

Swiss Practice Recommendations for the Treatment of Acne

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Short Title: Treatment Recommendations Acne

Key Message: These treatment recommendations provide practical guidance for the choice of induction treatment and maintenance therapy of acne that is indicated in all patients independent of disease severity; furthermore, the choice of therapy should be based on acne severity, duration of disease, current treatment and history of relapse.

Keywords: Acne, Swiss Treatment Recommendations, Acne Severity, Induction Therapy, Maintenance Therapy

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Abstract

Acne is one of the most common skin diseases. It has a high impact on the quality of life of the affected patients. It is now recognized that in some patients, acne shows characteristics of a chronic disease. Nonetheless, there are no current recommendations/guidelines from Switzerland available on the management of acne. For this reason, a group of hospital and private practice based dermatologists, specialized in acne, as well as an experienced general practitioner revised the available literature on acne and its treatment. This group subsequently developed several consensus statements regarding grading, treatment and monitoring of acne. The experts agreed that acne severity should be determined by a subjective method and that, for short-term therapy, treatment success is defined as an approximately 50% reduction of inflammatory lesions within 3 months.

The choice of induction treatment is based on the severity of the disease. Its main component is a topical retinoid alone or – in more severe case – in combination with benzoyl peroxide (BPO). Only in moderate to severe forms of acne or if a more rapid resolution of inflammatory lesions is desired, a systemic antibiotic should be added to induction treatment. For severe acne with a tendency to scarring, systemic retinoids are the induction treatment of choice in the absence of contra-indications. Maintenance therapy is indicated in all patients with acne, independent of disease severity. The choice of maintenance therapy should always be based on acne severity, duration of disease, current treatment and history of relapse. The preferred options for maintenance therapy are topical retinoids with/without BPO. While treating acne, a special focus should lie on the prevention of scars. For this reason, patients should be evaluated 3 months after treatment initiation to determine whether they have responded or whether further therapeutic options should be considered. The expert group also recommends counselling patients on nutrition, psychological aspects, stress, use of contraceptives, skin care, use of cosmetics and use of other drugs (like steroids). Monitoring of patients with acne should particularly focus on compliance and quality of life. Patients with severe forms of acne (acne with a tendency of scarring, patients with acne conglobata or acne fulminans), patients with insufficient treatment response after 3 months and patients with frequent relapses should be referred to a dermatologist.

Introduction

Incidence and burden of acne

Acne is one of the most common skin diseases seen in everyday practice. About 75% to 90% of adolescents show some acne lesions and the disease is often persisting into adulthood [1, 2]. Acne is not a disease of the modern age. Already in 1931, a Swiss study found a prevalence of acne of 88 to 99% in young men and of 88 to 97% in young women [3].

Acne is often judged as a natural part of growing up, as a simple and self-limiting disease. However, it is now recognized that in some patients, acne shows characteristics that generally can be found in chronic diseases such as a prolonged course, a pattern of recurrence or relapse and a manifestation in acute episodes or in outbreaks with slow onset [4]. An update from the global burden of disease study 2013, published in 2017, found that skin conditions contributed by 1.79% to the global burden of disease, measured in disability-adjusted life years (DALYs). Acne is ranging on second place with 0.29% of the total burden [5]. In addition, many studies have shown that acne can be a psychologically damaging condition that lasts for many years [6-11]. Acne may also cause scarring which will even aggravate the negative psychological effects and the burden of this disease [4].

About 60% of the adolescents affected by acne have a mild form [1]. These patients, in general, treat their acne by using non-prescription preparations without consulting their physician. The remaining 40% of acne patients seek medical advice and treatment [1].

Pathophysiology of acne

Different pathophysiological factors contribute to the development of acne. There is an increased activity of the sebaceous glands with modifications in quality and quantity of sebum production (seborrhea). Alterations in the differentiation of the follicular keratinocytes lead to hyperkeratosis. Hyper-colonization with *Cutibacterium acnes* is responsible for the formation of a biofilm triggering an immune response [12, 13].

It seems that there are many more factors involved in the development of acne than expected. Already in early acne

lesions interleukin-1-alpha and T-cells can be detected. In addition, androgens, skin lipids as well as regulatory neuropeptides are part of this multifactorial process [1,12-15]. Androgens, especially dehydroepiandrosterone sulfate, cause a proliferation of follicular keratinocytes with micro-comedo formation and hyperproliferation of sebocytes followed by an increased sebum production. Excess androgen activity in puberty causes inflammatory processes, which are intensified by neuroendocrine regulatory mechanisms, follicular bacteria, pro-inflammatory sebaceous lipids and smoking. It seems that insulin resistance as well as hyperinsulinemia also play an essential role in the development of acne. Increased levels of insulin-like growth factor 1 correlate with the total number of acne and inflammatory lesions [14].

Clinical features and severity

Acne is a polymorphic chronic inflammatory skin disease [16]. In most cases, it is affecting the face but frequently the back and chest are also affected. Clinically, open and/or closed comedones as well as inflammatory lesions including papules, pustules and nodules can be found. Often scarring and post inflammatory hyperpigmentation can be seen.

Rationale and objective

Although acne is common and has a tremendous impact on the quality of life of the patients – not only due to its acute episodes but also due to the potential of scarring – there are no current treatment recommendations/guidelines for Switzerland [16,17].

As many acne patients are treated by their general practitioner, there is a need for convenient practical guidance on the management of acne. The objective of this publication is to provide such guidance based on a review of the current literature and expert consensus.

Methods

A group of hospital and private practice based dermatologists, specialized in acne, as well as an experienced general practitioner have met to revise the available literature on acne and its treatment. Based on the literature and under the lead of the first author of this publication, several expert statements – for example regarding grading of disease severity, treatment goals and treatment options – have been developed. Then, in a multi-step approach using the Delphi method, the whole group of experts has reviewed and revised the different statements until at least 80% of the experts agreed to them [18]. These statements (marked in italics) will be presented hereafter.

Practice recommendations on acne management

Determination of acne severity

Acne severity should be determined by a physician's subjective method that assesses which lesions are predominant. In most of the cases the subjective method is sufficient. In cases where a precise documentation is required, e.g. when the therapy must be changed or when continuity in medical care cannot be ensured, the use of the objective Leeds-Method is recommended (Fig. 1) [19]. To describe the treatment of acne based on the subjective method, the following classification was used in these recommendations: (1) mild, (2) mild to moderate, (3) moderate to severe and (4) severe acne. Subjective assessment of severity is generally not very reliable because of high inter- and intraevaluator discrepancies. However, its reliability can be improved using a picture based support. There are different existing classification systems and they are difficult to compare [16]. However, to link this subjective classification with the Leeds revised acne grading and a picture based support, the following mapping, based on Nast et al. 2016 [16], is suggested by the expert group:



Fig. 1. Suggested objective acne classification for the face: To link the subjective classification (mild, mild to moderate, moderate to severe and severe acne) the use of the objective Leeds-Method is recommended. Mild acne: Leeds face 1-3; Mild to moderate acne: Leeds face 4-7; Moderate to severe acne: Leeds face 8-10; Severe acne: Leeds face 11-12.



Fig. 2. Suggested objective acne classification for the back and upper chest: To link the subjective classification mild, mild to moderate, moderate to severe and severe acne the use of the objective Leeds-Method is recommended. Mild acne: Leeds back and upper chest 1-2; Mild to moderate acne: Leeds back and upper chest 3-4; Moderate to severe acne: Leeds back and upper chest 5-6; Severe acne: Leeds back and upper chest 7-8.

Mild acne: Leeds face 1-3; Mild to moderate acne: Leeds face 4-7; Moderate to severe acne: Leeds face 8-10; Severe acne: Leeds face 11-12.

Mild acne: Leeds back and upper chest 1-2; Mild to moderate acne: Leeds back and upper chest 3-4; Moderate to severe acne: Leeds back and upper chest 5-6; Severe acne: Leeds back and upper chest 7-8.

Definition of treatment success

There was consensus in the expert group that short-term treatment success is defined as more than approximately 50% reduction of inflammatory lesions within 3 months. Resolution of non-inflammatory lesions may take longer. The long-term therapeutic goal for most patients is a "clear or almost clear" skin (clear = no lesions, almost clear = hardly visible from a social distance, a few comedones and papules). The time necessary to reach this goal depends on many factors. A major factor is the acne severity before treatment. As treatment success in acne can vary, therapeutic goals have to be discussed with the patient. Patient satisfaction should be one of the main factors to determine treatment success.

Induction therapy

• Induction therapy in mild acne

In mild acne, topical retinoids with low irritation potential (e.g. Adapalene 0.1%) should be used as induction therapy [16]. Topical retinoids are the preferred substance because of their ability to suppress the formation of new microcomedones. They should be applied on the entire affected area, not on single lesions. In mild acne with predominantly papulopustular or inflammatory lesions benzoyl peroxide (BPO) can also be considered as induction therapy. Azelaic acid can be considered as 2nd line topical therapy, e.g. for patients suffering from skin irritation, during pregnancy or if pregnancy is planned.

• Induction therapy in mild to moderate acne

Induction therapy in mild to moderate acne should be performed either with a combination therapy OR with topical retinoid alone switching to combination after 6-12 weeks, depending on the treatment success [16]. The preferred treatment strategy is the combination of retinoid/BPO. If irritation is a problem retinoid-BPO can be used intermittently, every other day, or a combination of tretinoin with clindamycin can be used. If there is a predominance of papulopustular acne, initiation with BPO/clindamycin or tretinoin/clindamycin is an option.

• Induction therapy in moderate to severe acne

A combination of high-dose topical retinoid (e.g. Adapalene 0.3%) with BPO might be used for induction therapy in moderate to severe acne [17, 20, 21]. In case of irritation an alternative treatment should be offered, for example the combination of tretinoin with clindamycin or BPO/clindamycin. The addition of a systemic antibiotic to a topical retinoid and BPO can be considered, e.g. if a patient wants a fast symptom relief, if many inflammatory lesions are present and to avoid scarring. This might also improve compliance with treatment.

• Induction therapy in severe acne

Systemic isotretinoin is the current gold standard for induction therapy in severe acne, except in case of contraindications [16]. Further indications for an induction therapy with isotretinoin are early tendency for scarring, previous topical treatments with insufficient response or a severe psychological burden through the acne [22]. A daily dose of systemic isotretinoin of at least 0.5 mg/kg body weight in severe cases (or at least 0.3mg/kg body weight in moderate cases with early tendency for scarring, previous topical treatment failure or severe psychological burden), given over a sufficiently long period of time, may prevent the patient from acne relapse. The maximal total dose should be 120-150 mg/kg body weight, but may vary, based on acne severity. Patients should be treated until the skin is "clear or almost clear". If the treatment goal is reached, induction therapy with isotretinoin should be continued for another 2 to 3 months without tapering and then maintenance treatment should be initiated.

Due to its side effects profile and to improve patient adherence, isotretinoin should only be administered by dermatologists and specialists with adequate experience with this treatment modality. Contraindications as well as regular clinical and laboratory follow-up have to be strictly observed and pregnancy prevention is of utmost importance (for more details see www.swissmedinfo.ch).

If contraindications to isotretinoin exist or based on patients' preference systemic antibiotics in combination with a topical retinoid plus BPO may be considered as second line treatment option in patients with severe acne.

• Use of antibiotics in induction therapy

Both topical and systemic antibiotics should only be used in combination with topical retinoids and/or BPO. If systemic antibiotics are used, doxycycline and lymecycline (which is less phototoxic) should be preferred over minocycline for the treatment of moderate to severe acne [23, 24].

Although minocycline has shown good efficacy in the treatment of moderate to severe acne, it may cause severe drug reactions and the risk-benefit profile must be assessed. In addition, a twice-daily administration regimen might affect patient's compliance [25-27]. Due to those reasons, minocycline is not considered as a first choice for acne treatment.

Maintenance therapy

• Indication for maintenance therapy

Maintenance therapy is recommended in all patients, regardless of acne severity [17, 28]. There was consensus in the expert group that when the long-term treatment goal "clear or almost clear" is achieved, a switch to maintenance therapy is recommended.

• Choice of maintenance therapy

There was consensus in the expert group that the choice of maintenance therapy should always be based on severity of illness, duration of illness, current treatment and history of relapse.

In maintenance therapy, the use of a topical retinoid with/without BPO is recommended. Retinoids have a unique mode of action, reducing formation of acne precursor lesions (microcomedones) and limiting development of new lesions [17, 29]. Retinoids maintain skin clearance and may prevent scar formation [30,31]. After successful treatment of moderate to severe acne the preferred maintenance therapy is the combination of a retinoid with BPO [17]. If a high dose of topical retinoid/BPO was used during induction therapy, a switch to a lower dose of topical retinoid/BPO or a retinoid alone can be considered for maintenance treatment.

The therapy regimen chosen can be applied daily or every other day. Azelaic acid is a good alternative for maintenance treatment.

Combinations used for topical maintenance therapy should not contain any antibiotics, due to the potential risk of antibiotic resistance.

In more complicated cases (e.g. for patients treated with oral isotretinoin) the choice of maintenance therapy may differ. Therefore, these cases should be managed by a specialist.

• Duration of maintenance therapy

The experts group agreed that maintenance therapy should generally last at least 6 months, and if necessary (e.g. in case of previous severe acne or some flares during maintenance therapy) up to 12 months or longer [16].

Prevention of scars

Effective treatment should include prevention of scars with early adequate treatment according to acne severity and individual tendency of scarring. Patients should be evaluated 3 months after treatment initiation to determine whether they have responded or whether further therapeutic options should be considered. It is the shared responsibility of the treating physician and the patient that acne is treated effectively to prevent acne scar formation [28,30].

Skin care

Topical and systemic acne therapy has an irritation potential and may induce photosensitivity. It is important to discuss this issue with the patients in order to protect them from side effects and to ensure treatment compliance. It is recommended to apply topical retinoids and BPO in the evening.

Skin care should take into account patient preferences, age, acne severity, actual skin condition and concomitant drug therapy. Light formula moisturizing products (oil/water emulsion) should be preferred. Day and night skin care lotions have to be oil free and should not contain comedogenic ingredients (e.g. paraffin). Emulsifier free and fat free lotions are most appropriate. Skin cleanser should be soap free (pH 4.5 to 5.5). Depending on the situation, the use of an oil free sun lotion may be recommended.

A periodic physical comedones removal can be considered, in particular when open and closed comedones and inflammatory lesions are present. This should be particularly considered when starting treatment with oral isotretinoin in order to prevent flare up during the first weeks of isotretinoin treatment.

Further counselling

The expert group recommends providing further counselling on nutrition, psychological aspects, stress, use of contraceptives, skin care, use of cosmetics, smoking and use of other drugs (like steroids) to the patient.

Practice recommendations for monitoring

• Compliance

A treatment plan containing goals regarding acne severity/lesions and timelines should be agreed upon with the patient [32]. Also, potential side effects should be explained in order to improve treatment adherence.

• Quality of life

Quality of life is an important issue for patients with acne. It should be assessed and monitored in patients with acne, either by informal assessment during consultation or standardized instruments such as the Dermatology Life Quality Index (DLQI).

Referral to a dermatologist/other specialists

Severe forms of acne (including acne with a tendency of scarring, patients with acne conglobata or acne fulminans) should be referred to a dermatologist (or other specialist) for an expert opinion.

Further reasons for referral are:

- Patients with insufficient response after 3 months as defined in the recommendation
- Patients with frequent relapses
- Patients with severe acne and other dermatologic/rheumatologic symptoms (syndromal acne), acne in the context of virilisation or putative hormonal disorders.

Expert referral may also be beneficial for patients showing non-compliance with acne therapy or for patients who are not satisfied with the therapy.

Conclusion

Acne is a frequently occurring skin disease. In many cases it is not just a self-limiting condition of teenagers. It is now recognized that acne shows some characteristics of a chronic disease and can have a severe psychological and social impact. Therefore, early and aggressive treatment is warranted and maintenance treatment is recommended in all patients for optimal outcomes. The treatment recommendations presented here want to provide guidance for the choice of treatment options in acne of variable severity.

Tab. 1. Overview of treatment recommendations for the induction and maintenance therapy of acne.

	Mild acne	Mild to moderate acne	Moderate to severe acne	Severe acne
	Leeds face 1-3	Leeds face 4-7	Leeds face 8-10	Leeds face 11-12
Induction Therapy 1st choice	Topical retinoid or BPO (to be considered when predominantly papulopustular or inflammatory lesions)	Topical retinoid + BPO or Topical retinoid alone, after 3 months: Topical retinoid + BPO	High-dose topical retinoid + BPO or Topical retinoid + BPO *	Systemic isotretinoin
Alternative	Azelaic acid	If papulopustular lesions are predominant, initiation with: BPO + clindamycin or tretinoin + clindamycin	In case of irritation: tretinoin + clindamycin or BPO + clindamycin	If contraindication to isotretinoin or patient's preference: systemic antibiotics ** with retinoid + BPO
Maintenance 1st choice	Topical retinoid w or w/o BPO		Topical retinoid + BPO	
Alternative	Azelaic acid		Retinoid alone or Azelaic acid	
	No antibiotics, due to the potential risk of antibiotic resistance			

* Addition of systemic antibiotics to be considered

** If systemic antibiotics are used, doxycycline and lymecycline (which is less phototoxic) should be preferred over minocycline due to potential severe drug-reactions.

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Disclosure Statement

Antonio Cozzio: Advisory board member for AbbVie, Celgene, Galderma, Lilly, Janssen, MSD, Novartis, Pfizer, Sanofi, Leo

Jean-Philippe Görög: Advisory board member for Galderma

Laurence Imhof: Advisory board member for Galderma
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Emmanuel Laffitte: Advisory board member and/or speaker and/or investigator for AbbVie, Celgene, Galderma, Lilly, Janssen, MSD, Novartis, Pfizer, Sanofi, Leo.

Severin Läubli: Advisory board member and/or speaker for AbbVie, Galderma, Meda, Mimedx, Urgo.

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Nikhil Yawalkar: Advisory board member for Galderma.

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Author Contributions

All authors participated in consensus statement development and in the drafting, critical revision and approval of the final version of the manuscript.

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