GUIDELINES

Swiss S1 guideline for the treatment of rosacea

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Abstract

Rosacea (in German sometimes called 'Kupferfinne', in French 'Couperose' and in Italian 'Copparosa') is a chronic and frequently relapsing inflammatory skin disease primarily affecting the central areas of the face. Its geographic prevalence varies from 1% to 22%. The differential diagnosis is wide, and the treatment is sometimes difficult and varies by stage of rosacea. For erythematous lesions and telangiectasia, intense pulsed light (IPL) therapy and lasers are popular treatment option. In addition, a vasoconstrictor agent, brimonidine, has recently been developed. For papulopustular rosacea, topical antibiotics, topical and systemic retinoids, as well as systemic antibiotics are used. A topical acaricidal agent, ivermectin, has undergone clinical development and is now on the market. In the later stages, hyperplasia of the sebaceous glands develops, resulting in phymatous growths such as the frequently observed bulbous nose or rhinophyma. Ablative laser treatments have largely replaced classical abrasive tools. Here, we reviewed the current evidence on the treatment of rosacea, provide a guideline (S1 level) and discuss the differential diagnosis of rosacea.

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Conflicts of interest

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Key message

This article provides an extensive review on the treatment of rosacea and is a practical guideline for the clinician.

Introduction and Epidemiology

Rosacea is a common centrofacial skin disease most often of the middle-aged and elderly.[1,2] It can start with flush-like temporary dilation of capillaries and fleeting erythema, subsequently telangiectasias develop and persisting erythematous macules, especially on cheeks and nose. In more severe cases, development of pustules and disfiguring growth of hyperplastic sebaceous glands on the nose and other facial regions occurs.

The incidence is 165/100 000 per year,[1] and the prevalence varies greatly between countries from 1% to 22%.[3,4–7] Persons with fair skin type have an increased risk of rosacea.[8,9–11] Various studies revealed conflicting data on rosacea's gender

preference, which might vary between distinct populations.[1–2,4,7,12] The usual age of onset is between 30 and 50 years; however, in rare cases, rosacea can already occur in children.[13]

While recently, an expert panel of dermatologists and ophthalmologists has agreed on a phenotype-based classification (transient and persistent erythema, telangiectasias, inflammatory papules or pustules, and phyma),[14] the most commonly used and the best known classification refers to subtype I or erythematotelangiectatic rosacea (ETR), subtype II, or papulopustular rosacea (PPR), subtype III (phymatous rosacea) and subtype IV (ocular rosacea).

Pathomechanism

Genetics

Rosacea has genetic risk factors[15] including a genomewide association signal in polymorphisms nearby the *BPTK3*[16] as well as signals in the MHC class II molecules. Twin studies[17] revealed that about half of the risk of apparent rosacea is due to genetics, the other half to environment factors. It is considered a complex disorder and does not show Mendelian inheritance in pedigrees. An autosomal-dominant genodermatosis called Haber's syndrome is the only example whereby rosacea – as part of a syndrome with multiple other clinical features – can be inherited directly.[18]

Environment

Environmental trigger factors include exposure to extremes of temperature (hot and cold air), temperature changes, caffeine, alcohol, hot and spicy foods, sunlight, exercise, acute psychological stresses, menstruation, demodex mites and certain medications.[8,19] There is controversy whether *H. pylori* should be considered a trigger factor or rosacea as well.[20–23]

Cytokines

Due to an impaired permeability barrier in the stratum corneum,[24–30] the release of various cytokines such as tumour necrosis factor α (TNF-α), IL-1 and IL-6 is triggered, leading to cutaneous inflammation, perhaps in an attempt of the epidermis to initiate self-repair.[27–30] These pathomechanisms can lead to neurological symptoms such as stinging and burning sensations.[27,29,30]

Antimicrobial peptides

Recently, overproduction of antimicrobial peptides (AMPs) has been identified as a cause of rosacea lesions.[31] AMPs include defensins and cathelicidins, such as LL-37.

Toll-like receptors

Keratinocytes express Toll-like receptors in order to sense pathogen-associated patterns (PAMPs).[32,33] Toll-like receptor 2 (TLR2)[33] and Toll-like receptor 4 (TLR4)[34] have been shown to be overexpressed in rosacea skin.

Adaptive immune cells

T cells (especially Th1/Th17-polarized immune cells), macrophages, mast cells and neutrophils are present in rosacea of all subtypes I-III. Neutrophils are assumed to play an essential part in the pathogenesis of rosacea.[35–38] Reactive oxygen species (ROS) and other proteases are produced by neutrophils and damage blood vessels. This causes inflammation as well as angiogenesis, subsequently leading to telangiectasias.[8] Recently, an involvement of B cells in the pathomechanism of rosacea was shown as well.[37]

Mites

Demodex mites, even though they are present in normal adult skin as well, can be found in increased numbers in numerous rosacea patients.[39–43] A decrease in demodex mites in human skin correlates with improvement of rosacea symptoms.[44]

Blood vessels

Vascular dilatation results in erythema, in its fleeting form often perceived as facial flushing. In rosacea, the papillary dermal vasculature is dilated and perfusion of the skin is increased.[40,45]

Nerves

Sensory nerve endings are activated to release vasoactive neuropeptides by transient receptor potential (TRPs) channels.[46–48] Two calcium channel blockers and members of the TRP family, transient receptor potential vanilloid 1 (TRPV 1) and Ankyrin 1 (TRPA 1) are of special interest in rosacea as they mediate inflammatory response(s). They are triggered by spices, alcohol consumption and temperature changes. When depolarized, TRPV 1 and TRPA 1 induce neuropeptides such as pituitary adenylate cyclase-activating polypeptide (PACAP), substance P (SP) as well as calcitonin gene-related peptide (CGRP) that overall cause flushing and erythema through vasodilatation. PACAP, SP and CGRP also lead to an inflammatory response through activation of mast cells, macrophages, neutrophils and T cells.[49]

Due to the multifactorial pathogenesis that cannot be easily addressed therapeutically, treatment strategy currently focuses on symptomatic suppression of inflammation and reduction of disfiguring features. Clinically, four types of rosacea are differentiated according to apparent features and severity.

Clinical manifestations and subtypes of rosacea

Patients with subtype I have centrofacially located erythematous macules due to dilated capillaries in the face, especially on the nose and cheeks. Episodes of transient erythema (flushing) or non-transient (persistent) erythema can occur.[40,45] ETR flares are due to acute vasodilatation and innate inflammation. Once the vasculature becomes chronically dilated, persistent facial erythema develops. Additionally, chronic oedema due to

extravascular fluid leakage and perivascular inflammation can occur.[24–26,50–53] Differential diagnosis in subtype I includes menopausal flushes, insufficiently controlled arterial hypertension, emotional distress, lupus erythematosus, seborrhoeic dermatitis, (photo-)allergic or phototoxic reactions, erythema facial perstans, heliotropic rash in dermatomyositis, familial facial erythema due to atopic eczema, nitrite/sulphite ingestion, alcohol ingestion, caffeine withdrawal, autonomic hyperreflexia, pheochromocytoma, VIPoma, carcinoid syndrome, brain tumours, renal cell carcinoma, Frey syndrome, mastocytosis, polycythemia vera, Parkinson's disease, as well as multiple sclerosis. In subtype II, inflammatory papules and pustules are seen in the central region of the face. In addition, signs of subtype I rosacea can be present as well. Erythema in subtype II patients can be due to either acute or chronic vasodilation secondary to inflammation.[24–26,53–56] Important differential diagnoses in subtype II include papulopustular acne, perioral dermatitis, allergic or toxic contact dermatitis, granulomatous rosacea, *lupus miliaris disseminatus faciei*, cutaneous sarcoidosis, gramnegative folliculitis and demodicosis but also *perifolliculitis capitis* and eosinophil folliculitis.

Disfiguring growth of hyperplastic sebaceous glands on the nose and other facial regions is seen in subtype III rosacea. Most often encountered is rhinophyma. Laymen wrongly attributed it to excessive alcohol consumption, even though so far it has not statistically been associated with abuse of ethanol.[57] Important differential diagnoses of subtype III include eosinophilic granuloma, Chilblain lupus, angiosarcoma and facies leontina.

Ocular rosacea can include symptoms such as conjunctivitis, blepharitis, irritation, dryness or keratitis.[58,59] The prevalence rates reported range from 3% to 72%; however, most sources assume a prevalence of more than 50% of all rosacea patients.[1,8,53,60–66] Ocular manifestations occur in around 20% before, 27% during and in 53% after skin symptoms of subtype I-III have evolved.[63] An ophthalmologist should be involved to confirm the diagnosis as it can also result in complications such as alterations of the lids, cornea, sclera and anterior chamber (uveitis). It is often accompanied by oedema of the lid or the periorbital regions.[58,59] As differential diagnoses, bacterial and viral conjunctivitis as well as allergic conjunctivitis and infectious keratitis needs to be considered.

Rare conditions imitating rosacea include Morbihan's disease,[67–69] which produces persistent lymphoedema and erythema of the mid-third and upper aspects of the face. It is sometimes imitated by a Melkersson–Rosenthal syndrome with additional solid persistent facial oedema.[70] Rosacea fulminans, previously called pyoderma facial or rosacea conglobata, occurs almost exclusively in young women, predominantly in their 20s or 30s with a sudden appearance of an eruption including erythema, papules, sterile pustules, coalescing cystic nodules and draining sinuses.[71,72] Important differential diagnoses include acne conglobate, Gram-negative folliculitis and lupus erythematosus. A Gram-negative variant of rosacea has also been described.[62]

Steroid-triggered (or induced) rosacea is important to recognize but often missed. It can arise due to prolonged systemic or topical use of glucocorticosteroids.[62] It first produces macular erythema with telangiectasia and later results in follicular papules and pustules. Steroids need to be stopped, even though this leads to an initial flare of skin lesions. Reddish-brown papules or nodules presenting concomitantly with diffuse facial erythema are the hallmark sign for granulomatous rosacea also known as lupoid rosacea.[8] Atypical presentations of rosacea include persistent erythema in locations such as the scalp or the scrotum (Table 1).

Process for differential diagnosis

Clinical diagnosis of rosacea should include history, symptoms, skin lesions age and gender as initial stratification tools. Clinicians particulary look for centrofacial erythema, telangiectasia, papules and pustules, and phymatous growths on nose, chin, glabella and front. In addition, clinical signs that are less well compatible with a diagnosis of rosacea are sought, such as extended scaling (seborrhoeic dermatitis, tinea), sharp demarcation of erythema (sometimes in erysipelas), extended scarring, unilateral inflammation (i.e. demodicosis), exclusively perioral or periorbital inflammation with a millimetre-wide non-inflamed zone around the orifices (perioral dermatitis), exquisite sensitivity to sunlight (lupus, polymorphic light dermatosis) and many more (see Table 2). In the vast majority of cases, the diagnosis of rosacea remains a purely clinical one and distinctive investigations such as skin biopsies are usually not needed. However, it can be life-saving not to miss an angiosarcoma that in the early stage is an important imitator of rosacea. A biopsy should always be analysed additionally with direct immunofluorescence for lupus erythematosus in cases of high clinical suspicion of lupus erythematosus, and the results should be compared with a biopsy taken from non-sun-exposed skin to avoid false-positive interpretation. Clinical evaluation should define potential differential diagnosis such as lupus erythematosus, polymorphic light eruption, perioral dermatitis, acne, for example, and finally the relatively new entity of mixed facial dermatosis which is an important and possibly quite common disorder that shows overlapping features of both seborrhoeic dermatitis and rosacea.[73]

Dermatopathology (skin biopsy)

All subtypes of rosacea show dilated blood and lymph vessels in the upper and mid-dermis. A superficial perivascular and perifollicular mononuclear lympho-histiocytic infiltrate is routinely observed. Oedema and thickened elastic fibres may be seen. In subtype I, histologic changes are sparse. In subtype II, epithelia

Table 1 Differential diagnosis of rosacea

Do not miss	Differential Diagnosis	Distinguishing Features
!	Acne vulgaris	Scarring, comedones, no telangiectasia
!	Acute cutaneous lupus erythematosus	Sharp demarcation, sensitivity to sunlight
	AIDS	Acute outbreak of seborrhoeic dermatitis, coccidioidomycosis,
!	Angiosarcoma	Doughy oedema, erysipelas-like inflammation
	Arterial hypertension	Flushing associated with high blood pressure
	Carcinoid syndrome	Systemic symptoms during flush
	Chronic actinic dermatitis	Photodistribution
	Cutaneous sinus histiocytosis (Rosai–Dorfman disease)	Mostly young, dark-skinned persons
!	Demodicosis	Unilateral follicular inflammation
	Dermatomyositis	Periocular oedema, Gottron papules
	Eosinophilic granuloma	Swelling and pain around osteolytic lesions
	Folliculitis	Pustules are located at the follicle opening
	Glucagonoma	Crusts, blisters
	Granuloma faciale	Few, larger plaques. Can have telangiectasia. No epidermal involvement.
	Granulomatous periorificial dermatitis	Granulomatous histology
!	Haber's syndrome	Seborrheic keratosis in axillary and inguinal regions
	Halogenoderma	Often epilepsy, history of bromide or iodine
!	Lupus miliaris disseminatus faciei	Brownish papules in diascopy
	Lupus vulgaris	Solitary lesion at beginning, quantiferon positive
	Lymphoedema	Scarce inflammation
	Mastocytosis	Mostly flushing, more monomorphic papules
!	Facies ethylica	Anamnestic C2 abusus, liver enzymes
	Facies mitralis	Mitral stenotic systolic heart sound
	Mixed connective tissue disorder	Hyperkeratotic nail fold, U1-RNP antibodies
!	Mixed facial dermatosis	Features of seborrhoeic dermatitis and rosacea
	Pellagra	Photodistribution of lesion
	Perifolliculitis capitis	Pustules are located mainly on the scalp
	Perioral dermatitis	Exclusively periorificial inflammation with demarcation zone
	Pheochromocytoma	Systemic symptoms, flush only
	Photosensitive drug reaction	History of drug intake.
	Polycythaemia vera	Pruritus after contact with warm water, blood tests.
!	Polymorphous light eruption	Monomorphic, densely set papules to plaques. Less frequent on face. Mostly younger persons.
	Recurrent erysipelas	Confluent erythematous lesions
	Rubeosis diabeticorum	Hyperglycaemia, polyuria
	Sarcoidosis	No epidermal involvement, few signs of rosacea
!	Seborrhoeic dermatitis	Scaling and erythema, retroauricular and scalp involvement
	Syringomas	Brownish / translucent 1-5 mm papules, little inflammation
	Tinea faciei	Sharply demarcated, accentuated at the edge, scaling
	Trichoepitheliomas	Whitish-yellow papules, when disseminated check Brooke syndrome
	Zinc deficiency	Periorificial eczematous lesions

of follicular infundibula can show spongiotic changes and intrafollicular neutrophils as well as lymphohistiocytic infiltrates. In subtype III, sebaceous glands are hyperplastic and granuloma formation and cysts develop. In the granulomatous subtype of rosacea, non-caseating epithelioid cell granulomas arise.[74–76] Demodex mites are found in around 10% of routine biopsies and cause follicular dilation, folliculitis and perifollicular inflammation.[77,78]

Methods

This guideline was created under the auspices of the Swiss Society of Dermatology and Venereology. On 1 November 2016, a literature search in PubMed and Google Scholar using the reference words 'rosacea', 'erythematotelangiectatic rosacea', 'papulopustular rosacea', 'phymatous rosacea' and 'ocular rosacea' was performed to collect all relevant publications between 1990 and 2016. A total number of more than 300 publications were incorporated in the

Table 2 Level of evidence according to Lebwohl.

A:
• ≥1 prospective randomized, double-blind, controlled trial.
• No major design flaws.
B:
• Prospective clinical trials (≥20 participants).
• No adequate controls or lacking of another key facet of design.
C:
• Small trials (<20 participants).
• Clinical trials with significant design limitations.
• Case reports (overall ≥20 cases reported).
• Retrospective analyses of data.
D:
• Case series (≥5 participants)
E:
• Case reports.
• Case series (<5 participants).

Level of evidence A (green), B (yellow), C (light orange), D (dark orange), E (red).

final analysis leading to this work. The data were discussed with 13 national experts on rosacea, who came to an informal (S1) consensus towards the recommendations as given in this guideline.

The level of evidence (A-E) was measured according to Lebwohl [79] and refers to the strength of evidence published (Table 2). Table 3 encompasses the level of evidence for all therapeutic options. To demonstrate the utility of compounds in daily practice, we have summarized the Swiss Recommendations in Table 4.

Treatment

General recommendations

In our opinion, the trigger factors as mentioned above should be strictly avoided. Non-occlusive sunscreen is recommended, but the ambient heat from infrared light can still act as a trigger factor itself.[25,26,54,56,80,81] Irritation of facial skin either due to soap or to occlusive cosmetics has to be strictly prevented using mild facial cleansers and light cosmetics.[28] To restore the barrier of the stratum corneum, remoisturizing products can be applied, even though scientific evidence for their effectiveness is slim.[82]

Treatment of erythematotelangiectatic rosacea

Erythema of the face, flushing and telangiectasias are the main symptoms of ETR. Only few studies have been performed on patients with rosacea subtype I.

Brimonidine tartrate (BT) Brimonidine 0.33–1% gel 3 mg/g, a vasoconstrictive alpha-2 adrenergic receptor agonist, once daily, is registered for subtype I rosacea. BT has traditionally been used to treat open angle glaucoma, but recently emerged as a therapy for rosacea-induced facial erythema.

Two randomized, vehicle-controlled, phase II trials (n = 122, n = 269) using BT 0.07%, 0.18% and 0.5% showed dose-dependent effects in the treatment of moderate-to-severe facial erythema.[83] Two phase III, randomized, multicentre, controlled studies (n = 260, n = 293) of moderate facial erythema using BT observed 1 and 2 grade improvements. Another similar study came to almost identical results.[84] In its ability to reduce erythema, BT is superior to azelaic acid 15% gel.[85] There is no significant effect on telangiectasias. First responses can be seen within 30 min.[19,86] Adverse effects include burning sensation, contact dermatitis, flushing as well as rebound erythema.[87,88] One study reported the occurrence of a persistent erythema located adjacent to an area being treated with brimonidine for 7 months.[89]

There are no long-term data on brimonidine in the treatment of facial erythema. Two randomized, double-blind and vehicle-controlled trials of BT yielded a good safety profile.[19] A pharmacokinetic study compared the bioavailability and pharmacokinetics of BT gel (0.07%, 0.18% and 0.5%) to the ophthalmic solution. Additionally, the safety profile was evaluated showing that the cutaneous application was safer.[90] In the experience of the authors, many patients are unable to achieve homogeneous reduction of erythema and tend to stop the treatment again. Also, it may not be useful to treat erythema with BT when papulopustules are present, as these become more exposed in the process.

The official limitation for this drug is moderate-to-severe rosacea, which means that it can only be prescribed in a fraction of cases of subtype I.[19,83,86,91] Even though it seems to be effective also in erythema due to other causes than rosacea,[92–104] this is considered off-label and may not be covered by the insurance.

Conclusion: Brimonidine is recommended for moderate-to-severe subtype I rosacea (level of evidence: A).

Laser Laser therapy can reduce erythema and telangiectasias.[95] A variety of laser and light-based devices have been demonstrated to be useful in the treatment of the vascular manifestations of rosacea. Usually, one to four sessions are needed to achieve good results.[96–112] Neodymium-doped, yttrium–aluminium–garnet (Nd:YAG), pulsed dye laser (PDL) or intense pulsed light (IPL) are physical options for facial erythema and telangiectasias.

The Nd:YAG laser can cause haemoglobin destruction.[99,113,114] A double-blind, randomized, controlled trial comparing the effectiveness of a 595-nm pulsed dye laser and a microsecond 1064-nm Nd:YAG laser including 16 patients showed slightly more efficient data for the PDL for fair skinned patients, while Nd:YAG induced less pain. Nd:YAG lasers are efficient and safe.[115] The combination of topical retinaldehyde and a 532 nm Nd:YAG laser led to a greater degree of improvement than using laser alone, as a prospective randomized blinded clinical trial with 14 patients showed.[96]

Table 3 Level of evidence of topical and systemical treatments in rosacea.

	I	II	III
Topical steroids	Contraindicated	Contraindicated	Contraindicated
Topical brimonidine	**A**	ND	ND
Intense Pulsed Light (IPL)	**A**	ND	ND
Pulsed Dye Laser (PDL)	**B**	ND	ND
Neodymium-doped, yttrium–aluminium–garnet (Nd:YAG)	**B**	**B**	ND
Propranolol	**C**	ND	ND
Nadolol	**D**	ND	ND
Carvedilol	**D**	ND	ND
Topical metronidazole	ND	**A**	ND
Topical azelaic acid	ND	**A**	ND
Botulinum toxin	**D**	ND	ND
Topical ivermectin	ND	**A**	ND
Pimecrolimus	ND	**A**	ND
Tacrolimus	**D**	**D**	ND
Topical retinoids	ND	**A**	ND
Topical permethrin	ND	**A**	ND
Topical benzoyl peroxide/clindamycin	ND	**A**	ND
Topical erythromycin	ND	**A**	ND
Topical dapsone	ND	**A**	ND
Oral doxycycline/ tetracycline	ND	**A**	**A**
Doxycycline (low-dose)	ND	**A**	ND
Oral minocycline	ND	**A**	ND
Oral metronidazole	ND	**B**	ND
Oral ampicillin	ND	**A**	ND
Oral azithromycin	ND	**B**	ND
Oral clarithromycin	ND	**B**	ND
Oral isotretinoin	ND	**A**	**A**
Oral zinc sulphate	ND	**A**	ND
Oral ivermectin	ND	**D**	ND
Surgery/Blepharoplasty	Not appl.	Not appl.	**C**
Ablative laser treatment	Not appl.	Not appl.	**C**

Level of evidence A (green), B (yellow), C (light orange), D (dark orange), E (red), ND (no data).

Pulsed dye lasers (PDL) use a wavelength of 595 nm and target haemoglobin, leading to an obstruction of blood vessels.[95,99,113,116] Several studies have confirmed the safety and efficacy of pulsed dye lasers in rosacea. The largest trial consisted of 40 patients,[100] but multiple smaller ones with 32,[109] 25,[103] 16,[104] 16,[111] 12,[110] 12,[107] 11[101] and 9[97] patients have also been performed. All came to the same conclusion that PDL represents a safe and effective treatment option for facial erythema and/or telangiectasias. These trials were prospective, and some of them were randomized,[101,103] controlled, but none of them was blinded. The additional application of topical niacin showed a beneficial treatment effect in dark-skinned Asians, a randomized, prospective, split-face trial with 15 patients concluded.[80]

The improvement lasts a number of years. Intense pulsed light has a wavelength between 550 and 670 nm, which is absorbed by melanin and oxyhaemoglobin.[113,117,118] A randomized, controlled, single-blind, split-face trial with 29 patients showed significant benefits of intense pulsed light therapy.[102] Similar studies with 60,[98] 34,[106] 32[119] and 4[108] patients led to almost identical conclusions. Combining IPL and radiofrequency in 21 patients with moderate-to-severe rosacea over the period of 5 months improved erythema, flushing and telangiectasias. The same efficacy was achieved after 3 and 5 treatments. No significant adverse effects were reported.[111]

At present, pulsed dye laser (PDL) and IPL are typically used. IPL has with a larger spot size and fewer side-effects some advantages over PDL. Despite the published efficacy of devices for rosacea treatment, they are usually not reimbursed by health insurances.[78]

Conclusion: IPL (level of evidence: A) Nd:YAG (B), and PDL (B) treatment are recommended for rosacea subtype I.

β-Blockers Non-selective β-blockers can reduce flushing by blocking β-receptors on cutaneous blood vessels.[119]

Table 4 Swiss treatment recommendations for rosacea

	Rosacea grade (classical)	I		II	III	IV
	Rosacea grade (new)	Erythema	Telangiectasias	Papules/Pustules	Phyma	Ocular Rosacea
Topical drugs	Azelaic acid	+	No data	+++	No data	(+)
	Botulinum toxin	–	No effect	No data	No data	No data
	BPO/Clindamycin	No data	No data	++	No data	No data
	Brimonidine	+++	No effect	No data	No data	No data
	Dapsone	No data	No data	Not available in CH	No data	No data
	Erythromycin	No data	No data	++	No data	No data
	Ivermectin	No data	No data	+++	No data	+
	Metronidazole	+	No data	+++	No data	++
	Permethrin	No data	No data	+	No data	No data
	Pimecrolimus	+	No data	++	No data	No data
	Retinoids	No data	No data	++	No data	No data
	Steroids	–	–	–	–	+
	Tacrolimus	+	No data	–	No data	+
Oral drugs	Ampicillin	No data	No data	+	No data	No data
	Azithromycin	No data	No data	+	No data	++
	Carvedilol	+	No data	No data	No data	No data
	Clarithromycin	No data	No data	+	No data	No data
	Doxycycline (low dose)	No data	No data	+++	+++	+++
	Doxycycline/ tetracycline	No data	No data	+++	++	+++
	Isotretinoin	No data	No data	++	++	No data
	Ivermectin	No data	No data	+	No data	No data
	Metronidazole	No data	No data	+	No data	No data
	Minocycline	No data	No data	–	No data	No data
	Zinc sulphate	No data	No data	+	No data	No data
Physical / phototherapy	IPL, PDL, Nd:YAG	+++	+++	+	No data	No data
	Surgery/Blepharoplasty	No data	Not appl.	Not appl.	+++	+
	Ablative laser treatment	No data	Not appl.	Not appl.	+++	Not appl.
	Physical therapy	No data	Not appl.	Not appl.	Not appl.	+++
Eyedrops	Tear replacements	No data	Not appl.	Not appl.	Not appl.	+++
	Ocular cyclosporin	No data	Not appl.	Not appl.	Not appl.	+++
	Ocular azithromycin	No data	Not appl.	Not appl.	Not appl.	++
	Ocular tetracyclines	No data	Not appl.	Not appl.	Not appl.	++

Green, recommended; Red, not recommended.

Propranolol has shown clinical benefits in a case series of nine patients[120] and a non-randomized, non-blinded, non-placebo-controlled cohort study including 78 patients.[121] However, it is hardly ever used for the treatment of rosacea-induced facial flushing due to its adverse effects as hypotension an bradycardia.[122] In one case series with 15 patients using the non-selective β-blocker, nadolol, no clear benefit on the flushing reactions was detected.[123]

Carvedilol, an α_{1}-, β_{1}- and β_{2}- antagonist, is effective in some patients. One case report[124] and one case series with 11 participants [125] showed some efficacy.

Conclusion: Propranolol (evidence level: C) and nadolol (evidence level: E) is not recommended for flushing in rosacea. As an off-label therapy, carvedilol, for example at a dosage of 6.25 mg twice a day, can be considered (D).

Topical metronidazole Topical metronidazole has shown to reduced erythema of rosacea in six double-blind studies,[126–131] including two multicentre trials[128,131] with up to 113 patients.[130] However, those studies were performed on patients suffering from subtype II. There is no trial exclusively on patients with erythematotelangiectatic rosacea.

Conclusion: A treatment with topical metronidazole 0,75-1% cream or gel may be attempted in patients with subtype I. As there are no studies available exclusively on subtype I patients, no level of evidence statement can be given.

Topical azelaic acid A randomized, double-blind, multicentre study (n = 116) showed efficacy of azelaic acid in the treatment of erythema.[132] Two vehicle-controlled, randomized phase III studies (n = 664) showed improvement of erythema using

azelaic acid 15% gel.[133] Nonetheless, those studies included only patients with papulopustular rosacea.

Conclusion: The application of topical azelaic acid 15% cream or gel can be attempted in patients with subtype I. As there are no studies available exclusively on subtype I patients, no level of evidence statement can be given.

Botulinum toxin Botulinum toxin is a neurotoxic protein. Intradermal injection of botulinum toxin was evaluated in a clinical, non-randomized, non-placebo-controlled, non-blinded trial with 25 patients suffering from facial erythema of erythematotelangiectatic rosacea. Only 15 patients completed the study, and the others were excluded in the statistical analysis, which may greatly bias the results. The reported data claimed a significant improvement of facial erythema.[134]

Conclusion: Not recommended at this point, the evidence is in our opinion insufficient/potentially biased (level of evidence: D).

Tacrolimus A small study with 10 patients evaluated the efficacy of tacrolimus in eight patients with subtype I rosacea and two with steroid-induced rosacea. Tacrolimus showed good effects causing complete remission in 6 of 10 patients after 6 weeks.[135] Similar positive effects were described in a case report using the combination of azithromycin and tacrolimus 0.1% ointment in a subtype III patient.[136] Adverse effects include burning sensations upon treatment initiation.[135] Also, consumption of ethanol can induce paradoxical erythema of the treated skin.

Conclusion: Tacrolimus can be considered for subtype I rosacea (level of evidence: D).

Pimecrolimus Pimecrolimus 1% cream was effective in reducing erythema of rosacea in two prospective, open-label studies ($n = 26$, $n = 40$).[137,138] Patients suffered, however, from subtype II. Notably, other data have suggested that calcineurin inhibitors can induce a rosacea-like dermatitis,[139,144] and in one case, a rosacea-like demodicidosis was caused.[145]

Conclusion: The use of pimecrolimus may be considered in subtype I rosacea patients. As there are no studies available exclusively on subtype I patients, no level of evidence statement can be made. In therapy-resistant cases, the use can be considered.

Ondansetron, praziquantel, TDT068, oxymetazoline, 4-ethoxybenzaldehyde 1%, laropiprant and calcium channel blockers are all not recommended, please see the in Data S1.

Treatment of papulopustular rosacea

Inflammatory lesions such as papules and pustules as well as erythema occur in subtype II. In mild manifestations of papulopustular rosacea, topical treatments alone can be successful. For more severe cases, systemical treatment or combinations thereof are recommended.[8,55] A combination of local and systemic therapies is recommended.

Topical treatment of papulopustular rosacea

Metronidazole Metronidazole (MTZ) is a nitroimidazole antibiotic. For subtype II rosacea, 0.75–1% cream or gel[129,130,146,147] are most commonly used and should be applied twice daily. In Europe, multiple formulation with metronidazole are on the market. However, one study found no difference in efficacy between 0.75% and 1% metronidazole.[146] It remains unclear whether the higher dose is associated with improved efficacy. The efficacy of MTZ has been confirmed in multiple double-blind studies.[126–131] Compared to azelaic acid (AZA), similar or even superior results of azelaic acid in reducing facial erythema have been observed.[147–149] However, MTZ is considered to have a more tolerable profile than AZA.[150] In a head-to-head trial with pimecrolimus 1%, both agents reduced erythema equally. No improvement of telangiectasias was seen.[151] The strongest reduction in lesion count is clinically observed around 6 weeks.[152] MTZ has a similar efficacy as oral (oxy)tetracycline, a randomized double-blind trial ($n = 51$) reported. Noteworthy, an improvement was observed in 90% of both groups.[153]

Conclusion: Metronidazole is recommended (A) for subtype II rosacea patients.

Tacrolimus One study with 24 patients suffering from subtype I and II rosacea showed no effect on the number of papules, but reduced erythema.[154]

Conclusion: Tacrolimus is not recommended (D) for subtype II rosacea patients.

Azelaic acid Azelaic acid is a saturated dicarboxylic acid. Azelaic acid inhibits the production of ROS and upregulation of pro-inflammatory cytokines as IL-1, IL-6 and TNF-α. Also, phosphorylation of ERK1/2 and p38 as well as UV-induced NF-κB activation is downregulated. PPARγ inhibits inflammatory responses and is induced by azelaic acid.[8,155] Multiple, mostly randomized, double-blind, multicentre studies have provided good data on the beneficial effects of azelaic acid on subtype II rosacea. Erythema as well as inflammatory lesions responded very well.[133,147,156–162]

Conclusion: Azelaic acid is recommended (A) for subtype II rosacea patients.

Ivermectin Ivermectin is a broad-spectrum antiparasitic agent. In one phase 3, investigator-blinded, randomized, parallel-group, head-to-head trial ($n = 962$) ivermectin 1% cream showed superiority over metronidazole 0.75% cream.[152] It is newly registered in Switzerland, many other European countries and the USA.[152,160,163]

Conclusion: We recommend the use of topical ivermectin (A).

Pimecrolimus The calcineurin inhibitor, pimecrolimus 1%, has successfully been used in the treatment of subtype II rosacea. It

has shown efficacy in a placebo-controlled, randomized trial ($n = 40$).[164] Compared to metronidazole 1% cream, no superiority of pimecrolimus cream was observed.[151] Topical pimecrolimus 1% also showed some efficacy in two case reports of a patient with granulomatous rosacea.[165,166] Flares and facial erythema after alcohol intake have been described in patients using calcineurin inhibitors.[167] As mentioned above, induction of rosacea by pimecrolimus has been reported.[139–144]

Conclusion: Pimecrolimus can be considered (A) for subtype II rosacea patients.

Retinoids Regarding the study mentioned above, tretinoin 0.025% gel in combination with clindamycin phosphate 1.2% has not shown beneficial results.[168] In contrast, a randomized, double-blind trial ($n = 20$) described significant improvement and identical results of oral low-dose isotretinoin and tretinoin 0.025% cream after 16 weeks.[169] In a randomized open trial with 55 patients, adapalene was efficacious in the treatment of subtype II rosacea patients.[170] Topical retinoids can be irritative and should be only used if well tolerated.

Conclusion: Retinoids, tretinoin 0.025% and adapalene gel can be used (A, but conflicting data) in subtype II rosacea patients. However, in each patient, the individual tolerance of topical retinoids must be considered.

Permethrin One pilot study ($n = 6$)[171] and one randomized double-blind placebo-controlled study ($n = 63$)[129] with subtype II patients have been successfully performed. The data of both studies showed that the rosacea-induced erythema and papules were reduced with topical permethrin 5% cream, but there was no effect on pustules nor telangiectasias.

Conclusion: Even though solid evidence (A) is available on some outcomes, but not all relevant end points. Topical permethrin may be considered, but is rarely used in Switzerland.

Benzoyl peroxide formulations Two double-blind, randomized, vehicle-controlled clinical trials ($n = 53$, $n = 50$) of a combination of benzoyl peroxide/clindamycin gel observed significant superiority of BP/C.[172,173] Another placebo-controlled trial ($n = 64$) provided similar results.[174] To find the best dosage a randomized, phase 2, dose-ranging study ($n = 92$) with encapsulated benzoyl peroxide gel was performed and yielded results that showed superiority of the 5% vs. the 1% gel.[175] Benzoyl peroxide-erythromycin gel is efficient in decreasing demodex folliculorum when compared to metronidazole gel.[176] Benzoyl peroxide can be irritative and should be only used if well tolerated.

Conclusion: BP/C 5% gel can be used (A) for subtype II rosacea patients.

Erythromycin Topical erythromycin was efficacious in several studies.[176–178] In a head-to-head trial, metronidazole 0.75% gel as well as erythromycin 2% gel lead to cutaneous improvements in papulopustular rosacea.[178] It was comparable in efficacy to topical azithromycin in a phase II, randomized, double-blind, single-centre study ($n = 20$).[177] In combination with benzoyl peroxide, it was superior compared to metronidazole.[176] Conclusion: We recommend (A) the use of topical erythromycin 2% gel for subtype II rosacea patients.

Dapsone In a double-blind randomized clinical trial ($n = 56$), 5% dapsone gel was as effective as 0.75% metronidazole gel.[179]

Conclusion: Based on the evidence, topical dapsone could be recommended (A), but it is not available in many European countries as Switzerland.

Neodymium-doped yttrium–aluminium–garnet laser In an open clinical trial ($n = 66$), the Nd:YAG laser was shown to be safe and effective against papulopustular lesions.[180]

Conclusion: In therapy-resistant cases, we recommend (B) the treatment with Nd:YAG lasers.

Systemic treatments for papulopustular rosacea

Doxycycline Doxycycline is an antibiotic drug of the tetracycline family. While doxycycline is administered at 100 mg (or 200 mg) daily in other diseases, low-dose doxycycline (40 mg: 30 mg immediate-release and 10-mg delayed-release) has shown to provide similar results with less adverse effects in rosacea.[181]

At a dosage of 40 mg, no antibiotic selection pressure is produced leading to the avoidance of antibiotic resistance, even when administered over a prolonged duration of several months.[181–184]

Several multicentre, randomized, double-blind, active control study with ($n = 40$, $n = 91$, $n = 134$, $n = 269$, $n = 268$), one retrospective study ($n = 826$), and a community-based assessment (ORCA), open-label study ($n = 1197$) yielded very good results in terms of reduction of erythema and inflammatory lesions.[162,181,183,185–188]

In a randomized, open clinical trial focusing on erythema and telangiectasia, no difference between clarithromycin 250 mg twice daily for 4 weeks, then 250 mg once daily for 4 weeks ($n = 23$) or doxycycline 100 mg twice daily for 4 weeks, then 100 mg once daily for 4 weeks ($n = 17$) was seen. The decrease in rosacea lesions was more rapidly seen in the group treated with clarithromycin.[189]

A randomized, open, clinical trial compared azithromycin (first month: 500 mg three times a week; second month: 250 mg three times a week; third month: 250 mg twice weekly) to doxycycline 100 mg daily. Doxycycline was not inferior to azithromycin ($n = 67$).[190]

In a 16-week, double-blind, randomized, placebo-controlled study comparing doxycycline 40 mg and topical metronidazole gel 1% vs. solely metronidazole topical gel 1%, the combination therapy proved to be effective and well tolerated.[191]

In severe cases, multiple centres in Switzerland have had good experience in using 200 mg daily for 4 weeks, reducing to 100 mg daily for another 4 weeks. Afterwards 40 mg once daily for prolonged periods of time can be applied.[192]

Conclusion: We recommend (A) oral tetracycline for subtype II rosacea patients.

Tetracycline In a randomized, double-blind, clinical trial ($n = 56$) tetracycline and ampicillin showed comparative effects.[193]

One randomized, double-blind study of 40 patients with subtype II rosacea showed no significant difference between oral oxytetracycline and metronidazole.[194]

Conclusion: We recommend (A) oral tetracyclines for subtype II rosacea patients.

Isotretinoin Retinoids can have anti-inflammatory properties.[168,195,196] One randomized, double-blind trial with 20 patients compared oral low-dose isotretinoin with the topical retinoid, tretinoin 0.025% cream. The group treated with oral isotretinoin showed a more rapid onset of improvement. However, after 16 weeks, both groups showed equally beneficial results.[169]

A multicentre study with 92 patients described oral isotretinoin to be highly effective.[197] A placebo-controlled, randomized clinical study with 573 patients of subtype II and III showed complete remissions in 24% and an improvement in 57% of patients treated with isotretinoin, using 0.3 mg/kg.[168]

An open-label study ($n = 25$) published data indicating a significant improvement of patients receiving isotretinoin 20 mg daily. When treatment was halted, within 11 months 45% of the patients relapsed.[206]

Conclusion: Low-dose isotretinoin treatment (0.3 mg/kg) can be recommended (A) for subtype II rosacea patients. From personal experience, we find that also a dose of 0.15 mg/kg can be effective.

Ampicillin In a randomized, double-blind clinical trial ($n = 56$), randomized effects were shown between ampicillin and tetracycline.[200]

Conclusion: Oral ampicillin can be used (A) for subtype II rosacea patients; however, the available evidence is stronger for doxycycline. To our knowledge, it is not used any European countries.

Metronidazole A double-blind trial ($n = 29$) showed superiority of oral metronidazole compared to placebo.[198]

Conclusion: Oral metronidazole may be used for subtype II rosacea (B).

Azithromycin A randomized, open clinical trial ($n = 67$) comparing oral azithromycin (500 mg 3 times weekly for 4 weeks, afterwards reducing the dosage to 250 mg 3 times a week for 8 weeks) to doxycycline 100 mg daily demonstrated an equal efficacy of both treatments.[190] Four case reports have described an efficacy of oral azithromycin 500 mg once daily.[116,136,199,200]

Three open-label studies ($n = 34$, $n = 18$, $n = 10$) also showed significant treatment benefits. The dosage slightly varied amongst those studies.[201–203]

Conclusion: Oral azithromycin may be used (B) for subtype II rosacea patients; however, the available evidence is stronger for tetracyclines.

Clarithromycin Compared to doxycycline 100 mg twice daily in a randomized, open clinical trial (=40), clarithromycin was not inferior.[189]

Conclusion: Oral clarithromycin may be used (B) for subtype II rosacea patients; however, the available evidence is stronger for tetracyclines.

Zinc sulphate Zinc sulphate 100 mg daily showed significant superiority over placebo in a randomized, controlled, double-blind trial ($n = 25$).[204]

Conclusion: Oral zinc may be used (A) for subtype II rosacea.

Minocycline No difference in efficacy was found in a randomized double-blind trial compared with topical metronidazole ($n = 51$).[153] Because rarely, autoimmune hepatitis occurs due to minocycline, it is not recommended any longer.[195]

Conclusion: Because of rare but severe side-effects, we do not recommend oral minocycline for subtype II rosacea patients (level of evidence: A).

Ivermectin There are several case reports[206–210] and one case series[211] where oral ivermectin (200 microg/kg) mostly in combination with topical permethrin 5% cream[207,208,211] lead to treatment success in some cases, even in immunocompromised patients.[207,208,211]

Conclusion: Oral ivermectin can be used (D) for rosacea subtype II.

Treatment of phymatous rosacea

For phymatous rosacea, ablative laser treatments as well as classical surgery are available (level of evidence: C). In subtype III, systemic treatment with isotretinoin 0.3 mg per kg bodyweight once daily off-label (level of evidence: A) or with low-dose doxycycline (level of evidence: A) together with surgical interventions are typically used.[168] We are not aware of any clinical studies of oral drugs for the treatment of phymatous rosacea; thus, no statement on the level of evidence can be made

Treatment of ocular rosacea

For ocular rosacea, we recommend lid hygiene and lid massages, the application of warm wet tissues to unblock the meibomian glands, lipid containing tear replacements[212–217] as well as

topical cyclosporine,[218,219] azithromycin,[220–224] tetracyclines[225] or grade I steroids.[226] Long-term use of topical corticosteroids should be prevented due to side-effects as glaucoma or cataract.[32] In moderate-to-severe ocular rosacea, oral antibiotics such as tetracycline as doxycycline 100 mg once or twice daily for 6–12 weeks can be used.[32,66,227–229] Oral azithromycin is also a viable treatment option.[237] In extreme cases, blepharoplasty might become necessary.[68,231,232] All therapies mentioned in this article have been tried to some extend as off-label treatments for ocular rosacea. The current lack of high-quality studies specifically addressing ocular rosacea precludes systematic recommendations.

Granulomatous rosacea (GR)

There are limited data on patients treated for granulomatous rosacea. Only case reports and case series have been published.

Minocycline,[233] dapsone,[234,235] isotretinoin[236] and intense pulsed light (IPL)[237] have been published as successful treatments.

Additionally, in one patient, all symptoms of GR disappeared after an eradication of Helicobacter pylori with clarithromycin, metronidazole and pantoprazole had been performed.[238] Topical treatments with pimecrolimus cream[166] and azelaic acid gel[239] were successful.

One patient was treated with PDT using δ-aminolevulinic acid (ALA), which led to a remission of symptoms. However, six treatments were needed.[240]

Besides the known trigger factors for rosacea, also an infection with herpes simplex virus 2[241] or treatment with tacrolimus[242] has been discussed to be a possible trigger factor. A possible association with ulcerative colitis has been mentioned.[243]

GR appeared during the use of etanercept, and no relapse of symptoms was found after the administration of infliximab.[244]

In practice, treatment that has qualified for papulopustular rosacea can be used for GR.

Rosacea fulminans (RF)

Also in rosacea fulminans, there is a lack of sufficient data.

Multiple therapies have been used, according to publications dating back to 1940.[245] Therapies included high-caloric foods, vitamins A, B and C, topical treatment with Vleminckx's solution, Nomland's lotion, Ayers' ointment, benzoyl peroxide facial massage, hot compresses, sulphur, UV or X-ray radiation, typhoid vaccine, oral contraceptives as well as surgical modalities.[245]

Topical (clindamycin 1% lotion) and oral antibiotics (cotrimoxazole, minocycline, oxytetracycline, flucloxacillin, metronidazole, diaminophenylsulfone) as well as oral corticoids, sometimes in combination, have been used with mixed success.[72,245–247]

Isotretinoin, in various dosages from 0.2 to 1 mg/kg, showed good overall good results.[246,248–253]

In one case, minocycline alone showed a decline in skin changes, but no complete remission. The combination of minocycline and dapsone led to a full response. Also another case report described a remission under dapsone.[254]

A possible association with Crohn's disease,[253] ulcerative colitis[251] and erythema nodosum[255] has been reported. Infliximab, also in combination with azathioprine, followed by methotrexate resulted in no significant improvement. Subsequently, oral doxycycline, topical antibiotic and corticosteroid preparations, and serial intralesional triamcinolone acetonide injections, slowly lead to some improvement.[256]

Morbihan's disease

There are a few publications on Morbihan's disease.

Intralesional injection of triamcinolone as well as surgery showed good results in two case series.[16,68] Surgery followed by lymphatic drainage also showed beneficial results in a case report.[69] In one patient, surgery did not improve any symptoms.[16]

Overall, in at least seven cases, isotretinoin leads to an improvement of symptoms.[257–259] In one case, no changes were seen.[260]

A mixed response to minocycline was reported.[259,261,262] Oral doxycycline as well as oral prednisone showed no improvements.[16]

The use of ketotifen (1–2 mg/day) in combination with isotretinoin has shown efficacy in two case reports.[263,264]

Combination treatment

Often, systemic and topical treatments can be combined. Nonetheless, due to increase antibiotic resistance, combination of topical and systemic antibiotics is not recommended.[265,266]

Discussion and conclusion

Patient information and avoidance of trigger factors in rosacea patients are not always possible, and therefore, effective treatment options are routinely introduced. The treatment of rosacea continuously improves and new options become available. With lasers such as PDL and IPL, topical brimonidine and ivermectin, as well as the off-label use of systemic drugs such as isotretinoin, we can nowadays achieve long-standing treatment successes. It has to be considered that the use of most drugs is off-label. In some cases, treatments that are not reimbursed by insurances have to be included for optimal results. In the future, we will most likely have even more efficient drugs to control rosacea and potentially even approach disease resolution at some point.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Data S1. Recommendations for drugs rarely used for rosacea.