	ne	t > aa LE 4
Adapalene (a)	a > v LE 1	BPO = a LE 1	aa = a LE 4	X	a = i LE 4	a ≥ t LE 1
Isotretinoin (i)	i > v LE 1	BPO = i LE 3	ne	a = i LE 4	X	i > t LE 4
Tretinoin (t)	i > v LE 1	t ≥ BPO LE 4	t > aa LE 4	a ≥ t LE 1	i > t LE 4	X

a: adepalene; aa: azelaic acid; BPO: benzoyl peroxide; i: isotretinoin; LE: level of evidence; ne: no evidence; top.: topical; t: tretinoin; v: placebo/vehicle.

Table 4 Efficacy: comedonal acne – antibiotics vs. placebo/BPO/azelaic acid/top. retinoids

Efficacy: comedonal acne – antibiotics vs. placebo/BPO/azelaic acid/top. retinoids						
	Placebo/vehicle (v)	BPO	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
Clindamycin (c)	c > v LE 1	BPO ≥ c LE 1	aa > c LE 4	ne	ne	t ≥ c LE 3
Erythromycin (e)	e ≥ v LE 1	BPO > e LE 4	ne	ne	e = i LE 3	ne
Nadifloxacin (n)	ne	ne	ne	ne	ne	ne
Tetracycline (t)	t > v LE 1	BPO > t LE 3	ne	ne	ne	ne

a: adepalene; aa: azelaic acid; BPO: benzoyl peroxide; c: clindamycin; e: erythromycin; i: isotretinoin; LE: level of evidence; n: nadifloxacin; ne: no evidence; t: tetracycline; top: topical; v: placebo/vehicle.

Table 5 Efficacy: comedonal acne – top. combination therapy vs. top. therapy/combinations

Efficacy: comedonal acne – top. combination therapy vs. top. therapy/combinations							
	BPO	Erythromycin (e)	Adapalene (a)	Isotretinoin (i)	Clindamycin (c)	Tretinoin (t)	Clindamycin-BPO (c-BPO)	Adapalene-BPO (a-BPO)
Clindamycin-BPO (c-BPO)	c-BPO = BPO LE 1	ne	a = c-BPO LE 4	ne	c-BPO > c LE 1	ne	X	c-BPO = a-BPO LE 4
Adapalene-BPO (a-BPO)	a-BPO ≥ BPO LE 3	ne	a-BPO ≥ a LE 3	ne	ne	ne	c-BPO = a-BPO LE 4	X
Isotretinoin-erythromycin (ie)	ne	ie = e LE 3	ne	ie = i LE 3	ne	ne	ne	ne
Tretinoin-erythromycin (te)	ne	ne	ne	ne	ne	ne	ne	ne

a: adapalene; BPO: benzoyl peroxide; c: clindamycin; e: erythromycin; i: isotretinoin; LE: level of evidence; ne: no evidence; top.: topical; t: tretinoin.

Benzoyl peroxide shows superior efficacy on NIL compared with topical antibiotics (clindamycin[54–58,92,93] LE 1, tetracycline[94] LE 3, erythromycin[59] LE 4; Table 4).

Benzoyl peroxide shows superior efficacy against NIL compared with azelaic acid[86,95] (LE 3), although there is some conflicting evidence (Table 3).

There are very little data comparing the efficacy of adapalene, topical isotretinoin or topical antibiotics with azelaic acid[45,86,95] (no evidence or LE 4, Tables 3 and 4).

More evidence is available for a comparison of tretinoin and clindamycin, and shows comparable-to-superior efficacy for tretinoin[72,96] (LE 3). The evidence also shows erythromycin to have comparable efficacy to isotretinoin[66] (LE 3, Table 4).

Study results on the comparative efficacies of the topical retinoids against NIL are partly conflicting. The efficacy of adapalene against NIL is comparable, if not superior, to the efficacy of tretinoin[97–106] (LE 1). Isotretinoin, however, shows comparable

efficacy to adapalene[107] (LE 4), and superior efficacy compared with tretinoin[108] (LE 4, Table 3).

VI.2.1.3 Topical combination therapies

The combination of BPO and clindamycin shows comparable efficacy against NIL to monotherapy with BPO[54–58,93,109–112] (LE 1) and superior efficacy compared with clindamycin monotherapy[54–58,93,110] (LE 1, Table 5).

The combination of BPO and adapalene shows a comparable-to-superior efficacy compared with BPO[50,51,60,88] (LE 3) or adapalene alone[50,51,60,88] (LE 3, Table 5).

Erythromycin plus isotretinoin shows comparable efficacy to both erythromycin[66] (LE 3) and isotretinoin alone[66] (LE 3, Table 5).

There were no trials comparing the efficacy of the fixed combination of tretinoin and erythromycin against its components.

The combination of BPO and clindamycin and the combination of BPO and adapalene have comparable efficacy against NIL[113] (LE 4, Table 5).

Since this trial was published after the deadline of literature search, it was not officially included in the assessment, and since the safety/tolerability profile was inferior, the guidelines group did not deem it necessary to update the guideline and to change its conclusions.[114,115]

VI.2.1.4 Laser and light sources

Although there are some studies of the treatment of NIL with laser and light sources, the published evidence is still very scarce. A standardized treatment protocol and widespread clinical experience are still lacking.

VI.2.2 Tolerability/safety

Only one trial looked specifically at comedonal acne. It showed a superior safety/tolerability profile for azelaic acid compared with tretinoin (LE 4).[45]

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 7.2.2 Tolerability/safety.

VI.2.3 Patient preference/practicability

There is only indirect evidence from trials in patients with papulopustular acne that shows a preference among the topical retinoids for adapalene.[116,117]

VI.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 patho-physiological support for the use of topical retinoids for comedonal acne.[118,119]

VI.3 Summary

No high strength recommendation was given because of the general lack of direct evidence for the treatment of comedonal acne.

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

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

The use of a fixed-dose combination of BPO + clindamycin does not lead to a clinically relevant increase in the efficacy against NIL.

The fixed-dose combination of BPO + adapalene shows a trend towards better efficacy against NIL when compared to its components as a monotherapy. However, there is also a trend towards inferiority with respect to the tolerability profile.

The tolerability of topical retinoids and BPO is comparable; there is a trend towards azelaic acid having a better tolerability/safety profile.

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.

There is a lack of standard protocols, experience and clinical trials for the treatment of comedonal acne with laser and light sources.

VII Treatment of papulopustular acne

VII.1 Recommendations

VII.1.1 Mild-to-moderate papulopustular acne*

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 clindamycin and BPO 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
Topical retinoids can be recommended for the treatment of mild to moderate papulopustular acne‡
In case of more widespread disease, a combination of a systemic antibiotic with adapalene can be recommended for the treatment of moderate papulopustular.

Low strength of recommendation

Blue light monotherapy can be considered for the treatment of mild to moderate papulopustular acne

The fixed-dose combination of erythromycin and tretinoin can be considered for the treatment of mild to moderate papulopustular acne

The fixed-dose combination of isotretinoin and erythromycin 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

In case of more widespread disease, a combination of a systemic antibiotic with either BPO or with adapalene in fixed combination with BPO can be considered for the treatment of moderate papulopustular

Negative recommendation

Topical antibiotics as monotherapy are not recommended for the treatment of mild to moderate papulopustular acne

Treatment of mild to moderate papulopustular acne with 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

Open recommendation

Due to a lack of sufficient evidence, it is currently not possible to make a recommendation for or against treatment with red light, IPL, Laser or PDT in the treatment of mild to moderate papulopustular acne

*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).

†Limited to a treatment period of 3 months.

‡Adapalene (see Chapter 9.1).

VII.1.2 Severe papulopustular/moderate nodular acne

High strength of recommendation

Oral isotretinoin monotherapy is strongly recommended for the treatment of severe papulopustular acne

Medium strength of recommendation

Systemic antibiotics can be recommended for the treatment of severe papulopustular acne in combination with adapalene,¶ with the fixed-dose combination of adapalene/BPO or in combination with azelaic acid†,‡

Low strength of recommendation

Oral anti-androgens in combination with oral antibiotics can be considered for the treatment of severe papulopustular acne†,§

Oral anti-androgens in combination with topical treatment can be considered for the treatment of severe papulopustular acne§

Systemic antibiotics in combination with BPO can be considered for the treatment of severe papulopustular/moderate nodular acne

Negative recommendation

Single or combined topical monotherapy is not recommended for the treatment of severe papulopustular acne

Oral antibiotics as monotherapy are not recommended for the treatment of severe papulopustular acne

Oral anti-androgens as monotherapy are not recommended for the treatment of severe papulopustular acne

Visible light as monotherapy is not recommended for the treatment of severe papulopustular acne

Artificial UV radiation sources are not recommended as a treatment of severe papulopustular 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 and laser in severe papulopustular acne

Although PDT is effective in the treatment of severe papularpustular/moderate nodular acne, it cannot yet be recommended due to a lack of standard treatment regimens that ensure a favourable profile of acute adverse reaction

*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).

†Doxycycline or lymecycline, limited to a treatment period of 3 months.

‡Adapalene (see Chapter 9.1).

§Hormonal anti-androgens for female patients.

¶Only studies found on systemic AB + adaplene, Isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.

VII.2 Reasoning

Choice of topical vs. systemic treatment

There are limited data comparing topical treatments with systemic treatments. Most of the available trials compare topical treatment with systemic treatment plus antibiotics. The general impression of a systemic treatment being more effective than a topical treatment could not be confirmed from the included trials. When looking at all comparisons between any topical therapy and systemic antibiotic treatments, five trials showed superiority of topical treatment, ten showed comparable efficacy and only three showed superior efficacy of systemic treatment.

Owing to the risk of the development of antibiotic resistance, topical monotherapy with antibiotics is generally not recommended. 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 treatment is used. In addition, better adherence and patient satisfaction is anticipated. Efficacy can be further enhanced by adding a topical therapy (see below).

VII.2.1 Efficacy

Superior efficacy was defined as a difference of ≥ 10 in head-to-head comparisons (see also Chapter 3.3.3.).

Table 6 Efficacy: papulopustular acne – top. therapy vs. top. therapy

Efficacy: papulopustular acne – top. therapy vs. top. therapy						
	Placebo/vehicle (v)	BPO	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	BPO > v LE 1	X	BPO = aa LE 2	BPO = a LE 2	BPO > i LE 3	Conflicting LE 4
Azelaic acid (aa)	aa > v LE 1	BPO = aa LE 2	X	aa = a LE 4	ne	ne
Adapalene (a)	a > v LE 1	BPO = a LE 2	aa = a LE 4	X	i = a LE 4	a = t LE 2
Isotretinoin (i)	i > v LE 1	BPO > i LE 3	ne	i = a LE 4	X	i = t LE 4
Tretinoin (t)	t > v LE 1	conflicting LE 4	ne	a = t LE 2	i = t LE 4	X

a: adapalene; aa: azelaic acid; BPO: benzoyl peroxide; i: isotretinoin; LE: level of evidence; ne: no evidence; top.: topical; t: tretinoin; v: placebo/vehicle.

Table 7 Efficacy: papulopustular acne – top. combination therapy vs. top. therapy/combinations

Efficacy: papulopustular acne – top. combination therapy vs. top. therapy/combinations							
	BPO	Erythromycin (e)	Adapalene (a)	Isotretinoin (i)	Clindamycin (c)	Tretinoin (t)	Clindamycin-BPO (c-BPO)
Clindamycin-BPO (c-BPO)	c-BPO > BPO LE 1	ne	c-BPO > a LE 4	ne	c-BPO > c LE 1	ne	X
Adapalene-BPO (a-BPO)	a-BPO ≥ BPO LE 3	ne	a-BPO > a LE 1	ne	ne	ne	c-BPO = a-BPO LE 4
Isotretinoin-erythromycin (ie)	ne	ie = e LE 3	ne	ie > i LE 3	ne	ne	ne
Tretinoin-erythromycin (te)	ne	ne	ne	ne	ne	ne	ne
Zinc-erythromycin (ze)	ne	conflicting LE 4	ne	ne	ze > c LE 4	ne	ne

a: adapalene; BPO: benzoyl peroxide; c: clindamycin; e: erythromycin; i: isotretinoin; LE: level of evidence; ne: no evidence; top.: topical: t: tretinoin; z: zinc.

VII.2.1.1 Topical monotherapy vs. placebo
Superior efficacy against IL, compared with placebo, is observed with topical antibiotics (erythromycin[59,66,82–85,120–125] LE 1, clindamycin[58,72,76–79,126–133] LE 1, tetracycline[80,81,134] LE 1, nadifloxacin[135] LE 4), azelaic acid[45–47] (LE 1), BPO[48–56,58–60,136–140] (LE 1) and topical retinoids (adapalene[50,51,60–64] LE 1, isotretinoin[49,65,66,141] LE 1, tretinoin[67–75,133,142,143] LE 1).

VII.2.1.2 Topical monotherapy vs. topical monotherapy
The efficacy of azelaic acid against inflammatory lesions is comparable to the efficacy of BPO[86,95,144] (LE 2, Table 6).

The efficacy of adapalene against IL is comparable to the efficacy of azelaic acid[86] (LE 4); there are no trials comparing isotretinoin or tretinoin with azelaic acid (Table 6).

The efficacy of BPO is comparable to the efficacy of adapalene[50,51,60,86–88] (LE 2); there is conflicting evidence for BPO compared with tretinoin[89–91,145] (LE 4) and there is one trial indicating superior efficacy of BPO over isotretinoin[49] (LE 3, Table 6).

The efficacy of adapalene is comparable to the efficacy of tretinoin[97–106,146] (LE 2) and isotretinoin[107] (LE 4). The efficacy of tretinoin is comparable to efficacy of isotretinoin[108] (LE 4).

Monotherapy with topical antibiotics is not recommended due to the risk of antibacterial resistance, and so is not further considered within this section; please see tables for individual trial results.

VII.2.1.3 Topical monotherapy vs. topical fixed-combinations (BPO/clindamycin, BPO/adapalene, tretinoin/isotretinoin, erythromycin/zinc)
The combination of adapalene and BPO against IL shows superior efficacy compared with adapalene alone[50,51,60,88] (LE 1) and has comparable-to-superior efficacy compared with BPO alone[50,51,60,88] (LE 3, Table 7).

The combination of clindamycin and BPO shows superior efficacy against IL compared with BPO alone[54–56,58,93,109,111,112,136,147] (LE 1) or clindamycin alone[54–56,58,93,136,147] (LE 1, Table 7).

Table 8 Efficacy: papulopustular acne – top. therapy vs. sys. therapy

Efficacy: papulopustular acne – top. therapy vs. sys. therapy				
	Sys. isotretinoin/clindamycin/ erythromycin/lymecycline	Sys. tetracycline (st)	Minocycline (m)	Doxycycline (d)
BPO	ne	ne	BPO = m LE 3	d > BPO LE 4
Azelaic acid (aa)	ne	st ≥ aa LE 3	ne	ne
Clindamycin (c)	ne	c = st LE 1	c ≥ m LE 3	ne
Erythromycin + zinc (ez)	ne	ez > st LE 3	ez > m LE 4	ne
Erythromycin (e)	ne	e > st LE 3	ne	ne
Top. tetracycline (tt)	ne	st ≥ tt LE 3	ne	ne

aa: azelaic acid; BPO: benzoyl peroxide; c: clindamycin; d: doxycycline; e: erythromycin; LE: level of evidence; m: minocycline; ne: no evidence; sys.: systemic; top.: topical; t: tetracycline; z: zinc.

Table 9 Efficacy: papulopustular acne – sys. therapy vs. sys. monotherapy/sys.–top. combination

Efficacy: papulopustular acne – sys. therapy vs. sys. monotherapy/sys.–top. combination					
	Sys. isotretinoin (si)	Clindamycin (c)	Sys. tetracycline (st)	Lymecycline (l)	Doxycycline (d)
Doxycycline + top. adapalene (d-a)	ne	ne	ne	ne	d-a = d LE 4
Doxycycline + top. adapalene + BPO (d-a-BPO)	ne	ne	ne	ne	d-a-BPO > d LE 3
Minocycline + azelaic acid (m-aa)	m-aa = si LE 4	ne	ne	ne	ne
Sys. tetracycline + top. tetracycline (st-tt)	ne	ne	st-tt > st LE 4	ne	ne
Tetracycline + top. adapalene (t-ta)	si > t-ta LE 4	ne	ne	ne	ne
Lymecycline + adapalene (l-a)	ne	ne	ne	l-a > l LE 4	ne

a: adapalene; aa: azelaic acid; BPO: benzoyl peroxide; c: clindamycin; d: doxycycline; LE: level of evidence; l: lymecycline; m: minocycline; ne: no evidence; sys.: systemic; top.: topical; t: tetracycline.

The combination of adapalene and BPO against IL shows comparable efficacy to the combination of clindamycin and BPO[113] (LE 4, Table 7).

The combination of erythromycin and isotretinoin against IL shows a superior efficacy compared with isotretinoin alone[66] (LE 3) and is comparable to erythromycin alone[66] (LE 3, Table 7).

There were no trials comparing the combination of erythromycin and tretinoin to its individual components.

There is insufficient evidence for the additional benefit of adding topical zinc to topical erythromycin.[148,149] (LE 3, Table 7).

VII.2.1.4 Topical monotherapy vs. systemic monotherapy
There are no trials comparing topical retinoids with systemic treatments.

Systemic treatment is generally considered to be more efficacious than a topical treatment, however, this could not be con-

firmed from the included trials. Of all comparisons between any topical therapy and systemic antibiotic treatments, three trials showed superiority of topical monotherapy,[150–152] ten showed comparable efficacy[80,127,128,153–159] and only three showed superior efficacy for systemic therapy[81,160,161] (Table 8). However, the definition of acne severity grades, inclusion criteria and trial methodology were not always comparable.

Evidence would suggest that efficacy is not increased by switching from a topical treatment to a systemic antibiotic treatment. Instead, a topical-systemic combination treatment should be considered.

VII.2.1.5 Systemic monotherapy vs. combination of topical therapy and systemic therapy
All included trials combining a topical treatment with a systemic antibiotic treatment showed at least a trend towards increased efficacy with combination therapy.

Table 10 Efficacy: papulopustular acne – contraceptives vs. systemic antibiotic

Efficacy: papulopustular acne – contraceptives vs. systemic antibiotic			
	Tetracycline (t)	**Lymecycline (l)**	**Minocycline (m)**
EE-CPA	EE-CPA > t LE 3	ne	EE-CPA = m LE 4
EE-CPA + tetracycline	EE-CPA + t > t LE 3	ne	ne

EE-CPA: etinylestradiol and cyproteronacetate; LE: level of evidence; l: lymecycline; m: minocycline; ne: no evidence; t: tetracycline.

The combination of systemic doxycycline with topical adapalene showed a trend towards superior efficacy compared with doxycycline alone[162] (LE 4). Adapalene combined with BPO and systemic doxycycline showed superior efficacy compared with doxycycline alone[115] (LE 3, Table 9).

The combination of lymecycline and adapalene shows superior efficacy compared with lymecycline monotherapy[163] (LE 4, Table 9).

VII.2.1.6 Systemic monotherapy vs. other systemic monotherapy

There are no trials comparing systemic isotretinoin and monotherapy with systemic antibiotics.

Systemic isotretinoin shows a comparable efficacy against IL to minocycline plus azelaic acid[164] (LE 4). However, isotretinoin showed a more rapid onset of action (Table 9).

Systemic isotretinoin shows superior efficacy compared with tetracycline plus adapalene[165] (LE 4, Table 9).

Minocycline[166] (LE 3) and tetracycline[167] (LE 3) both show superior efficacy compared with zinc.

From the available data, it is very difficult to draw conclusions on the differences in efficacy between the anti-androgens.

Ethinylestradiol and cyproteronacetate (EE-CPA) show superior efficacy compared with ethinylestradiol and levonorgestrel (EE-LG)[168–170] (LE 2).

EE-CPA shows comparable efficacy to ethinylestradiol and desogestrel (EE-DG)[171–174] (LE 4).

Ethinylestradiol and chlormadinon (EE-CM) show superior efficacy compared with EE-LG[175] (LE 4).

Ethinylestradiol and drospirenone (EE-DR) show comparable efficacy to ethinylestradiol and norgestimate (EE-NG)[176] (LE 3).

EE-DG shows comparable efficacy to EE-LG[177–179] (LE 3). This, however, can be influenced by the dosage used.

The evidence comparing oral contraceptives with systemic antibiotic therapy is scarce and conflicting: minocycline shows comparable efficacy to EE-CPA[180] (LE 4), whereas EE-CPA shows superior efficacy compared with tetracycline[181] (LE 3). Combining EE-CPA and tetracycline shows no superior efficacy compared with EE-CPA alone[181] (LE 3, Table 10).

VII.2.1.7 Laser and light sources

Blue light has superior efficacy against IL/total lesion (TL) compared with placebo[182,183] (LE 3).

There is conflicting evidence regarding the efficacy of red light compared with placebo.

There is insufficient evidence regarding the efficacy of all other light and laser interventions compared with placebo.

A standardized treatment protocol and widespread clinical experience are still lacking.

VII.2.2 Tolerability/safety

To determine whether or not a safety and tolerability profile was 'superior', the number of drop-outs due to adverse events and the frequency and relevance and severity of the side effects were taken into consideration. In addition, an individual global assessment was performed.

VII.2.2.1 Topical monotherapy

The data on azelaic acid (15% or 20%) show a trend towards a superior tolerability/safety profile compared with BPO (5%)[86,95,144] (LE 3), topical adapalene[86] (LE 4) and tretinoin[45] (LE

Table 11 Safety/tolerability: papulopustular acne

Safety/tolerability: papulopustular acne					
	BPO	**Azelaic acid (aa)**	**Adapalene (a)**	**Isotretinoin (i)**	**Tretinoin (t)**
BPO	X	aa > BPO LE 3	BPO = a LE 4	BPO = i LE 4	BPO = t LE 4
Azelaic acid (aa)	aa > BPO LE 3	X	aa > a LE 4	ne	aa > t LE 4
Adapalene (a)	BPO = a LE 4	aa > a LE 4	X	a > i LE 4	a > t LE 4
Isotretinoin (i)	BPO = i LE 4	ne	a > i LE 4	X	i > t LE 4
Tretinoin (t)	BPO = t LE 4	aa > t LE 4	a > t LE 4	i > t LE 4	X

a: adepalene; aa: azelaic acid; BPO: benzoyl peroxide; i: isotretinoin; LE: level of evidence; ne: no evidence; t: tretinoin.

Table 12 Safety/tolerability: papulopustular acne – top. combinations vs. monotherapy or combination therapy

Safety/tolerability: papulopustular acne – top. combinations vs. monotherapy or combination therapy							
	BPO	Erythromycin (e)	Adapalene (a)	Isotretinoin (i)	Clindamycin (c)	Tretinoin (t)	Clindamycin-BPO (c-BPO)
Clindamycin-BPO (c-BPO)	c-BPO = BPO LE 1	ne	c-BPO > a LE 4	ne	c > c-BPO LE 3	ne	X
Adapalene-BPO (a-BPO)	BPO > a-BPO LE 3	ne	a ≥ a-BPO LE 4	ne	ne	ne	c-BPO > a-BPO LE 4
Isotretinoin-erythromycin (ie)	ne	ie = e LE 4	ne	ie = i LE 4	ne	ne	ne
Tretinoin-erythromycin (ie)	ne	ne	ne	ne	ne	ne	ne
Zinc-erythromycin (ze)	ne	e > ze LE 4	ne	ne	ze = c LE 4	ne	ne

a: adapalene; BPO: benzoyl peroxide; c: clindamycin; e: erythromycin; LE: level of evidence; ne: no evidence; top.: topical.

4). There is no evidence for a comparison with isotretinoin (Table 11).

Benzoyl peroxide has a comparable tolerability/safety profile to topical retinoids (adapalene[50,51,86–88] LE 4, isotretinoin[49] LE 4 and tretinoin[89–91,145] LE 4). Lower concentrations of BPO show a trend towards a better tolerability/safety profile (Table 11).

Among the topical retinoids, adapalene (LE 4) shows the best tolerability/safety profile followed by isotretinoin (LE 4) and tretinoin (LE 4) (Table 11).

Data on the safety and tolerabilities of combination therapies with topical antibiotics are not described, since topical antibiotics are not recommended as monotherapy.

VII.2.2.2 Topical combination therapies
The combination of BPO and clindamycin shows a similar tolerability/safety profile during the treatment of IL compared to monotherapy with BPO[54–56,58,93,109,111,112,136,147] (LE 1) and an inferior profile to monotherapy with clindamycin alone (LE 3, Table 12).

Benzoyl peroxide alone shows a superior safety/tolerability profile compared with a combination of BPO and adapalene[50,51,88] (LE 3), whereas adapalene has a comparable-to-superior safety/tolerability profile[50,51,88] (LE 4, Table 12).

The combination of erythromycin and isotretinoin shows a similar tolerability/safety profile to erythromycin or isotretinoin alone[66] (LE 4, Table 12).

The combination of BPO and clindamycin shows a superior safety/tolerability profile compared with the combination of BPO and adapalene[113] (LE 4).

VII.2.2.3 Topical monotherapy vs. 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.

In trials comparing topical and systemic treatments drop-out rates due to drug-related adverse events are higher in the topical treatment groups than in the systemic treatment groups (top. 24 patients vs. syst. 11 patients/11 trials,[127,128,151–154–160,184,185] assuming a similar distribution of patients in systemic and topical

Table 13 Safety/tolerability: papulopustular acne – sys. therapy vs. sys. monotherapy/sys.–top. combination

Safety/tolerability: papulopustular acne – sys. therapy vs. sys. monotherapy/sys.–top. combination					
	Sys. iso-tretinoin (si)	Clindamycin (c)	Sys. tetracycline (st)	Lymecycline (l)	Doxycycline (d)
Doxycycline + top. adapalene (d-a)	ne	ne	ne	ne	d-a = d LE 4
Doxycycline + top adapalene + BPO (d-a-BPO)	ne	ne	ne	ne	d-a-BPO = d LE 4
Minocycline + azelaic acid (m-aa)	m-aa > si LE 4	ne	ne	ne	ne
Sys. tetracycline + top. tetracycline (st-tt)	ne	ne	st-tt = st LE 4	ne	ne
Tetracycline + top. adapalene (t-ta)	ne	ne	ne	ne	ne
Lymecycline + adapalene (l-a)	ne	ne	ne	l > l-a LE 4	ne

a: adapalene; BPO: benzoyl peroxide; c: clindamycin; d: doxycycline; l: lymecycline; LE: level of evidence; m: minocycline; ne: no evidence; sys.: systemic; top.: topical; t: tetracycline.

arms). In six of the trials no information on drop-outs was provided.[80,81,150,155,156,161]

No reasonable conclusion seems justified with the available evidence, however, no immediate superiority of either systemic or topical treatment is apparent.

VII.2.2.4 Systemic antibiotics vs. systemic antibiotics
From the included trials, no clear conclusion can be drawn as to which antibiotic treatment has the best safety/tolerability profile.

Smith and Leyden[186] performed a systemic review analysing 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.

The 2003 Cochrane review from Garner *et al.*[187] provided no further clear evidence on the safety profile of minocycline and doxycycline and underlines the ongoing debate and need for further evidence.

See also Chapter 9.2 Choice of type of systemic antibiotic.

Treatment with anti-androgens

From the included trials, no clear comparison of the safety/tolerability profiles of anti-androgens with other systemic treatments can be made. An assessment to compare the safety profile of the different anti-androgens is out of the scope of these guidelines. For the use of anti-androgens, 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 9.5.) (Table 13).

VII.2.3 Patient preference/practicability
Split-face trials show a patient preference for adapalene over tretinoin[188,189] (LE 3).

VII.2.4 Other considerations
For further discussion on the use of isotretinoin as a first line treatment for severe papulopustular acne, see Chapter 9.3.

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. However, the dose response rates, the relapse rates after treatment and the pharmacoeconomic calculations strongly favour systemic isotretinoin.

VII.3 Summary
The best efficacy against IL was found to be achieved with the fixed-dose combinations of BPO plus adapalene and BPO plus clindamycin, when compared with topical monotherapies.

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

Systemic monotherapy with antibiotics shows no superiority to topical treatments, therefore combining systemic therapy with a topical agent should always be preferred.

For severe cases, a 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.

VIII Treatment nodular/conglobate acne

VIII.1 Recommendations*,†

High strength of recommendation
Oral isotretinoin is strongly recommended as a monotherapy for the treatment of conglobate acne
Medium strength of recommendation
Systemic antibiotics can be recommended for the treatment of conglobate acne in combination with azelaic acid
Low strength of recommendation
Oral anti-androgens in combination with oral antibiotics can be considered for the treatment of conglobate acne‡,§
Systemic antibiotics in combination with adapalene, BPO or the adapalene-BPO fixed-dose combination can be considered for the treatment of nodular/conglobate acne
Negative recommendation
Topical monotherapy is not recommended for the treatment of conglobate acne.
Oral antibiotics are not recommended as monotherapy for the treatment of conglobate acne
Oral anti-androgens are not recommended as monotherapy for the treatment of conglobate acne
Artificial UV radiation sources are not recommended for the treatment of conglobate acne
Visible light as monotherapy is not recommended for the treatment of conglobate acne
Open recommendation
Due to lack of sufficient evidence, it is currently not possible to make a recommendation for or against treatment with IPL, or laser in conglobate acne
Although PDT is effective in the treatment of moderate 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

*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).

†Expert opinion: for the initial treatment phase with isotretinoin a combination with oral corticosteroids treatment can be considered in conglobate acne.

‡Doxycycline or lymecycline limited to a treatment period of 3 months.

§Hormonal anti-androgens for female patients.

VIII.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.

VIII.2.1 Efficacy
Superior efficacy was defined as a difference of ≥ 10 in head-to-head comparisons (see also Chapter 3.3.3).

VIII.2.1.1 Systemic monotherapy vs. placebo
Systemic isotretinoin has superior efficacy compared with placebo[190] (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.

VIII.2.1.2 Topical monotherapy vs. systemic monotherapy
Systemic treatment with tetracycline has superior efficacy against noduls/cycsts (NO/CY) compared with topical clindamycin[153] (LE 3).

Systemic treatment with tetracycline has a comparable efficacy against NO/CY to azelaic acid[155] (LE 3).

VIII.2.1.3 Systemic monotherapy vs. systemic monotherapy
There are eight trials comparing different dosage regimens of systemic isotretinoin. Most of these used 0.5 mg/kg bodyweight as one comparator. With this dosage, the mean reduction of NO/CY was around 70%.[191–198]

Systemic isotretinoin shows superior efficacy against NO/CY compared with systemic minocycline[199] (LE 4) or systemic tetracycline[200] (LE 3, Table 14).

Systemic isotretinoin shows comparable efficacy to systemic minocycline combined with topical azelaic acid[164] (LE 4, Table 14).

Systemic isotretinoin shows comparable efficacy against deep IL (indirect evidence) to systemic tetracycline in combination with topical adapalene[165] (LE 4).

The addition of topical clindamycin and topical adapalene to systemic isotretinoin does not provide superior efficacy compared with isotretinoin monotherapy[201] (LE 4, Table 14).

VIII.2.1.4 Laser and light sources
Due to there being insufficient evidence, it is not currently possible to make a recommendation for or against treatment with IPL, laser or PDT in conglobate acne.

Table 14 Efficacy: nodular/conglobate acne

Efficacy: nodular/conglobate acne		
	Sys. tetracycline (st)	Sys. isotretinoin (si)
Top. clindamycin (tc)	st > tc LE 3	ne
Azelaic acid (aa)	aa = st LE 3	ne
Sys. minocycline (sm)	ne	si > sm LE 4
Sys. tetracycline (st)	ne	si > st LE 3
Azelaic acid + minocycline (aa-m)	ne	si = aa-m LE 4
Tetracycline + adapalene (t-a)	ne	si = t-a LE 4
Isotretinoin + clindamycin + adapalene (i-c-a)	ne	si = i-c-a LE 4

a: adapalene; aa: azelaic acid; c: clindamycin; i: isotretinoin; LE: level of evidence; m: minocycline; ne: no evidence; sys.: systemic; top.: topical; t: tetracycline.

VIII.2.2 Tolerability/safety
See also Chapter 7.2.2 on the tolerability/safety of papulopustular acne treatments.

From the trials specifically investigating 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 (LE 4).

VIII.2.3 Patient preference/practicability
There is no evidence on the treatment preferences of patients suffering from conglobate acne.

VIII.2.4 Other considerations
For comment on EMEA directive see also Chapter 9.3.

VIII.3 Summary
Systemic isotretinoin shows superior/comparable efficacy in the treatment of conglobate acne compared with systemic antibiotics in combination with topical treatments. The expert group considers that greatest effectiveness in the treatment of conglobate acne in clinical practice is seen with systemic isotretinoin, although this can only be partly supported by published evidence, because of the lack 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.

There are insufficient data on the efficacy of other treatment options for conglobate acne.

There is a lack of standard protocols, experience and clinical trial data for the treatment of papulopustular acne with laser and light sources other than blue light.

IX General considerations

IX.1 Choice of type of topical retinoid
Adapalene should be selected in preference to tretinoin and isotretinoin.

IX.1.1 Reasoning/summary
All topical retinoids show comparable efficacy against IL (see Chapter 7.2.1.2), whereas against NIL the evidence is conflicting (see Chapter 6.2.1.2).

Among the topical retinoids, adapalene shows the best tolerability/safety profile followed by isotretinoin and tretinoin (see Chapter 7.2.2).

Patient preference favours adapalene over tretinoin (see Chapter 7.2.3).

IX.2 Choice of type of systemic antibiotic
Doxycycline and lymecycline should be selected in preference to minocycline and tetracycline.

IX.2.1 Reasoning
General comment: In addition to the literature included in the guidelines, the Cochrane review on the efficacy and safety of minocycline[187] and the systematic review by Simonart *et al.*[202] were taken into consideration.

IX.2.2 Efficacy
Doxycycline, lymecycline, minocycline and tetracycline all seem to have a comparable efficacy against IL (see Chapter 7.2.2.4).

There is a trend towards comparable-to-superior efficacy for tetracycline compared with clindamycin[203,204] and erythromycin[205–207] (LE 4).

IX.2.3 Tolerability/safety
From the included trials, no clear results can be drawn as to which antibiotic treatment has the best safety/tolerability profile.

The 2003 Cochrane review from Garner *et al.*[187] provides no further clear evidence on the safety profiles of minocycline and doxycycline. The review showed no significant difference in the number of dropouts due to adverse events when comparing minocycline with doxycycline, lymecycline or tetracycline. Overall, an adverse drug reaction (ADR) was experienced by 11.1% of the 1230 patients receiving minocycline, 13.1% of the 415 patients receiving tetracycline or oxytetracycline and 6.1% of the 177 patients receiving doxycycline.

Two analyses of reported ADRs have shown lower incidence rates and lower severity of ADRs with doxycycline compared with minocycline.[186,208]

The most frequent ADRs for doxycycline are manageable (sun protection for photosensitivity and water intake for oesophagitis), whereas the most relevant side effects of monocycline (hypersensitivity, hepatic dysfunction, lupus like syndrome) are not easily managed.[209]

The phototoxicity of doxycycline is dependent on dosage and the amount of sun light.[210,211]

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.[209,212]

IX.2.4 Patient preference/practicability
Doxycycline, lymecycline and minocycline have superior practicability compared with tetracycline due to their requirement for less frequent administration. The Cochrane review by Garner *et al.* included one trial showing a patient preference for minocycline over tetracycline.[187]

IX.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.

IX.2.6 Summary
The efficacies of doxycycline, lymecycline, minocycline and tetracycline are comparable.

Tetracycline has a lower practicability and patient preference compared with doxycycline, lymecycline and minocycline.

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

IX.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 lead to better response rates whilst having less favourable 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

IX.4 Oral isotretinoin considerations with respect to EMEA directive
Bettoli/Layton/Ochsendorf

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

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."[213] The inference of this being that it should now not be used at all 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 Guidelines, support systemic isotretinoin being considered as the first-choice treatment for severe papulopustular, moderate nodular, and severe nodular/conglobate acne.[11,214–216] Acne treatment guidelines written some years ago pointed out that oral isotretinoin should be used 'sooner rather than later'.[217] It is well known that a quick reduction of inflammation in acne may prevent the occurrence of clinical and psychological scarring and also significantly improves quality of life and reduces the risk of depression.[218,219] 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, reach a different conclusion. Theoretically, in EU countries clinicians are free to prescribe drugs, such as oral isotretinoin, according to their professional experience. However, in the event of any medical problems, they could be deemed liable if they have failed to follow recommended prescribing practice.[220]

For many reasons, systemic isotretinoin must be considered the first-choice treatment for severe acne: clinical effectiveness, prevention of scarring and quick improvement of a patient's quality of life.

The EMEA 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 Guidelines group agrees with these recommendations of the EMEA, although expert opinion suggests that being less than 12 years old (point 2) does not necessarily contra-indicate the use of isotretinoin and we did not identify any evidence to support the avoidance of wax epilation and peeling for at least 6 months after isotretinoin treatment (point 4).[220]

IX.5 Consideration on isotretinoin and the risk of depression
Nast

A systematic literature search to investigate the risk of depression during treatment with isotretinoin was not conducted. To specifically assess this issue at an evidence-based level, the data presented in the included trials were supplemented with the systematic review by Marqueling et al.[221] They reported that rates of depression among isotretinoin users ranged from 1% to 11% across trials, with similar rates in oral antibiotic control groups. Overall, 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 towards 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. The current literature does not support a causative association between isotretinoin use and depression; however, there are important limitations to many of the trials. The available data on suicidal behaviour during isotretinoin treatment are insufficient to establish a meaningful causative association. Prior symptoms of depression should be part of the medical history of any patient before the initiation of isotretinoin and during the course of the treatment. Patients should be informed about a possible risk of depression and suicidal behaviour.

IX.6 Risk of antibiotic resistance
Simonart/Ochsendorf/Oprica

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.[222] However, the development of strains with still unidentified mutations suggests that new mechanisms of resistance are evolving in *P. acnes*.[222] 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).[223] 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.[224] Resistance is more common in patients with moderate-to-severe acne and in countries with high outpatient antibiotic sales.[225] 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.[10,222,223] Although some data suggest that resistant isolates disappear after antibiotic treatment is stopped,[226] other data suggest that resistance persists and can be reactivated rapidly.[227]

There have been an increasing number of reports of systemic infections caused by resistant *P. acnes* in non-acne patients, e.g.

post-surgery.[225] In addition, a transmission of factors conferring resistance to bacteria other than *P. acnes* is described.[82,228] Although antibiotic use in acne patients has been shown to be associated with an increased risk of upper respiratory tract infection, 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.[223,229] Some trials have suggested a clear association between *P. acnes* resistance to the appropriate antibiotic and poor therapeutic response.[223,229] 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.[230] In contrast, there is so far no evidence that the efficacy of oral tetracycline or topical clindamycin has decreased in the last few decades.[165,202,230]

Studies on *P. acnes* resistance have highlighted the need for treatment guidelines to restrict the use of antibiotics to limit the emergence of resistant strains. As a consequence, the use of systemic antibiotics should be limited (both indication and duration) and topical antibiotic monotherapy should be avoided. Other recommendations include stricter cross-infection control measures when assessing acne in the clinic and combining any topical/systemic antibiotic therapy with broad-spectrum antibacterial agents, such as BPO.[10,27,223]

X Maintenance therapy
Dréno/Gollnick

This chapter is based on expert opinion and a narrative literature review only. These recommendations were not generated by systematic literature search with formalized consensus conference.

Acne lesions typically recur for years, and so acne is nowadays considered to be a chronic disease.[12] It has been shown that microcomedones significantly decrease during therapy but rebound almost immediately after discontinuation of a topical retinoid. Hence, the strategy for treating acne today includes an induction phase followed by a maintenance phase, and is further supported by adjunctive treatments and/or cosmetic treatments. Therefore, a maintenance therapy to reduce the potential for recurrence of visible lesions should be considered as a part of routine acne treatment. However, it is important to emphasize the lack of definitions surrounding the topic. One possible definition is: 'Maintenance therapy can be defined as the regular use of appropriate therapeutic agents to ensure that acne remains in remission'.

Since 1973 it has clearly been shown that, after a controlled intervention phase with oral antibiotic and topical tretinoin, patients continuing to receive the topical retinoid in a controlled maintenance phase experience a significantly lower relapse rate.[231]

Several controlled trials have now been performed with topical retinoids to show the value of maintenance treatment, with a topical retinoid decreasing the number and preventing the development of microcomedones in different severity grades of acne.

To date, adapalene regimens have been most extensively studied as maintenance treatments for acne in four controlled trials (one on micro comedones) and two uncontrolled trials.

One clinical trial evaluating tazarotene and one involving maintenance treatment with tretinoin after oral tetracycline and tretinoin topical treatment have also been published. In all except one trial (Bettoli *et al.*[232] after oral isotretinoin therapy), topical retinoid monotherapy was been evaluated after an initial 12 weeks of combination therapy comprising a topical retinoid plus an oral or topical antibiotic. The majority of trials has lasted 3–4 months (up to 12 months) and shows a significant trend towards continuing improvement with topical retinoid maintenance therapy and relapse when patients stop treatment. This suggests that a longer duration of maintenance therapy is likely to be beneficial.

Two open studies with long-term use of adapalene have been conducted,[233,234] providing additional evidence supporting the concept of maintenance therapy.[235]

Topical azelaic acid is an alternative to topical retinoids for acne maintenance therapy. Its efficacy and favourable safety profile are advantageous for long-term therapy.[236]

To minimize antibiotic resistance, long-term therapy with antibiotics is not recommended as an alternative to topical retinoids. If an antimicrobial effect is desired, the addition of BPO to topical retinoid therapy is preferred.

In future studies, it would be useful to present data on the proportion of patients who were able to maintain a defined level of improvement (e.g., 50% from baseline). Other issues that should be addressed include creating a standardized definition of successful maintenance, determining the most appropriate patient populations for maintenance therapy and identifying the ideal length of observation of patients.

For a successful long-term treatment, any acne maintenance therapy must be tolerable, appropriate for the patient's lifestyle and convenient. The natural history of acne suggests that maintenance therapy should continue over a period of months to years depending upon the patient's age. Ongoing research will help to define the optimal duration of therapy and, perhaps, refine patient selection. Some patients with significant inflammation may need to be treated with a combination of topical retinoid and antimicrobial agents. This should be further studied.

Education about the pathophysiology of acne can enhance patient adherence to maintenance therapy. However, the psychosocial benefits of clearer skin may be the most compelling reason for consistent maintenance therapy. Finally, it may also be helpful to explain to patients that acne is often a chronic disease that requires acute and maintenance therapy for sustained remission.

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XI Supporting information

Additional supporting information may be found in the online version of this article:

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Table S3 Conglobate acne

Table S4 Laser and light treatment

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