



S2k guideline: Rosacea

Professional Societies involved:

DDG – Deutsche Dermatologische Gesellschaft (German Dermatological Society)

BVDD – Berufsverband der Deutschen Dermatologen (Professional Association of German Dermatologists)

SGDV – Schweizerische Gesellschaft für Dermatologie und Venerologie (Swiss Society for Dermatology and Venereology)

GD – Gesellschaft für Dermopharmazie (Society for Dermatopharmaceutics)

Deutsche Rosazea Hilfe e.V. (German Rosacea Aid)

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Summary

This updated and upgraded S2k guideline deals with the diagnosis and treatment of rosacea, which is a common, chronic inflammatory skin disease mostly affecting the face. Initially, rosacea is characterized by recurrent erythema, telangiectasia and flushing. Later, the inflammatory component predominates, with persistent erythema with follicular papules, papulopustules and pustules. The development of phyma, which usually occurs on the acral localizations, is the most severe manifestation. For the treatment of rosacea, the interdisciplinary guideline committee, with representatives of the German Dermatological Society (DDG), the Professional Association of German Dermatologists (BVDD), the German Ophthalmological Society (DOG), the Society for Dermopharmacy (GD), the Swiss Society for Dermatology and Venereology (SGDV) and the German Rosacea Aid e. V., recommends the avoidance of trigger factors and topical applications of metronidazole, azelaic acid or ivermectin. For

symptomatic treatment of persistent centrofacial erythema, the topical vasoconstrictors brimonidine or oxymetazoline can also be used. Systemic therapy is recommended for therapy-resistant and severe forms of rosacea papulopustulosa. The drug of choice is low-dose doxycycline. Alternatively, low-dose isotretinoin can be recommended. Ocular rosacea should be treated with lid margin hygiene. For topical treatment, ciclosporin eye drops, azithromycin, ivermectin or metronidazole are suggested.

Introduction

For a standardized representation of the recommendations, the wordings and symbols listed in Table 1 were used.

This guideline is an updated version of the German guideline which was last published in 2013, but has now been upgraded to the level of S2k. Some passages were adopted from the earlier version [2].

Overview of therapeutic options

The following figure offers an overview of the therapeutic options for rosacea (Figure 1, adapted from [3]).

Definition

Rosacea is a common, chronic-inflammatory disease which mostly affects the face (especially cheeks and nose, but

occasionally also forehead and chin) but can also involve the eyes. It is most frequently found in middle-aged adults with light skin (Fitzpatrick types I and II). This dermatosis was until recently categorized into distinct subtypes according to clinical presentation, with the subtypes occurring chronologically one after the other. Lately, a classification of rosacea according to defined phenotypes has been recommended

Epidemiology

There are hardly any reliable data on the epidemiology of rosacea. A British study found an incidence of 165 diagnosed cases per 100,000 inhabitants per year [4].

Prevalence of rosacea differs from study to study. A systematic review with meta-analysis of 41 patient cohorts covering a total number of 26 million persons found prevalences between 0.09 % and 22.41 % with an average of 5.46 % [5]. In Germany, a general prevalence of 2.3 % was

Table 1 Strengths of recommendation – wording, symbolism and interpretation (modified in accordance to Kaminski-Hartenthaler et al., 2014 [1]).

Strength of Recommendation	Wording	Symbol	Interpretation
Strong recommendation in favor of a procedure	“is recommended”	↑↑	In our opinion, all or nearly all informed people would decide in favor of this procedure. Clinicians need to spend less time with the patient when deciding on this procedure. In most clinical situations, this procedure can be considered a general recommendation.
Weak recommendation in favor of a procedure	“is suggested”	↑	In our opinion, most informed people would decide in favor of this procedure, but a substantial minority would not. Clinicians and other health professionals need to take more time with the patient to make sure that choosing this procedure with its possible consequences reflects the individual patient’s values and preferences. Decision procedures in the health care system require in-depth discussion and inclusion of many persons involved in the process.
No recommendation regarding a procedure	“may be considered”	○	At this point in time, no recommendation for or against a certain procedure can be given due to certain circumstances – for example lack of evidence, unclear or unfavorable benefit-risk balance, etc.)
Recommendation against a procedure	“is not recommended”	↓	In our opinion, all or nearly all informed people would decide against this procedure.

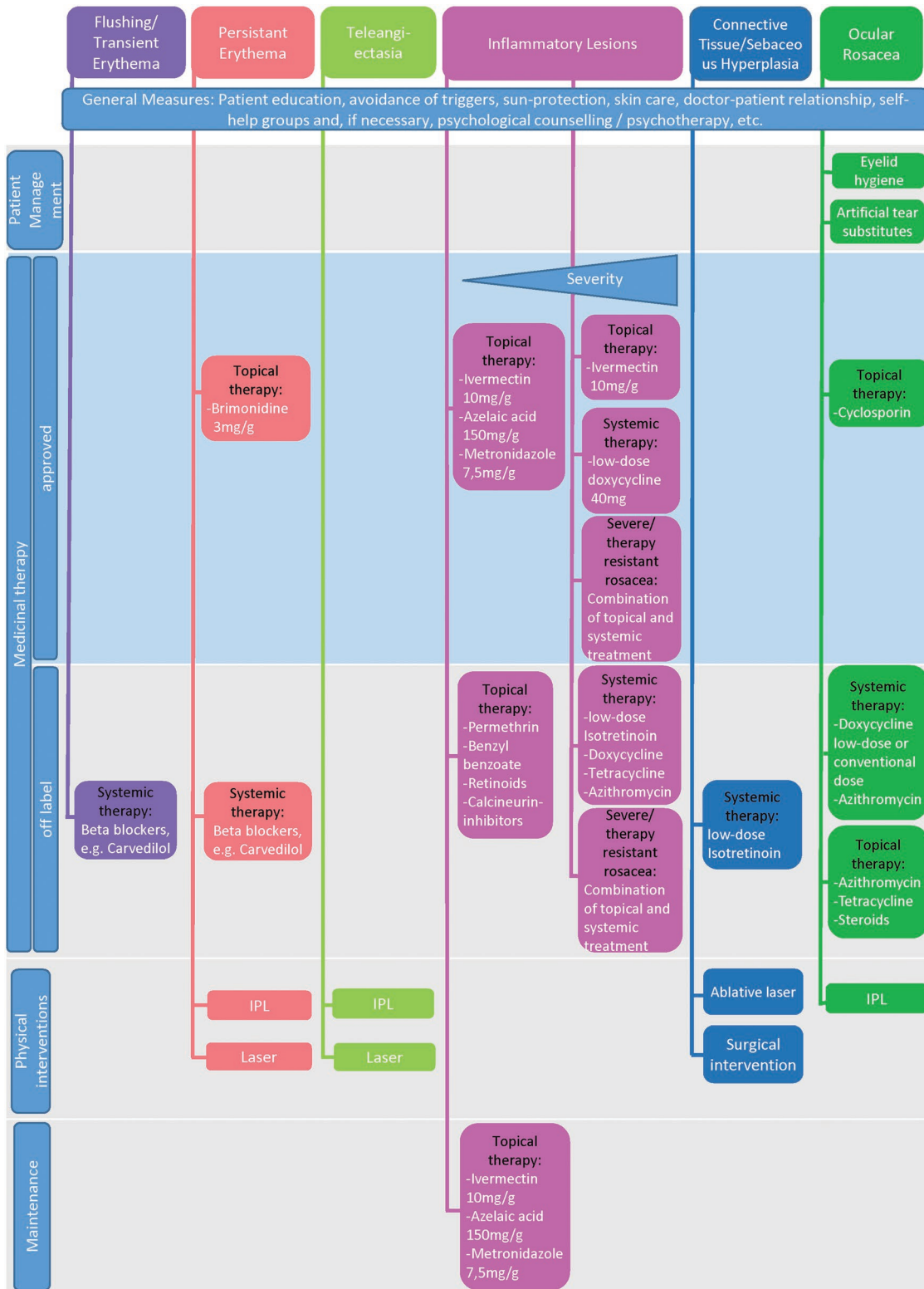


Figure 1 Overview of treatment options (adapted from Schaller et al. 2016) [3].

calculated in 2014, based on statutory health insurance data from a total of 90,800 people. According to this analysis, the highest prevalence found was 6.24 % in the age group between 45 and 60 [6].

Data on the sex distribution of rosacea are conflicting.

Rosacea is most frequently diagnosed in persons with light, Celtic skin (Fitzpatrick I–II) and much less frequently in persons with skin types IV–VI [7, 8]. This however is not due to a lower prevalence but to a larger diagnostic gap since clinical presentation in persons with skin types IV–VI is less clear [7]. A world-wide, systematic review did not find any differences of prevalence according to latitudes [5].

Pathogenesis

Both genetic and environmental influences contribute to the development of rosacea. The initial mechanisms leading to early forms of rosacea remain unknown. As with other chronic-inflammatory skin diseases, innate and adaptive immune responses as well as the vascular system (blood and lymph

system) and the neuronal system play a role. A genetic base for rosacea has been suspected for a long time, indicated by epidemiological data, but has not yet been scientifically proven. Genetic studies on polymorphisms and twin studies indicate that a genetic predisposition for the development of rosacea is very probable [9]. The connection between this predisposition and the trigger factors typical for rosacea (see below) on the molecular level are however still unclear [10–13].

Trigger factors for rosacea and their possible cellular activation pathways are listed in Table 2 [12].

Clinical presentation

General

In the vast majority of cases, rosacea affects the centropacial skin. The nose and cheeks are affected very frequently, and the forehead and chin frequently. More rarely, adjacent skin areas such as the neck, cleavage, and scalp may also be involved.

Table 2 Trigger factors of rosacea and potential activation pathways.

Trigger factors	Published incidence in (%)	Presumed cellular activation pathways
UV radiation	81	NALP3, TLR2, TRPV4
Emotional stress	79	NALP3, TLR2, TRPV1
“Hot” weather	75	TRPV1,2
Wind	57	NALP3, TLR2, TRPV(?)
Strenuous exercise	56	NALP3, TLR2, TRPV1
Alcohol intake (some but not all patients, depending on alcohol concentration)	52	NALP3, TLR2, TRPV1, TRPV2
Hot baths	51	TRPV1, TRPV2
Very cold weather	46	TRPA1
Spicy food	45	TRPV1
Humidity/osmotic changes	44	TRPV3, TRPV4
Changes from cold to heat and vice-versa	41	TRPV1
Some cosmetics and skin care products	41	NALP3, TLR2, TRPA1
Hot steam	36	TRPV1
Some types of make-up, some topical medications, some cosmetics (for example those containing formaldehyde)	27	NALP3, TLR2, TRPA1
Medications such as niacin	15	?
Micro-organisms	NR	NALP3, TLR2
Garlic, mustard oil	NR	TRPA1
Psychological stress, excitement	NR	PACAP, SP, CRH, adrenomedullin?

<http://www.rosacea.org/patients/materials/triggersgraph.php>; modified from [12].

Characteristic symptoms of rosacea include flushing or persistent erythema with teleangiectasia, later also papules, pustules, and lymphedema. Potential other symptoms include plaques, edema, dry skin, phyma of the facial acra, and involvement of the eyes. For the patient, however, the most bothersome symptoms are subjective such as tension, burning, dry skin, stinging, and a sensation of heat [14, 15].

Until recently the disease was categorized into the classic subtypes I to IV, but lately a classification according to symptoms or phenotypes is preferred, facilitating targeted treatment.

Classification according to phenotypes

Since 2017, the ROSacea COnsensus Panel has recommended classification according to symptoms. These are categorized into diagnostic symptoms, major symptoms, and minor symptoms [3, 16, 17]. This categorization is modular and flexible and thus much better reflects clinical reality.

Diagnostic symptoms include phymata as well as persistent erythema which deteriorates as a response to triggers – even one of these symptoms allows the diagnosis of rosacea. Major symptoms include flushing, transient erythema which deteriorates as a response to triggers typical for rosacea, papules and pustules, ocular symptoms, and teleangiectasia. Diagnosis of rosacea requires a combination of at least two major symptoms. Minor symptoms are burning, stinging, edema and swelling, as well as a feeling of skin dryness. The symptoms or phenotypes are also assessed according to frequency, duration, intensity, and extent. This assessment is helpful for describing the severity of symptoms [17].

Special forms

The section on special forms can be found in the AWMF long version.

Histopathology

The section on histopathology can be found in the AWMF long version.

General measures

Recommendation	Strength	Consent
It is recommended to avoid individual provocation factors (trigger factors) as far as these can be recognized based on disease progression.	↑↑	100 %

Since external factors can substantially aggravate disease progression in rosacea, patients should be informed about avoidable potential trigger factors, and of course these factors should subsequently be avoided.

UV protection

Recommendation	Strength	Consent
It is recommended to protect affected areas (such as skin or eyes) from UV exposure, on the one hand by avoiding direct sunlight and on the other hand by wearing hats or sunglasses as well as sunscreen.	↑↑	100 %

It is considered proven that rosacea symptoms can be induced by UV exposure which significantly increases the expression of various pro-inflammatory cytokines. Wearing sun hats, avoiding direct sunlight, and using broad-spectrum sunscreen with both UV-A and UV-B protection should be mandatory for daily management of rosacea. This is explained in more detail in the section “dermocosmetics”.

Food

Recommendation	Strength	Consent
Avoidance of food leading to vasodilation (such as alcohol, spicy food, very hot food or beverages) is recommended .	↑↑	100 %

Factors that may lead to vasodilation or flush symptoms in the face should be avoided. These include alcohol, spicy food, very hot beverages, as well as physical or psychological stress.

Topical treatment

Recommendation	Strength	Consent
It is recommended to choose the most appropriate active substance, concentration, and base for the individual patient according to the phenotypic characteristics of the rosacea, acuity, and skin type.	↑↑	100 %
For treatment-refractory and severe forms of papulopustular rosacea it is recommended to combine topical treatment with systemic treatment.	↑↑	100 %

Topical treatment is often sufficient for rosacea with transient or persistent erythema (erythematous rosacea) as well as rosacea with papules, pustules, and occasionally additional erythema (papulopustular rosacea) if the latter is mild to moderate. But even severely inflammatory forms of rosacea are treated with supporting topical medications, in combination with systemic treatment (see section: Combined treatment).

In Germany, the following medications are approved for topical treatment of rosacea: 0.75 % metronidazole in various bases (gel, cream, lotion, micro-emulsion) [18], 15 % azelaic acid gel, 0.33 % brimonidine gel, and 1 % ivermectin cream. All of these have been proven efficacious in randomized, vehicle-controlled double-blind studies or head to head comparisons. Additional topical substances are being used off-label for treating rosacea [3].

Choosing the appropriate substance and its concentration is an individual decision based on rosacea phenotype [17, 19, 20], acuity of the disease, and the patient's skin type.

In severely inflammatory forms, topical treatment is combined with systemic treatment (see section: Combined treatment).

Apart from the medically active substance, the various bases and other ingredients of topical medications will significantly affect tolerability and efficacy of topical medications, since rosacea patients usually have very sensitive and irritable skin. Simultaneous use of cleansing (soaps, syndets) and skincare products (day or night creams, moisturizers, or sunscreens) as well as changes in treatment routines [21] can have a significant impact on the progression of rosacea (see section: Dermocosmetics).

Before topical rosacea treatment is initiated, patients require thorough information on (Table 3):

Table 3 Patient information before starting topical rosacea treatment.

- ▶ Method of use (once or twice a day, always after removal of decorative cosmetics)
- ▶ Increased sensitivity of facial skin in most rosacea patients (higher rates of hypersensitivity reactions, irritation)
- ▶ Duration of treatment (usually many weeks or months)
- ▶ Therapeutic goal (absence of symptoms)
- ▶ Chronicity of the disease with potential long-term treatment or proactive subsequent treatment
- ▶ Known trigger factors such as UV radiation, heat, alcohol, spicy food
- ▶ Various phenotypes of the disease [22] and the possible transition into other phenotypes (such as the phyma stage)

Brimonidine and oxymetazoline

Recommendation	Strength	Consent
The vasoconstrictor brimonidine (0.33 % gel) is recommended for a purely symptomatic topical treatment of rosacea with persistent centropacial erythema (erythematous rosacea).	↑↑	100 %

Recommendation	Strength	Consent
The vasoconstrictor oxymetazoline (1 % cream) is suggested for a purely symptomatic topical treatment of rosacea with persistent centropacial erythema (erythematous rosacea) (off label).	↑	> 75 %

Brimonidine

Brimonidine tartrate (0.2% eye drops) is a highly selective α_2 -adrenergic receptor agonist. Due to its direct vasoconstrictive activity, it leads to strong, transient constriction of the pathologically dilated dermal arterioles in the facial skin of rosacea patients and thus to disappearance of erythema. This purely symptomatic effect starts about 20–30 minutes after application of a 0.33 % brimonidine gel, reaches a maximum after 3–6 hours, and continues for a total of 8–10 hours with slowly decreasing potency. As the binding of brimonidine to the α_2 receptor diminishes and the substance is metabolized, vasodilation recommences and erythema returns. Efficacy and tolerability of brimonidine were investigated in two parallel randomized, controlled clinical studies with identical design, and confirmed in a long-term study [23–25]. Teleangiectasia, however, cannot be controlled with this substance. Possible negative side effects include local erythema, pruritus, burning skin, and flushing (worsening of symptoms).

Inflammatory processes are also involved in the persistent erythema of erythematous rosacea [26]. Apart from its vasoconstrictive effect, brimonidine also displays anti-inflammatory properties [27].

In early 2014, the European Medicines Agency (EMA) approved brimonidine gel at a concentration of 0.33 % for symptomatic treatment of erythematous rosacea in adult patients. The medication is used once a day in the morning by applying at most one gram of the gel evenly on the face. Undesired topical side effects in the long-term study included worsening of rosacea, indicated by sudden flushing in 9.1 %, worsening of erythema in 6.5 %, and burning of the facial skin in 3.3 % of all patients. As to efficacy in erythema,

brimonidine gel was significantly superior to the gel base alone ($p = 0.001$) [24].

Oxymetazoline

In 2017, the US health authority FDA approved a second vasoconstrictor for the topical treatment of persistent erythema in rosacea, based on controlled, randomized clinical studies [28–31]. Oxymetazoline, a sympathicomimetic, is a selective α_{1A} adrenoreceptor agonist and has vasoconstrictive and anti-inflammatory properties. Once-daily use of 1 % oxymetazoline hydrochloride cream resulted in a significant decrease ($p > 0.001$) of erythema by two levels in the Clinician Erythema Assessment (CEA) and the Subject Self-Assessment-for-Rosacea-facial-Redness (SSA) scales. Long-term studies and direct comparisons with standard treatments are not available at this point in time. The medication is not approved in Germany.

None of the substances tested so far, used either topically or systemically, has shown satisfactory results in the treatment of transient rosacea erythema. There is a definite need for prospective, controlled clinical trials in this area.

One study showed that use of brimonidine led to improved quality of life in patients due to reduction of persistent erythema [32].

Metronidazole

Recommendation	Strength	Consent
Metronidazole is recommended for topical treatment of rosacea.	↑↑	100 %

Metronidazole has both antibiotic and antiparasitic efficacy and is the most commonly used topical medication for treating rosacea world-wide. The mechanism of action for this nitroimidazole compound in topical use is not fully understood. Most probably its efficacy is due to the proven anti-inflammatory, immunosuppressive, and antioxidative properties of the substance. Since skin parasites such as demodex mites are involved in the pathogenesis of rosacea, the antiparasitic efficacy of metronidazole may also play a significant role. Its efficacy when used twice a day has been proven in several randomized, placebo-controlled double-blind trials [33, 34] and has been summarized in a Cochrane review [20].

Various topical medications with 0.75 % metronidazole are available in Germany (cream, gel, lotion, emulsion). Their efficacy does not differ significantly [35]. Undesired side effects are comparatively rare after topical application. The most common side effects are local hypersensitivity reactions such as dry skin, erythema, burning, or stinging. Systemic reactions to metronidazole (nausea, impaired sense

of taste, peripheral neurological symptoms) are not usually expected from topical use due to low absorption and small treated areas in rosacea, but they have been reported in rare cases.

Azelaic acid

Recommendation	Strength	Consent
Azelaic acid is recommended for the topical treatment of rosacea.	↑↑	100 %

Azelaic acid is a naturally occurring dicarboxylic acid with antibacterial and anti-inflammatory properties and a positive influence on keratinization. In dermatology, it is mainly used for treating acne and rosacea.

In Germany, the 15 % gel preparation but not the corresponding 20 % cream is approved for treating papulopustular rosacea. In the USA, a foam preparation with 15 % azelaic acid is also available [36, 37].

The efficacy of azelaic acid in treating papulopustular rosacea is attributed to its anti-inflammatory properties and normalizing of keratinization [36, 38, 39]. A mildly positive effect on rosacea-induced erythema has also been shown [38, 40]. The gel is applied twice a day.

The most frequently reported undesired side effects include mild to moderate and transient burning, stinging, and pruritus. In a randomized, controlled, double-blind multicenter study, the 20 % azelaic acid cream (which is not approved for rosacea in Germany) has also shown significant superiority of the substance in reducing papules and pustules as compared to the cream base used in the control group [41]. Similar results were found in a double-blind study with the 15 % azelaic acid foam which is also not approved in Germany [37, 38].

Ivermectin

Recommendation	Strength	Consent
Ivermectin is recommended for the topical treatment of rosacea.	↑↑	100 %

Ivermectin is a semi-synthetic derivative of avermectin and has been used as a preventative or therapeutic medication in tropical medicine since 1987, for millions of people with parasitic diseases such as onchocercosis (river blindness) or Loa Loa filariasis (African eye worm). In 1994 (at that time off-label) it was also identified as an effective and safe therapeutic for severe forms of scabies (scabies crustosa) which is predominantly seen in immunocompromised patients [42]. Oral use in severe human scabies and for combating scabies

outbreaks was approved in Germany in 2015 (see AWMF guideline scabies 013-052).

The efficacy of ivermectin in rosacea is probably due to two different elements. On the one hand, the macrolide structure of the ivermectin molecule indicates an anti-inflammatory effect (anti-inflammatory effects are also known from other macrolides such as erythromycin, tacrolimus, and pimecrolimus), on the other hand ivermectin displays strong neurotoxic effects limited exclusively to non-vertebrates, so these parasites are eliminated within a short time. In rosacea, saprophytic hair follicle mites from the *demodex* species are the target for antiparasitic treatment. It has been shown that demodex mites play an important role in the pathogenesis of rosacea [43–45]. Reducing the number of mites can achieve significant improvement of the skin in rosacea patients. Permethrin (see below) for the treatment of rosacea presumably works in the same manner.

In Germany, 1% ivermectin cream was approved for treating papulopustular rosacea in adult patients in 2015. In the two parallel, randomized, double-blind, placebo-controlled pivotal trials [46], ivermectin was significantly superior to the control group treated with only the cream base in a total of 1,371 participants. The effect on inflammatory papulopustular eruptions appeared after only two weeks of treatment and showed superiority versus treatment with the cream base after twelve weeks (decrease of inflammatory eruptions compared with base value by 76 % respectively 75 %, with 50 % in the control group, $p < 0.001$ in both parallel studies).

As opposed to creams with metronidazole or azelaic acid, ivermectin cream is only used once a day and shows especially good results in severely inflammatory rosacea with papules and pustules.

Schaller et al. (2020) have successfully used ivermectin 1 % cream combined with low-dose doxycycline (40 mg/day) for severe rosacea [47].

Other topical preparations (off-label for rosacea)

Minocycline

Minocycline is a semi-synthetic tetracycline antibiotic. After successful systemic and topical use in acne vulgaris, it was also studied for rosacea with papules and pustules. Minocycline displays bacteriostatic and anti-inflammatory effects as well as inhibitory effects on vasodilation and granuloma formation. It is also considered a potent neutralizer of free oxygen radicals [48].

In May 2020, a foam with 1.5 % minocycline was approved in the USA for treating rosacea with papules and pustules. At this point in time, direct comparative studies against azelaic acid, metronidazole, or ivermectin in treating rosacea are not yet available [48].

Permethrin

Considering the role of demodex mites in the etiopathology of rosacea, clinical studies have investigated permethrin, an antiparasitic from the pyrethrin group, which is used as a topical treatment for scabies mites and lice [49–51]. In a twelve-week, double-blind split face study, 20 patients with papulopustular rosacea were treated with 5 % permethrin cream versus the cream base [51]. A significant reduction of demodex mites and rosacea symptoms was observed.

Clindamycin

Topical use of clindamycin (1 % cream) in papulopustular rosacea did reduce the number of papules, pustules, and nodules [52], but as with the other systemically used antibiotics erythromycin and tetracycline, topical use should if possible be avoided to prevent sensitization and development of resistance. In a placebo-controlled, randomized multicenter phase II study, 639 rosacea patients were treated with clindamycin cream at concentrations of 0.3 % or 1 %. An anti-inflammatory effect could not be confirmed with treatment either once a day or twice a day [53].

Topical retinoids: Adapalene and retinaldehyde

Topical retinoids have been studied in papulopustular rosacea based on their anti-inflammatory and keratolytic effects.

As compared with 0.75 % metronidazole gel, adapalene 0.1 % gel showed a more pronounced effect on inflammatory lesions but was inferior in reducing erythema [54]. Adapalene may potentially have a much delayed effect compared with metronidazole [55].

Therapeutic studies with topical retinaldehyde (0.05 % cream) in 23 women over a period of six months however showed a beneficial effect on the vascular component of rosacea: Improvement of erythema was reported in about 75 % of patients after five months of treatment ($p < 0.05$) [56].

Calcineurin inhibitors

The anti-inflammatory effects of the calcineurin inhibitors tacrolimus and pimecrolimus are the rationale for using these compounds in rosacea patients. They are used specifically for steroid-induced rosacea, partly to avoid a strong inflammatory rebound after discontinuation of glucocorticosteroids. Tacrolimus is used as 0.03 % cream or 0.1 % ointment [57–59], pimecrolimus as a 1 % cream [60–64]. The less fatty cream appears to be better tolerated on the face,

compared with the ointment base. Some dermatologists therefore prescribe tacrolimus in a modified base for use on the face. In an open clinical comparison, pimecrolimus 1 % cream showed comparable effects to 1 % metronidazole cream [63] and was well tolerated.

Apart from a handful of studies on rosacea treatment with tacrolimus, there have also been reports on the induction of rosacea-like dermatitis [65] and also granulomatous rosacea [66] by tacrolimus.

In an open study, pimecrolimus was used successfully in mild to moderate rosacea, reducing the score of papulopustular eruptions as well as erythema [64], but the compound can also induce rosacea-like dermatitis [67].

Due to the immunosuppressive effect of tacrolimus, periocular herpes simplex infection has been reported in a small number of cases – particularly after treatment of atopic dermatitis on the face.

In summary, the current database does not appear sufficient to either recommend or reject the use of calcineurin inhibitors for rosacea.

Benzoyl peroxide

In rosacea patients with more robust skin, benzoyl peroxide may result in an improved clinical appearance. However, in patients with sensitive skin the opposite effect was reported [59]. Combinations of benzoyl peroxide with clindamycin or erythromycin have also been studied for treatment of rosacea [68]. Leyden reported on a randomized, vehicle-controlled, double-blind multicenter study with encapsulated benzoyl peroxide at concentrations of 1 % or 5 % in 92 patients with mostly moderate papulopustular rosacea. Once-daily use of either concentration over a period of twelve weeks resulted in a significant decrease of papules and pustules, and in the case of the 5 % gel also in a reduction of the rosacea score to “healed or nearly healed” [69].

Topical maintenance treatment

Since rosacea is a chronic-inflammatory facial dermatosis, it shows a tendency to relapse after treatment has been discontinued. Skin improvements achieved through intensive systemic or combined systemic/topical treatment can be maintained for longer periods of time by topical maintenance treatment. Metronidazole has proven to be effective for successful maintenance treatment [70]. Long-term treatment studies with brimonidine 0.33 % gel and ivermectin 1 % cream have been conducted at standard doses over periods of 6–12 months each.

Systemic treatment

Recommendation	Strength	Consent
Systemic treatment is recommended for treatment-refractory and severe forms of papulopustular rosacea.	↑↑	100 %

Systemic treatments should be used in particular for severe forms or milder but treatment-refractory forms of rosacea. The most frequently used drugs, at this point in time, are tetracyclines, specifically doxycycline and minocycline. The only approved preparation for the treatment of rosacea is 40 mg doxycycline at an anti-inflammatory dosage and with modified drug release.

Tetracyclines

Recommendation	Strength	Consent
Low-dose doxycycline is recommended as the systemic treatment of choice.	↑↑	100 %

First generation

Tetracyclines have been used in the treatment of rosacea for decades. Twice-daily intake of 250 mg over a period of four weeks resulted in a significant improvement of skin appearance in 78 % of patients with papulopustular rosacea. Stable disease was achieved by daily intake or intake every other day of 250 mg tetracycline (*sensu stricto*). However, recurrence rates after discontinuation are high [71]. Antibiotic treatment is very effective against the inflammatory component of rosacea (papules and pustules), but the effect on erythema and teleangiectasia is poor. Tetracycline can be used at doses of 250–1000 mg per day [72]. According to current understanding, the efficacy of tetracyclines is due to non-antibiotic mechanisms of action. The molecular mechanism of action displayed by doxycycline may be based on inhibiting the proteolytic activation of peptidases related to kallikrein, which play an important role in the development of rosacea, as well as inhibiting activation of cathelicidine. This may mediate the anti-inflammatory effect of doxycycline [73] (see section: Pathogenesis).

Second Generation

The second generation of tetracyclines (minocycline, doxycycline) shows similar efficacy against inflammatory lesions in rosacea. As compared with first-generation tetracycline, these drugs offer the benefits of better bioavailability and longer half-life. These tetracyclines can also be taken with

food, thus reducing gastrointestinal side effects [74]. In the treatment of rosacea, doxycycline and minocycline are used (off label) at higher dosages of 100–200 mg per day [72].

Low-dose doxycycline treatment

The only approved medication for systemic treatment of papulopustular rosacea is currently 40 mg doxycycline with modified drug release. The 40 mg preparation is based on a galenic formulation combined from 30 mg with immediate release and 10 mg with retarded release. The solitary potency and the special galenic formulation result in different bioavailability and thus therapeutically significant differences. When used as intended, this drug does not have an antimicrobial effect [75]. Due to its clinically relevant sub-antimicrobial dosage, this treatment option is also called “anti-inflammatory doxycycline therapy” [76]. 40 mg doxycycline with modified drug release is the preferred treatment option based on the results of clinical trials and the approval in this indication.

This is also important for patients who reported side effects (candida infection, gastrointestinal side effects, sensitivity to light, hyperpigmentation) with earlier antibiotic treatments. According to a Cochrane review, there is high evidence in favor of the efficacy and safety of doxycycline in both low doses (40 mg per day) and conventional doses (100 mg per day) [77].

Two pilot studies with doxycycline at anti-inflammatory doses also found very high efficacy in ocular rosacea [78, 79].

Van der Linden et al. showed that minocycline 100 mg/day was non-inferior to sub-antimicrobial doxycycline 40 mg/day for the treatment of mild to severe papulopustular rosacea [80]. However, 100 mg minocycline is still not really suitable for treating rosacea due to possible hyperpigmentation of the skin and teeth, and some very rare but very severe potential side effects such as drug-induced lupus erythematosus or hypersensitivity syndrome [81]. The benefit-risk balance of doxycycline is thus much more favorable than that of minocycline. Minocycline should thus no longer be considered a first-line treatment for inflammatory dermatoses [82].

Macrolides

As an alternative, especially in cases of tetracycline intolerance, treatment refractory rosacea, or contraindications such as pregnancy, macrolides like erythromycin, clarithromycin, and azithromycin may be used.

Oral application of 250–1000 mg erythromycin per day is considered an effective treatment for papulopustular rosacea but is rarely recommended due to the frequent occurrence of gastrointestinal side effects [72]. Erythromycin should thus be used only for patients who have contraindications against tetracyclines [55]. Azithromycin and clarithromycin

are chemically more stable than the “older” erythromycin and are usually better tolerated.

250 mg clarithromycin twice a day for four weeks followed by 250 mg once a day for another four weeks effectively reduced both erythema and papules and worked faster than doxycycline [83].

Azithromycin has an affinity to inflamed tissue and has fewer side effects than other macrolide antibiotics. It reduces neutrophil migration, inhibits neutrophil and eosinophil activation, and suppresses both the release or reactive oxygen species and the formation of pro-inflammatory cytokines, and thus has an overall anti-inflammatory effect.

After twelve weeks of azithromycin treatment at decreasing doses, skin appearance was improved by 75 % and inflammatory lesions reduced by 89 % as compared to baseline [84].

In another study with patients who had papulopustular and ocular rosacea, a significant improvement of the ocular symptoms was achieved after only four weeks of treatment with azithromycin (500 mg three times a week) [84].

Due to a low quality of the studies, however, the Cochrane review categorizes the evidence level as “very low” [77], so the efficacy of azithromycin must be confirmed by future high-quality studies.

Metronidazole

Metronidazole 200 mg twice a day combined with 1 % hydrocortisone cream over a period of six weeks improved the severity level of rosacea in 10 out of 14 patients [85]. During metronidazole treatment, a disulfiram-like effect may cause alcohol-induced headaches. Thus alcohol should be avoided [86].

Other antibiotics

Studies have also shown efficacy for co-trimoxazole, clindamycin, chloramphenicol, and ampicillin. Experience however is limited and thus use of these compounds should be restricted [86, 87].

Small Intestinal Bacterial Overgrowth (SIBO) is significantly more common in rosacea patients than in control persons (46–51 % versus 5–23 %). Based on this association, there have been several reports on successful rosacea treatment with rifaximine [88].

Isotretinoin

Recommendation	Strength	Consent
Low-dose isotretinoin (0.1–0.3 mg/kg body weight [BW]) is suggested as a systemic treatment for rosacea (off label).	↑	100 %

Isotretinoin, a retinoic acid isomer, has been successfully used to improve rosacea in several studies [89–92]. As compared with antibiotics, however, the onset of effect may be delayed. Use of isotretinoin results in a substantial reduction of papules, pustules, and erythema [93]. Reduction of erythema may however be masked by isotretinoin-induced dermatitis and xerosis. According to laser Doppler examinations, skin blood flow in the facial skin is reduced. Even reduction of rhinophyma has been achieved [94]. As opposed to the standard dosage of 0.5–1.0 mg/kg BW per day, low-dose treatment with 10 to 20 mg daily can be just as successful and has a markedly reduced side effect profile. Isotretinoin has long been acknowledged as an effective drug for the systemic treatment of severe rosacea, but due to the lack of evidence-based clinical studies remains off label in this indication. In a large and methodically valid dose-finding and efficacy study [18] on the treatment of phenotype II and III rosacea with isotretinoin, this retinoid proved an excellent option for the systemic treatment of severe and moderate forms of rosacea. An isotretinoin dose of 0.3 mg/kg BW/day was shown to be effective with significant superiority over placebo and non-inferiority compared with doxycycline. Other studies confirmed a high efficacy of isotretinoin at low doses of 10–20 mg per day in the treatment of papulopustular rosacea, but also in cases of extrafacial location [95] and in patients whose rosacea had not responded to antibiotic treatment [96]. Due to the large database, evidence quality is considered high [77]. Based on our own observations, low-dose isotretinoin treatment with 10 mg per day is not contraindicated in ocular rosacea but leads to improvement of ocular symptoms in most patients. Isotretinoin is currently not approved for rosacea treatment, and simultaneous treatment with tetracyclines is strictly contraindicated. Due to the embryotoxic effect of isotretinoin, reliable contraception is mandatory when treating women of reproductive age.

Glucocorticoids

Glucocorticoids are not indicated for rosacea and may even worsen this disease. Exacerbation has been observed after discontinuing corticosteroids (steroid rosacea) [97]. The only exception is short-term use in rosacea fulminans.

Beta blockers

Recommendation	Strength	Consent
Carvedilol may be considered for systemic treatment of persistent erythema and flushing in rosacea (off label).	o	100 %

Beta blockers such as propranolol (a non-selective β receptor blocker) or carvedilol (a non-selective β receptor blocker with α_1 -antagonistic activity) are usually indicated for arterial hypertension, coronary heart disease, angina pectoris, and tachycardia.

In rosacea, beta blockers mainly reduce erythema respectively flushing. This effect is based on a number of factors. Blocking β -adrenergic receptors in the smooth muscles of cutaneous blood vessels leads to vasoconstriction. Anxiety and tachycardia, which can exacerbate flush symptoms, are mitigated as well. Carvedilol has additional antioxidative and anti-inflammatory properties.

There are several indications that systemic beta blocker treatment is effective for rosacea. Hsu and Lee treated eleven normotensive patients who had rosacea erythemato-telegenectatica with carvedilol in slowly increased doses up to a maximum of 31.25 mg per day. Within three weeks, all patients showed a significant improvement of their symptoms [98]. Another case series with five patients confirmed these results [99].

In a retrospective analysis of nine patients with idiopathic or rosacea-associated flushing who were treated with propranolol (initially 10 mg 3 times a day, then slowly increased to 20–40 mg 2–3 times a day), complaints improved. However, several patients reported side effects such as vertigo, fatigue, and bradycardia [100]. At this point in time, the sparse database does not support a recommendation for the use of beta-blockers.

Combined treatment

The relevant section can be found in the AWMF long version of this guideline.

Alternative treatment options

The relevant section can be found in the AWMF long version of this guideline.

Physical therapies

The specific recommendations can be found in the relevant section of the AWMF long version of the guideline “laser therapy of the skin”.

Ocular rosacea – clinical presentation

Epidemiological data

Ocular rosacea may occur either simultaneously with cutaneous disease (about 20–50 %), or as an isolated finding (up to 90 % in ophthalmological examinations). The relevant

aspects of underlying multifactorial pathophysiology are analogous to cutaneous rosacea [101]. Data on incidence show a large variation between dermatological and ophthalmological studies and range from 6–72 % [102, 103]. Eye involvement can significantly impair quality of life [104].

Clinical presentation and symptoms

Ocular symptoms of rosacea are usually bilateral and frequently independent of the clinical severity of cutaneous symptoms [105, 106]. Several studies, however, have reported a significant association between the ophthalmological findings and the severity of teleangiectasia [107, 108]. The incidence of recurrent chalazion is increased [105]. Clinical changes are dominated by Meibomian gland dysfunction (MGD) with various degrees of inflammation on the surface of the eye. Slit-lamp examination of the eyelid margins shows teleangiectasia, enlarged Meibomian glands, excessive sebaceous secretion, and “collarettes”. Meibomographies have verified a significantly reduced density of Meibomian glands [108, 109]. MGD results in alteration of the lipid composition of the tear film, with increased evaporation of tear fluid, reduced tear break-up time, and evaporative, dry eyes [102, 103, 105, 110]. If the tear film is significantly altered, chronic conjunctivitis frequently results, and in some individual cases fibrosing will lead to a pemphigoid-like appearance. Episcleritis and anterior uveitis are other rare occurrences [4]. Now and then, eyelid or periorbital edema may occur and give rise to a suspicion of Morbihan disease [111].

Symptoms

Recommendation	Strength	Consent
Ocular rosacea is a clinical diagnosis.	Statement	100 %
Clinical indications of ocular rosacea include posterior blepharitis, Meibomian gland dysfunction, and secondary inflammatory change(s) of the ocular surface.	Statement	100 %

The symptoms of ocular rosacea result from the MGD and the ensuing “evaporative dry eye”. Complaints frequently start early in the day and thus may offer an indication regarding the differential diagnosis of hypovolemic dry eye. In the latter case, symptoms frequently increase during the later part of the day. The complaints are non-specific and present as foreign body sensation, dry, burning, or tearing eyes, and erythema of the eyelid margins. In cases of severely compromised tear film, this may lead to varying visual impairment with blurred vision and increased sensitivity to light.

Diagnostics

Ocular rosacea is a clinical diagnosis based on one or more findings and symptoms. There is no specific test to confirm the suspected diagnosis. Clinical signs include posterior blepharitis, MGD, and secondary inflammatory change(s) of the ocular surface. Objective methods for assessing the severity of MGD and the extent of gland decline are available [108] (Meibography). Meibometry can measure the amount of oil in the eyelid margin reservoir [112]; however both methods offer only limited specific indications [113, 114].

Ocular rosacea – treatment

Recommendation	Strength	Consent
The indication for treating ocular rosacea depends on the severity of ocular involvement and is frequently independent of skin symptoms.	Statement	100 %

Recommendation	Strength	Consent
Eyelid margin hygiene is recommended as a general practice.	↑↑	100 %

Recommendation	Strength	Consent
Cyclosporin eye drops as well as azithromycin are suggested for the topical treatment of inflammation on the ocular surface (off label). Ivermectin or metronidazole (skin cream) is suggested for topical application on the eyelids (off label).	↑	100 %

Recommendation	Strength	Consent
Doxycycline or azithromycin as well as other macrolide antibiotics is suggested for systemic treatment (off label).	↑	100 %

Recommendation	Strength	Consent
Systemic treatment with ivermectin, with or without metronidazole and omega-3 fatty acids, may be considered for ocular rosacea (off label).	o	100 %

Recommendation	Strength	Consent
Intense Pulsed Light treatment may be considered for ocular rosacea.	o	100 %

There are no randomized controlled trials (RCT) on the best compounds or the optimal duration of treatment for ocular rosacea. The indication depends on the severity of ocular involvement. In mild forms of ocular rosacea, topical ophthalmological treatment should suffice. Eyelid margin hygiene is recommended (Guideline No. 11, Dry Eye, BVA and DOG, 2019) [115, 116]. This can be supported by warming of the eyelid margins to liquefy the secretions in the Meibomian glands. Use of lipid-containing artificial tears is recommended as a supporting practice. Various topical medications have been used to treat inflammation in ocular rosacea.

One study in 37 patients showed that ciclosporin eye drops 0.05 %, used twice a day over a period of three months, improved the objective ocular parameters measured by Schirmer's test ($p = 0.001$) and a prolonged tear break-up time (TBUT) ($p = 0.001$). Patients' quality of life improved significantly ($p = 0.01$) [117].

Via its influence of metalloproteinases, the antibiotic azithromycin 1.5 % (Azyter®), (twice a day on the first two days, once a day thereafter over a period of four weeks) also showed improvement of blepharitis in non-controlled studies [118].

Other non-controlled studies with the calcineurin inhibitor pimecrolimus (skin cream, Elidel®) and with metronidazole also showed positive results in reducing inflammation. The preparations are applied to the eyelid margins.

If complaints persist, or if skin involvement justifies this form of treatment, doxycycline (50–100 mg twice a day) has proven effective. In a pilot study, doxycycline at anti-inflammatory doses (2x 40 mg per day in week one, and 40 mg once a day thereafter) proved very effective in treating ocular rosacea [78]. Erythromycin appears to offer good results in young patients and in those with doxycycline/tetracycline intolerance [119]. Non-controlled studies have also shown efficacy of systemic clarithromycin and metronidazole.

Under the premise that *demodex folliculorum* is a crucial factor in the development of blepharitis, oral ivermectin (200 µg/kg), occasionally also in combination with oral metronidazole (250 mg three times a day for two weeks) has also been used successfully [120]. Topical ivermectin has also shown very good results in a non-controlled study [121]. However, no RCTs for either form of application are currently available.

To be effective in ocular involvement, any systemic treatment must be used for a long period of time. The first visible effect can be expected after a minimum of 6–8 weeks, and treatment durations of about 3–6 months are often required.

Different effects for systemic supplementation of omega-3 fatty acids in ocular rosacea have been observed. In a randomized controlled trial ($n = 130$), systemic treatment with omega-3 fatty acids (180 mg eicosapentaenic acid and 120 mg docosapentaenic acid), one capsule twice a day was compared with placebo. The ophthalmologic parameters showed a beneficial effect of the omega-3 fatty acids. Evaluation of a questionnaire

on the subjective assessment of “dry eyes” showed that patients preferred the omega-3 fatty acids over placebo ($p < 0.001$). A previous meta-analysis [122] however had not found any effect in six out of seven studies. Another randomized, controlled, double-blind study in a total of 449 patients with keratoconjunctivitis sicca, omega-3 fatty acids did not show any statistically significant benefit compared with placebo [123].

In recent years, there have been several publications on studies treating MGD diseases including ocular rosacea with intense pulsed light (IPL) [124]. These have not at this point in time led to recommendations; further studies are required.

Treatment of special forms

The relevant section can be found in the AWMF long version of this guideline.

Psychosocial aspects

The relevant section can be found in the AWMF long version of this guideline.

Differential diagnoses

Table 4 offers an overview of differential diagnoses.

Dermocosmetics

Cosmetics are defined as substances or mixtures that are intended for external use on the human body to cleanse or protect the skin, keep it in good condition, or change its appearance [125]. In the context of this guideline, this chapter covers cosmetics which offer a meaningful non-medical contribution to the successful management of rosacea. Use of appropriate dermocosmetics is crucial [126–132]. Ideally, all cosmetics (cleansers, skin care, sunscreens, and others) should be tailored to the skin's needs both during active relapses and during remission intervals.

Patients should be advised to prefer products for sensitive skin, or even products recommended especially for rosacea (medical cosmetics).

Dermocosmetic routines should be followed in the morning and at night, always in the order cleansing – skin care – sunscreen.

Cleansing

Recommendation	Strength	Consent
Gentle cleansing is recommended (tepid water, synthetic detergents adapted to the pH of healthy skin, patting the skin dry).	↑↑	100 %

Table 4 Differential diagnoses.

Rosacea erythemato-teleangiectatica	<ul style="list-style-type: none"> ▶ Polycythemia vera (increased blood values: hemoglobin, hematocrite, erythrocytes) ▶ Lupus erythematosus (direct immunofluorescence, ANA, hemogram) ▶ Dermatomyositis (LDH, creatine kinase, ANA, anti-Jo1) ▶ Mixed connective tissue disease (ANA, rheumatoid factor, U1-RNP antibodies) ▶ Carcinoid syndrome, for example from neuroendocrine tumors (5-hydroxyindole acetic acid excretion in 24-hour urine, serotonin in serum, imaging) ▶ Mastocytosis (histology: mast cell infiltration in the corium, serum tryptase, N-methylhistamine, respectively 1,4-methylimidazole acetic acid in 24-hour urine) ▶ Allergic contact eczema (medical history, patch testing) ▶ Arterial hypertension (measuring blood pressure) ▶ UV-induced damage of cutaneous vessels (medical history)
Papulopustular rosacea	<ul style="list-style-type: none"> ▶ Papulopustular acne (comedones present, age) ▶ Perioral dermatitis (eyes/mouth are spared, usually excessive skin care) ▶ Allergic or toxic contact eczema (medical history, patch test) ▶ Gram-negative folliculitis (detection of gram-negative bacteria from pustules) ▶ Eosinophilic folliculitis (histology: eosinophilic infiltration, eosinophils detected in the blood count, IgE) ▶ <i>Folliculitis et perifolliculitis capitis suffodiens et abscedens</i> (distribution, hair loss, abscesses) ▶ Demodicosis (mostly unilateral/asymmetric, detection of demodex mites, more acute dynamics)
Rosacea phymatosa	<ul style="list-style-type: none"> ▶ Lupus pernio/sarcoidosis (serum ACE concentration, soluble interleukin-2 receptor in serum, histology: epitheloid cell granuloma) ▶ Eosinophilic granuloma (computed tomography, immunohistochemistry)

Recommendation	Strength	Consent
It is recommended to avoid irritation when cleansing, such as scrubbing, peelings, substances that promote blood circulation, or adstringents.	↑↑	100 %

Skin cleansing in the morning and at night should be as gentle as possible. Because of possible vascular hyperreactivity and irritability of the skin, water should always be tepid and the skin should be dried by gentle patting [129].

Only “syndets” (synthetic detergents) with a slightly acidic pH similar to that of healthy skin should be used. Common cosmetic detergents with irritative potential, for example sodium lauryl sulfate, should be avoided [126, 129, 131–136]. Even plain water may remove a significant amount of natural moisturizing factors (NMF) from the skin when “rinse-off” cleansing products are used, so patients describe an uncomfortable feeling of tension. These NMF, such as amino acids, salts, glycerin, or urea, naturally occur in the skin and can be preserved by using cleansing fluids or micellar waters that are used without additional water (leave-on products).

Any irritation, such as scrubbing the skin, coarse washcloths or towels, mechanical or chemical peelings, as well as substances promoting blood circulation or irritating

substances (such as alcohol, essential oils, menthol, camphor, certain fragrances and preservatives) should of course be avoided [126, 131, 133].

Skin care

Recommendation	Strength	Consent
Light/hydrophilic skin care preparations are recommended for patients with rosacea.	↑↑	100 %

Recommendation	Strength	Consent
Cosmetics with active ingredients to improve complaints in rosacea are suggested .	↑	100 %

Recommendation	Strength	Consent
It is recommended to avoid irritating cosmetics and those promoting blood circulation.	↑↑	100 %

Rosacea patients should prefer hydrophilic skin care products; emulsions should be O/W (oil in water), with a low oil content [126, 133, 137].

Excessive oil content is occlusive and may thus aggravate complaints in rosacea [131], but appropriate skin care can

provide a fundamental contribution in alleviating symptoms such as tension, burning, or discomfort [129, 131, 132, 138].

“Medical cosmetics” sold in pharmacies also contain so-called active cosmetic ingredients (cosmeceuticals) that claim medical efficacy yet can only be marketed as cosmetics. Manufacturers offer products with anti-inflammatory, skin-calming, or vessel-stabilizing properties such as retinaldehyde, licocalchone A, or kinetin [56, 139, 140]. UV filters, usually with SPF 20 to 30, can be found in skin care products but can of course also be added after application of skin care products (see section below).

Just as in cleansing, irritating formulas should be avoided. These include products promoting blood circulation, “anti-ageing” products, but also creams for dry and atopic skin (with a high lipid content) and products for blemished skin (with keratolytics like glycolic acid or salicylic acid).

Sunscreen

Recommendation	Strength	Consent
Daily use of a broad-spectrum sunscreen with both UV-A and UV-B protection is recommended.	↑↑	100 %

Since UV radiation is a common trigger factor for rosacea, use of appropriate sunscreens is generally recommended. This not only applies to sunny summer days but also cloudy days and the winter months. Since hats are the only clothing article that can protect the face, and sunlight cannot always be avoided, the face should be protected with cosmetic sunscreens at all times. These are sometimes contained in skin care products, but in most cases only with a moderate sun protection factor (SPF 20–30). For longer times spent outdoors, use of higher sun protection factors is recommended.

Apart from using appropriately high sun protection factors with moderate (SPF 20–30) to high (SPF 50–50+) protection, it is important to use these products correctly and consider the chemical properties of the UV filters as well as the cosmetic base.

Additional dermocosmetic practices

Recommendation	Strength	Consent
It is recommended to use decorative cosmetics if this contributes to improved quality of life.	↑↑	100 %

In general, any further cosmetic procedures should be as gentle as possible so as not to cause irritation.

If feasible, decorative cosmetics should be kept to a minimum so any unnecessary irritation can be avoided. Skin care products for rosacea frequently already have a greenish tinge

to counteract the redness of erythema after application. Since outward appearance contributes considerably to a decreased quality of life in rosacea patients, such products can improve quality of life significantly [141, 142]. Note that the formulation of decorative cosmetics need to be considered as well – light powders or creams are preferable to heavy, lipid-rich products (such as “camouflage” creams) even though the latter offer more coverage for erythema.

Thermal water sprays are another cosmetic product suitable for acute use. Rosacea patients with irritated skin and a sensation of heat can spray these products on the skin as required, several times a day. Rapid evaporation conveys a feeling of refreshment and cooling. In addition, *in vitro* and *in vivo* studies have shown anti-inflammatory, anti-angiogenic, and calming effects with improved quality of life [143–147]. These are probably based on the special mineral and microbial composition of the natural healing waters.

Shaving the face is a topic which must be discussed with male rosacea patients. Dry shaving is preferable to wet shaving since the latter causes micro-trauma of the skin surface and thus impairs the skin barrier. Alcoholic after-shaves should be avoided because of their irritating properties.

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Conflict of interest

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